Anesthesiology
75:866–875, 1991

The Effects of Halothane on Ventricular Tachycardia in Intact Dogs

John D. Gallagher, M.D.,* Candyce A. McClernan, B.S.†

Halothane has either proarrhythmic or antiarrhythmic effects in a variety of clinical circumstances. This investigation tested the hypothesis that halothane would display different effects on ventricular tachycardia (VT) produced by different electrophysiologic mechanisms in intact dogs. Four models of VT produced by abnormal automaticity, reentry, delayed-afterdepolarization–induced triggered activity, and early-afterdepolarization–induced triggered automaticity (groups 1–4, respectively) were studied. In groups 1 and 2, the left anterior descending coronary artery (LAD) was ligated. In group 1 (n = 5), 24 h after LAD ligation and infarction, all dogs demonstrated incessant VT with 94.7 ± 2.3% of beats of ventricular origin. This ectopy presumably was due to abnormal automaticity. Halothane reduced the frequency of ventricular ectopy until at 2% halothane only 34.8 ± 15% of beats were of ventricular origin. One week after LAD ligation, programmed stimulation produced nonstimulated extrasystoles of presumably reentrant origin in six dogs. In three, halothane 1% abolished extrasystoles while increasing the ventricular refractory period by 23 ± 3.8% ($P < 0.05$). In the three other dogs, halothane had no effect (two dogs) or worsened the severity of VT (one dog), while the refractory period increased by 7.7% ($P > 0.05$). In group 3 dogs, ouabain was infused until VT secondary to triggered activity occurred. Halothane restored sinus rhythm in 4 of 5 dogs. Overall the percentage of sinus beats increased from 11.1 ± 2.8 to 97.4 ± 2.6% when halothane 2% was added during ouabain toxicity. Cesium chloride infusion increased the QT interval and produced complex VT in 5 dogs. In no experiment did halothane influence cesium chloride induced VT due to early afterdepolarizations or modify the QT prolongation produced by cesium (group 4). These experiments demonstrate that halothane has diverse effects on VT due to different cellular electrophysiologic mechanisms. (Key words: Anesthetics, volatile: halothane. Arrhythmia: long QT syndrome; reentry; ventricular tachycardia. Heart, electrophysiology: infarction. Pharmacology: ouabain, cesium.)

BECAUSE OF THE ABILITY of halothane to sensitize the heart to the arrhythmogenic effects of catecholamines, halothane traditionally has been considered an agent likely to produce intraoperative arrhythmias.[1] However, halothane suppresses the arrhythmias associated with digitalis intoxication.[2,3] This suggests that the effects of halothane on ventricular arrhythmias depend upon the specific mechanism responsible for the arrhythmia.

In experimental models, and presumably in humans, ventricular arrhythmias arise through a variety of pathologic mechanisms[4] that can be identified by electrophysiologic testing.[5,6] The effects of an antiarrhythmic drug on ventricular tachycardia (VT) produced in a well-defined model can give insights into the mechanisms responsible for the antiarrhythmic effect of the drug. Ultimately, such data may suggest the clinical circumstances in which the drug may be effective.[5]

The goal of the present investigation was to determine the effects of halothane on VT produced in dogs by several experimental manipulations. Suspected VT mechanisms studied included abnormal automaticity, reentry, triggered activity, and triggered automaticity. The rationale for this investigation was two-fold. First, halothane and other general anesthetics are often administered to patients with histories of VT. Knowledge of the effects of halothane on specific mechanisms for VT could improve patient care. Second, because halothane has either proarrhythmic or antiarrhythmic effects in different VT models, it would be helpful to clarify whether halothane will suppress a given arrhythmia.

Materials and Methods

The Institutional Animal Care and Use Committee approved this study. The experimental design was modeled after that used by Rosen *et al.*[5] and LeMarec *et al.*[6] Conditioned mongrel dogs were anesthetized with intravenous pentobarbital 30 mg/kg, and after tracheal intubation, the lungs were ventilated with room air using a mechanical ventilator. Muscle relaxants were not used. Through a left thoracotomy, bipolar left ventricular and left atrial pacing electrodes were placed, and a left atrial catheter was inserted for later administration of drugs and measurement of blood gases. Electrodes and catheters were exteriorized interscapularly. Additional surgical manipulations varied between groups as described below. After completion of surgery, dogs recovered in a monitored area, and when awake, the tracheas were extubated. After surgery, intramuscular morphine or butorphanol was administered for pain every 4 h and water was provided *ad libitum.*

Dogs in groups 1 and 2 underwent ligation of the left anterior descending coronary artery (LAD) just distal to the origin of the first diagonal branch.[7] Ligation of the

* Associate Professor of Anesthesiology, Dartmouth Medical School, Hanover, New Hampshire.

† Research Assistant, Deborah Research Institute, Browns Mills, New Jersey.

Received from the Deborah Research Institute, Browns Mills, New Jersey. Accepted for publication July 12, 1991. Supported by a Grant-in-Aid from the New Jersey Affiliate of the American Heart Association. Presented at the International Anesthesia Research Society Annual Meeting, Orlando, Florida, 1989.

Address reprint requests to Dr. Gallagher: Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 2 Maynard Street, Hanover, New Hampshire 03756.

LAD produces four distinct stages of ventricular tachyarrhythmias.[8-10] During phase 1, from 30 min to 1 h after LAD ligation, reentrant mechanisms in the ischemic zone are responsible for arrhythmias. Phase 2, from 1 to 4 h after ligation, is one of quiescence with few ventricular arrhythmias. In phase 3, from 4 to 48 h, abnormal automatic rhythms originate in partially depolarized cells in the ischemic border zone. During phase 4, beginning 4 d after LAD ligation, programmed electrical stimulation (PES) can induce reentrant VT. Our experiments dealt with rhythms occurring during phases 3 and 4.

Group 1: Abnormal Automaticity

Twenty-four hours after LAD ligation, survivors were placed in a sling. Four limb and one precordial ECG electrodes were positioned on the dog, and ECG leads 1, 2, and V1 were recorded (control recordings). Oxygen was then administered by mask and recordings repeated. In no case did administration of oxygen alter the arrhythmia. Halothane 0.5, 1, and 2% were then administered by mask in oxygen by way of a vaporizer calibrated with a mass spectrograph. Measurements were repeated after a minimum of 30 min at each halothane concentration. Animals breathed spontaneously, and left atrial blood gases were measured to avoid excessive hypercarbia (carbon dioxide tension $\geq$ 60 mmHg).

Group 2: Reentrant Ventricular Extrasystoles

Dogs that had undergone LAD ligation, including survivors of group 1, recovered for 1 week. Daily, the animals were placed in a sling and ECG leads placed for continued conditioning. On the day of the experiment, PES was performed to induce ventricular extrasystoles.[11] After 8 beats of ventricular pacing (S1) at 300- or 500-ms cycle lengths (CL), a single premature extrastimulus (S2) was introduced at 10 ms less than the basic S1–S1 CL. S2 was then administered at increasingly premature intervals (by 10 ms) until effective refractoriness was reached. S2 was then fixed at 20 ms above the effective refractory period (ERP) and a second premature extrastimulus (S3) was introduced. From the basic S1–S1 interval, diastole was scanned at 10-ms intervals with an S3 extrastimulus until S3 ERP was reached. If nonstimulated extrasystoles were noted, these were presumed to be reentrant. Halothane 1% was administered to these dogs and the pacing protocol repeated. If reentrant beats were eliminated by halothane, diastolic scanning with an S4 beat also was performed, following a protocol analogous to that described above. For PES with S4, S3 was fixed at 20 ms above the S3 ERP. This protocol is similar to that used in other investigations of anesthetic effects on inducibility of reentrant VT.[12-14]

Group 3: Triggered Activity Induced by Delayed Afterdepolarizations

Dogs were instrumented as in group 1, but the LAD was not ligated. After 1 week of daily conditioning, triggered activity was induced using ouabain 40 μg/kg through the left atrial catheter, followed by 10 μg/kg every 10 min until VT occurred. Ouabain was then given 10 μg/kg every 30 min to maintain toxic ouabain concentrations.[6] Halothane 0.5, 1, and 2% were next administered to these dogs. If sinus rhythm occurred during halothane administration, pacing for 20 beats at increasing rates was used to demonstrate triggered extrasystoles.[15,16]

Group 4: Triggered Automaticity Induced by Early Afterdepolarizations

Using a protocol analogous to group 3, dogs were given cesium chloride 1 mmol/kg through the left atrial catheter.[17] Cesium chloride was then infused at 2 $mmol \cdot kg^{-1} \cdot h^{-1}$ to initiate and maintain VT, and the effect of halothane 1% on these cesium toxic arrhythmias was determined. Spontaneous CL (RR interval), QT interval, and QT interval corrected for CL by the Bazett formula[18] (QT_C) were measured in the control state, after administration of cesium chloride, and after inhalation of halothane during continued cesium chloride infusion.

Data were analyzed with the use of analysis of variance (ANOVA) or paired t tests as appropriate.[19] Specific tests performed are noted under "Results." A $P < 0.05$ was considered significant. All results are reported as mean $\pm$ standard error of the mean.

Results

Group 1: Abnormal Automaticity

Seven dogs underwent LAD ligation, and five survived. Each survivor demonstrated incessant VT 24 h after in-

TABLE 1. Effects of Overdrive Pacing on Automatic Ventricular Tachycardia 24 h after Left Anterior Descending Coronary Artery Ligation

Experiment	Basic CL (ms)	Paced CL (30 s) (ms)	Return CL (ms)
1	265	200	360
2	395	250	560
3	485	350–200	Always sinus beat
4	490	350	360
		250	440
5	430	350	620
		250	640

Basic CL = basic cycle length of underlying predominantly ventricular rhythm; paced CL = cycle length during overdrive pacing for 30 s; return CL = cycle length following cessation of overdrive pacing.

TABLE 2. Suppression of Automatic Ventricular Tachycardia 24 h after Infarction by Halothane (n = 5)

	Ventricular Beats (%)	Heart Rate (beats per min)
Control	94.7 ± 2.3	152.8 ± 19.1
Halothane 0.5%	91.9 ± 3.3	154.0 ± 17.9
Halothane 1.0%	75.5 ± 18.9*	134.0 ± 15.3
Halothane 2.0%	34.8 ± 15.0*	130.8 ± 7.1

* $P < 0.05$ *versus* control by Duncan's multiple-range test after ANOVA.

farction, with 94.7% of beats ventricular in origin (range 83.9–100%). Overdrive pacing to produce overdrive suppression of the automatic focus[5] was used to document the automatic nature of the arrhythmia. Table 1 provides data on the response to overdrive suppression observed in each survivor.

With the exception of experiment 4, all dogs showed overdrive suppression; that is, the return CL after discontinuation of pacing was longer than the basic CL before pacing. In experiment 4 the response to overdrive pacing was less clear, but if triggered rhythms were responsible, the return CL after pacing at 250 ms should have been shorter than after pacing at 350 ms.[16]

Table 2 shows the effects of halothane on automatic VT. One animal was resistant to the effects of halothane. In this dog (experiment 1), halothane 2% reduced the percentage of ventricular beats from a control value of 93.8%, to 85.5%. In the other dogs, halothane reduced the percentage of ventricular beats to between 0–43.4%. In experiment 4, which did not show overdrive suppression, administration of 2% halothane decreased the percentage of ventricular beats from 100 to 35.9%.

Figure 1 shows the effects of halothane during VT 24 h after LAD ligation (experiment 3). In the control state, almost all beats were of ventricular origin. After administration of 2% halothane, the conversion to sinus rhythm was evident.

TABLE 3. Effects of Halothane on Programmed Stimulation-induced Extrasystoles 1 week after Myocardial Infarction

Experiment	Halothane Concentration (%)	S1–S1	S2 ERP	S3 ERP	S3 Range Yielding Reentrant Beats
1	0	300	110	240	250–270
	1%	300	140	270	None
2	0	300	130	270	280
	1%	300	150	300	None
3	0	300	110	220	230–260
	1%	300	140	270	None
4	0	500	130	260	270–280
	1%	500	140	270	280–290
5	0	300	130	250	260–270
	1%	300	140	260	270–290
6	0	300	Sustained monoform VT induced		
	0.5, 1, 2, 4%	No change in VT rate or morphology. VT degenerated to VF after attempted cardioversion.			

Data in milliseconds.

VT = ventricular tachycardia; VF = ventricular fibrillation; S1–S1 = cycle length of train of eight paced ventricular beats; S2 ERP = longest S1–S2 interval after eight-beat S1 train failing to capture the ventricle; S3 ERP = longest S2–S3 interval failing to capture the ventricle. S1–S2 fixed at S2 ERP + 20 ms.

GROUP 2: REENTRANT VENTRICULAR TACHYCARDIA

Table 3 describes the effects of halothane on PES-induced ventricular extrasystoles. Halothane "cured" presumably reentrant extrasystoles in three of six dogs. In the control state, PES induced from two to six nonstimulated extrasystoles. In these three dogs testing with S2, S3, or S4 stimulation was unable to induce extrasystoles after inhalation of halothane 1%.

In the remaining three dogs, halothane either had no effect on induced arrhythmias or apparent proarrhythmic effects. In one dog (experiment 4), before halothane was administered, PES reproducibly induced 2 extra beats when, after 8 paced beats at an S1–S1 interval of 500 ms and a premature S2 beat at an S1–S2 interval of 150 ms,

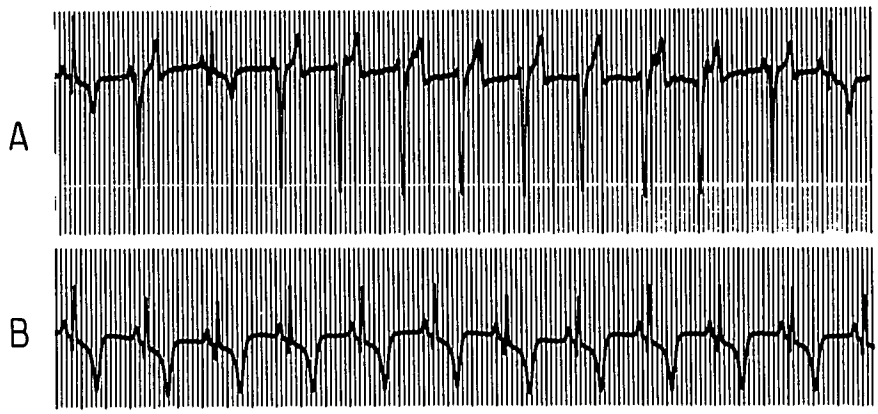

FIG. 1. Effects of halothane on ventricular tachycardia 24 h after coronary artery ligation. *A*: Control. Only the first, third, and final beats are of sinus origin. Others are ventricular in origin. *B*: After 2% halothane all beats are of sinus origin. Paper speed: 25 mm/s (1 line = 0.04 s).

an S3 beat was introduced at an S2–S3 coupling interval of either 270 or 280 ms. Halothane 1% increased S2 ERP from 130 to 140 ms in this dog. After repeated PES at an S1–S1 CL of 500 ms and S1–S2 interval of 160 ms, S3 stimuli at CL of either 280 or 290 ms repeatedly induced short runs of nonsustained VT (fig. 2). In a second dog (experiment 5), halothane administration had no effect on the reproducible occurrence of seven to ten nonstimulated extrasystoles. However, administration of halothane increased the range of S2–S3 intervals that resulted in the appearance of presumably reentrant beats by 50%, from 20 to 30 ms.

In experiment 6, a single extrastimulus (S2) after an 8-beat train of S1 beats at an S1–S1 CL of 300 ms induced sustained monomorphic VT. Halothane in concentrations of up to 2% changed neither the rate nor the morphology of the VT. After discontinuation of halothane, an attempt was made to restore the animal by cardioversion, but the rhythm degenerated into ventricular fibrillation from which the dog could not be resuscitated.

Although the number of dogs studied was small, the effects of halothane administration on S2 and S3 refractory periods were compared between dogs showing an antiarrhythmic effect of halothane and those showing no beneficial effect. The halothane-induced increase in S2 ERP in dogs "improved" by halothane, from 116.7 ± 6.7 to 143.3 ± 3.3 ms (23 ± 3.8%), was significantly greater than that in the remaining dogs, in which S2 ERP increased from 130 ± 0 to 140 ± 0 ms (7.7% increase, $P = 0.03$ by unpaired, two-tailed t test). Two-way repeated-measures ANOVA showed that halothane increased S2 ERP ($P = 0.025$) and that the increase differed between groups ($P = 0.03$).

Changes in S3 ERP, from 243.3 ± 14.5 to 280 ± 10 ms in dogs displaying an antiarrhythmic effect of halothane and from 255 ± 5 to 265 ± 5 ms in dogs not displaying an antiarrhythmic effect, are similar to those for S2 ERP. Halothane increased S3 ERP ($P = 0.0087$ by ANOVA), and the increase was greater in "improved" dogs ($P = 0.03$, t test). By analysis of variance, the difference between groups approached but did not achieve significance ($P = 0.053$).

Group 3: Ouabain-induced Ventricular Tachycardia

Ouabain infusion caused VT in each of five dogs, whereas halothane restored sinus rhythm in four of five dogs. Halothane 1% restored sinus rhythm in two dogs, and halothane 2% converted an additional two dogs. The remaining dog demonstrated no sinus beats during ouabain-toxic VT in the absence of halothane, 50% sinus beats after 1% halothane, and 87% sinus beats after 2% halothane.

Table 4 details the effects of increasing halothane concentration on ouabain-toxic VT. Halothane administration decreased heart rate in these dogs ($P = 0.0002$ by

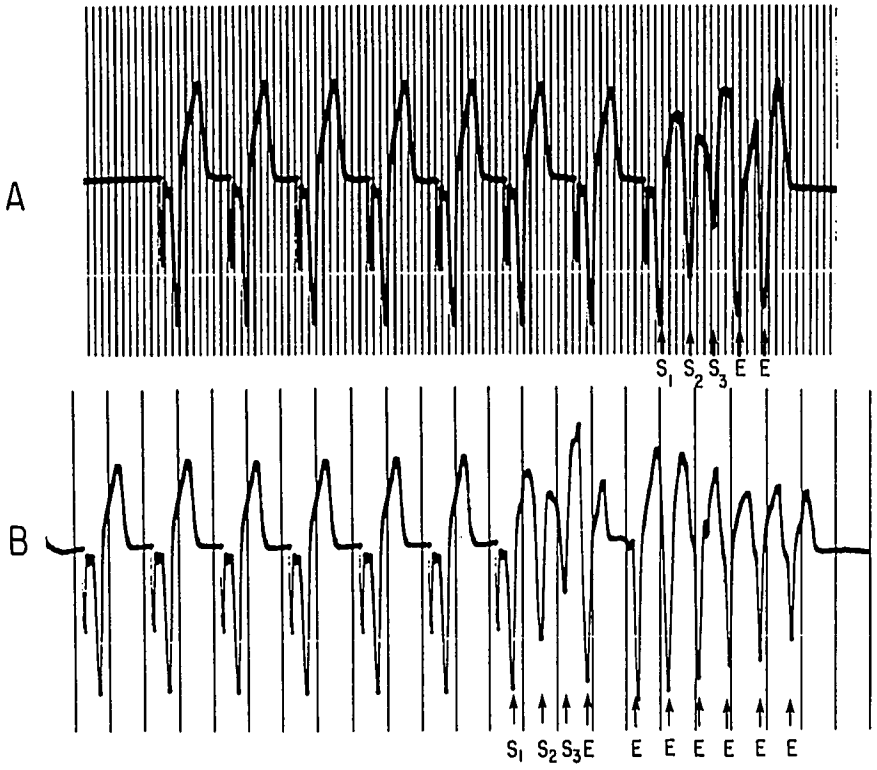

FIG. 2. Proarrhythmic effects of halothane on reentrant ventricular tachycardia. *A*: Control. Following an eight-beat train of paced beats (S_1), two premature extrastimuli (S_2 and S_3) induce two presumably reentrant extrasystoles (E). *B*: Halothane 1%. After eight S1 beats (seven shown), S_2 and S_3 extrastimuli reproducibly induced short runs of nonsustained ventricular extrasystoles (E). Paper speed: 25 mm/s; S_1–S_1 interval: 500 ms.

TABLE 4. Effects of Halothane on Ouabain-toxic Ventricular Tachycardia

	Rate (beats per min)	Sinus beats per min	Sinus Beats (%)
Ouabain toxic	191.86 ± 9.47	16.8 ± 3.07	11.13 ± 2.81
Halothane 1%	128.8 ± 13.07*	95.2 ± 13.94*	76.22 ± 10.80*
Halothane 2%	104.6 ± 9.06*	102 ± 9.74*	97.4 ± 2.60*†

* $P < 0.05$ *versus* control, Scheffé's test after ANOVA.

† $P < 0.05$ *versus* halothane 1%, Scheffé's test after ANOVA.

ANOVA) while increasing both the number of sinus beats per minute ($P = 0.0003$ by ANOVA) and percentage of sinus beats ($P = 0.001$ by ANOVA).

An example demonstrating the effects of halothane on ouabain-induced VT is shown in figure 3. In figure 3A, ventricular beats are interspersed with sinus and fusion beats. Observing ventricular and atrial electrograms from the epicardial electrodes confirmed the ventricular origin of beats. Halothane 1% restored sinus rhythm. It is a characteristic of delayed-afterdepolarization (DAD)–induced VT that rapid pacing often induces extra beats (*i.e.*, triggers extrasystoles).[15,16] Therefore, 20-beat runs of ventricular pacing were used in an attempt to induce triggering. Pacing at a 400-ms CL did not trigger extrasystoles, but faster pacing at a 250-ms CL triggered a brief run of VT (figs. 3C and 3D).

GROUP 4: CESIUM-INDUCED VENTRICULAR TACHYCARDIA

Intravascular infusion of cesium produced progressive increases in the QT interval and QT_C without significant change in the RR interval (table 5). Characteristically, as QT_C increased, episodes of trigeminy first appeared, followed by bigeminy and increasingly complex patterns of ventricular arrhythmias.[17] Inhalation of halothane 1% caused no further change in QT, QT_C, or RR intervals (table 5). In none of five dogs did halothane 1% beneficially affect cesium-induced VT. Two dogs also received halothane 2% without change in VT severity. QT_C in these two dogs after halothane 2% was 456 ± 7.5 ms, unchanged from values obtained during halothane 1% inhalation. Figure 4 shows cesium-induced VT recorded from 1 of these two dogs and the lack of benefit from halothane 1 or 2%. In figure 4D, torsades de pointes developed and degenerated to ventricular fibrillation.

Discussion

The present investigation examines the effects of halothane on four established canine models of VT: 1) VT occurring 24 h after myocardial infarction,[9,10] 2) VT occurring 1 week after infarction,[20,21] 3) VT due to acute ouabain toxicity,[22,23] and 4) VT induced by infusion of cesium chloride.[17] The present results indicate that halothane can have variable effects on these models of VT, ranging from proarrhythmic to antiarrhythmic. Mechanisms for VT and speculation as to possible halothane effects in each model studied are explored below.

TWENTY-FOUR-HOUR–POSTINFARCTION VENTRICULAR TACHYCARDIA

Twenty-four hours after two-stage ligation of the LAD in dogs,[7] the ECG displays incessant ectopic ventricular

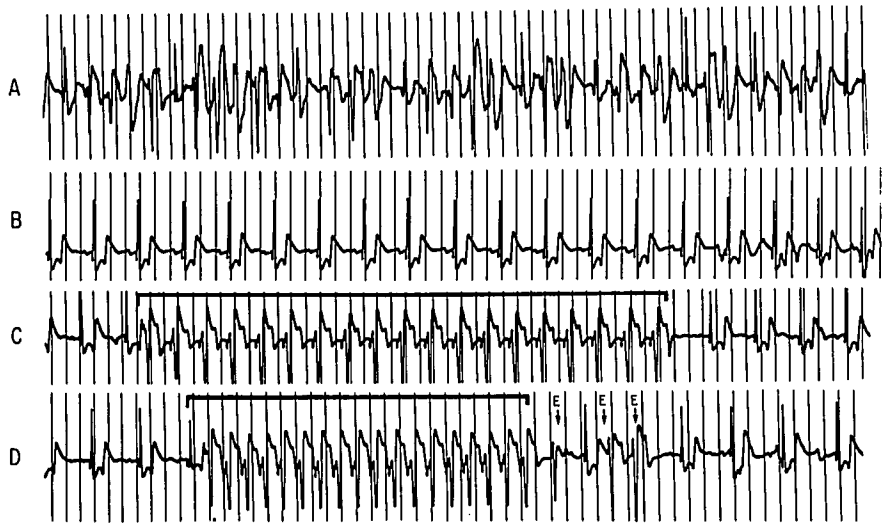

FIG. 3. Effects of halothane on ouabain-induced ventricular tachycardia. *A*: Control. Multiform ventricular tachycardia predominates with few sinus beats noted. Halothane 1% restored sinus rhythm (*B*). *C*: Overdrive pacing during halothane 1% administration in an attempt to trigger extrasystoles. Bar represents train of paced beats at 400-ms cycle length. After a brief pause attributable to overdrive suppression of the atrial pacemaker, sinus rhythm returns. *D*: A faster train of pacing at a 250-ms cycle length induces three extrasystoles (E). Paper speed: 25 mm/s.

TABLE 5. Electrophysiologic Effects of Cesium Chloride Infusion

	RR Interval	QT Interval*	QT_c Interval
Control	502 ± 45.9	248 ± 7.4	352 ± 17.4
CsCl	515 ± 48.1	335 ± 26.2	470 ± 17.8†
CsCl + Halo 1%	469 ± 66.1	310 ± 22.8	458 ± 13.3†

Data in milliseconds.
* $P = 0.033$ by ANOVA. $P = 0.048$ for control *versus* CsCl; $P = 0.054$ for control *versus* CsCl + halothane 1%.
† $P < 0.015$ *versus* control.

activity.[24] This arrhythmia is generally believed to be caused by abnormal activity of partially depolarized, slowly conducting subendocardial Purkinje fibers that survived the infarct.[10,24] The pathophysiology of abnormal automaticity may begin with ischemia-induced intracellular acidosis that inhibits membrane Na^+-K^+ pump function and alters sarcolemmal conductance, reducing intracellular K^+ activity.[25] Reduction of intracellular K^+ depolarizes membrane potential as predicted by the Nernst equation[26] and activates either inward Ca^{2+} or Na^+ currents.[27] Abolition of depolarization-induced automaticity by Ca^{2+}-channel antagonists emphasizes the important role of Ca^{2+} entry in the genesis of abnormal automaticity.[28] Na^+ entry through partially inactivated fast Na^+ channels or the nonselective cationic transient inward current provide sources for Na^+ generated arrhythmias.[25,27,29]

However, triggered activity due to DADs has been observed in similar preparations.[9,10,30] Intracellular Ca^{2+} overload can occur after ischemia.[31] When Ca^{2+} storage capability of the sarcoplasmic reticulum is exceeded, an oscillatory transient inward current carried by cations such as Na^+ and K^+ is induced.[27,29] The transient inward current manifests as DADs and triggered-activity–induced arrhythmias.[27] Similar requirements for elevated intracellular Ca^{2+} suggest that oscillatory increases in intracellular Ca^{2+} lead to triggered activity, whereas nonoscillatory increases in intracellular Ca^{2+} cause abnormal automaticity in otherwise similar circumstances.[32]

Logic *et al.*[33] in 1969 noted that halothane suppressed "idioventricular tachycardia" in nine dogs, 24–72 h after two-step ligation of the LAD. Figure 3 of their publication is similar to figure 1 in the present report. Turner *et al.*,[34] with the use of an *in vitro* model 1 day after LAD ligation, also observed preparations in which halothane suppressed abnormal automaticity, consonant with the present study. However, Turner *et al.*[34] also described examples of DAD-induced triggered activity, which halothane also abolished.

At the cellular level, halothane blocks the slow inward Ca^{2+} current,[35–37] abolishes Ca^{2+}-dependent action potentials,[38] decreases intracellular Ca^{2+} transients,[39] and inhibits release of Ca^{2+} from sarcoplasmic reticulum.[40] Each of these actions can antagonize either abnormal automaticity or triggered activity.

Nevertheless, evidence suggests that the predominant arrhythmogenic mechanism at 24 h after infarction is abnormal automaticity and not triggered activity.[10] Overdrive suppression of VT in four of the five dogs we studied is typical of automatic foci but not of triggered activity,[10] which is exacerbated by increases in pacing rate.[16] This differing response to pacing in intact animals may differentiate triggered activity from abnormal automaticity,[5,6] even though automatic arrhythmias occurring in depolarized cardiac fibers are not always overdrive-suppressible.[41] Conversion of 24-h-postinfarction VT to sinus rhythm after moricizine,[10] which is relatively selective for abnormal automaticity,[5] but not doxorubicin,[10] which specifically suppresses triggered activity,[6] also supports the hypothesis that abnormal automaticity is responsible

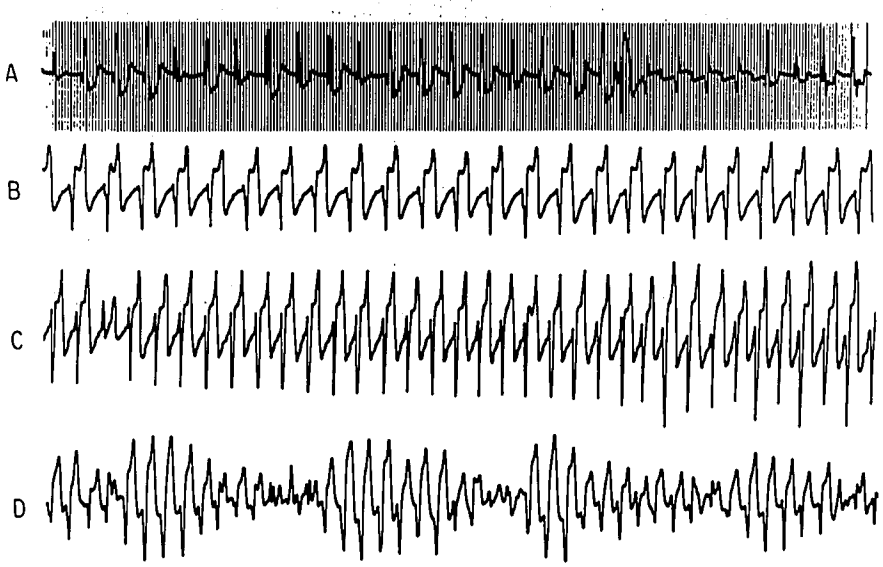

FIG. 4. Effects of halothane on cesium-induced ventricular tachycardia. *A*: Multiform ventricular tachycardia is seen after cesium chloride administration. *B*: Halothane 1% administration results in conversion to a more uniform morphology of ventricular tachycardia. *C*: Halothane 2% has little effect except possible acceleration of rate. The changes in ventricular tachycardia morphology and rate seen after halothane administration in this dog were not observed in the other dogs that received cesium. *D*: During administration of halothane 2%, torsades de pointes developed. This rhythm deteriorated into ventricular fibrillation. Paper speed: 25 mm/s.

for VT occurring 24 h after infarction. The present data suggest that the antiarrhythmic effects of halothane during VT occurring 24 h after infarction reflect inhibition of abnormal automaticity.

One-week–Postinfarction Ventricular Tachycardia

Ligation of the LAD in dogs produces a characteristic late (1 week) infarction with a 1–3-mm-thick rim of electrophysiologically abnormal surviving epicardial cells overlying a dense transmural core of infarction.[42] Programmed stimulation induces reentrant VT within the surviving epicardial layer[20,42] by producing an arc of functional block around which the reentrant wave of activation advances at a slow but uneven speed.[21] Termination usually occurs when the leading edge of activation encounters refractory tissue,[42] although complete block of conduction in the already slowly conducting tissue can also terminate the arrhythmia.[20,43]

Turner *et al.*,[34] who studied a 24-h infarction model, were interested primarily in the effects of halothane on reentrant VT. In seven *in vitro* preparations they found that halothane prolonged functional refractoriness, but not absolute refractoriness (ERP), and slowed conduction of premature impulses. The result in five of seven specimens was a widening of the zone of premature extrastimuli that induced reentrant responses. The authors suggested that this represented a proarrhythmic effect of halothane.[34] One of our dogs, 1 week after infarction, displayed a similar increase in the range of extrastimuli producing reentrant beats.

In studies more similar to the present investigation, using intact dogs studied by programmed stimulation several days to weeks after infarction, halothane demonstrated predominantly antiarrhythmic properties. Halothane prevented induction of VT in association with an increase in ERP[12–14] without changing ventricular conduction[12,13] or QRS duration.[12] Denniss *et al.*,[12] studying an LAD ligation model 1–3 weeks after infarction, found that halothane 2% was antiarrhythmic in 47% of dogs studied, 75% of which had prolongation of ERP. A proarrhythmic effect of halothane, defined as the appearance of inducible VT or ventricular fibrillation, was observed in 10% of the dogs studied.[12] Hunt and Ross,[14] studying a similar LAD ligation model 2–8 weeks after infarction, described an antiarrhythmic effect of halothane 2% in 5 of 10 dogs. Deutsch *et al.*[13] found a 50% antiarrhythmic incidence when halothane was administered to dogs 4–6 days after occlusion–reperfusion infarction. In 2 of 19 anesthetics administered to dogs without inducible VT or ventricular fibrillation, a proarrhythmic effect of halothane was observed by Deutsch *et al.*[13]

In the present study, 1 week after infarction, halothane appeared antiarrhythmic in three dogs, had no important effects on VT induction or refractory periods in two dogs, and was proarrhythmic in 1 dog. In dogs with an antiarrhythmic effect of halothane, ERP was increased by 23%, consistent with previous work.[12–14] Thus, it appears that an antiarrhythmic action of halothane against inducible reentrant VT is dependent on ERP prolongation, and that the inability of halothane to oppose inducible arrhythmias or even to facilitate them (proarrhythmia) correlates with no or minimal effects on ERP. It is well known that an antiarrhythmic drug effective against reentrant VT may be proarrhythmic and exacerbate reentrant VT.[44] Rinkenberger *et al.*[45] have demonstrated that drugs may facilitate initiation of VT by prolonging activation time while minimally increasing refractoriness of the reentrant circuit. These observations agree with our present data and previous findings.

The antiarrhythmic effect of halothane 24 h after infarction contrasts with the more variable effects 1 week or more after infarction. This suggests that the effects of halothane on VT after infarction appear to be quite dependent on the age of the infarction.

Ouabain-induced Ventricular Tachycardia

DADs are membrane potential oscillations that occur after completion of a preceding action potential.[22] They have been produced by toxic doses of cardiac glycosides, catecholamines, or hypercalcemia, and have been observed in infarcted tissue, atrial tissue, canine coronary sinus, and simian mitral valve tissue.[22] Cranefield[22] and, more recently, Wit and Rosen[23] summarized work by a number of investigators and concluded that Purkinje fibers exposed to ouabain develop DADs, the amplitude of which are increased by driving the fiber more rapidly. As a result, increased rate or premature impulses can bring the afterdepolarization to threshold, causing extrasystoles or a burst of triggered impulses.

The mechanism for ouabain-induced DADs involves inhibition of myocardial sodium–potassium adenosine triphosphatase by cardiac glycosides, resulting in an increased intracellular Na^+ concentration.[46] The increased intracellular Na^+ concentration subsequently enhances Na^+–Ca^{2+} exchange, elevating intracellular Ca^{2+} concentration as excess Na^+ ions are extruded.[46] As during ischemia,[31] the resultant elevation in intracellular Ca^{2+} causes DADs and triggered activity.[27,46]

Halothane increases the dose of digitalis glycosides required to produce ventricular ectopy or sudden death.[3] Reynolds *et al.*[47] in 1970 reported that, on the cellular level, halothane abolished tachyarrhythmias due to ouabain toxicity in isolated canine Purkinje fibers. Gallagher *et al.*[48] demonstrated that the reduction of ouabain-induced triggered arrhythmias may be due to a reduction

in the amplitude of DADs. Whether this relates to block of the channel responsible for DADs (*i.e.*, the transient inward current[49]) or reduction in intracellular levels of Ca^{2+}, the activator of the transient inward current,[50] has not been determined.

The present data confirm existing data indicating that halothane opposes digitalis-induced arrhythmias.[2,3,47,48] The present study extends these observations by use of a pacing protocol designed to show that halothane has inhibited ouabain induced triggered activity, evidenced by the ability of rapid trains of pacing to produce brief runs of extrasystoles (fig. 3).[15,16]

Cesium-induced Ventricular Tachycardia

Prolongation of the QT interval of the surface ECG, whether congenital or acquired, increases risk of malignant ventricular arrhythmias having a polymorphous configuration or torsades de pointes pattern.[51] Administration of cesium chloride prolongs the QT interval[17] and action potential duration[52] by blocking delayed outward K^+ currents[17] and induces complex VT, including torsades de pointes. In intact dogs, Levine *et al.*[53] recorded monophasic action potentials directly from the endocardial surface during cesium chloride administration. They identified early afterdepolarizations (EADs) that were suppressed by overdrive pacing in each dog.[53] EADs are membrane-potential oscillations distinguished from DADs by their occurrence before full repolarization from the preceding action potential.[53] The appearance of EADs related closely to the onset of ventricular arrhythmias.[53] Thus, cesium chloride may induce VT by producing EADs and triggered automaticity.[17,53]

The ionic currents responsible for EADs are not known precisely. Sensitivity of EADs to low doses of tetrodotoxin[17,53] or lidocaine,[54] which block Na^+ currents, suggested that an inward Na^+ current such as the Na^+ window current of the action potential plateau was responsible.[55] However, a recent study demonstrated a role for the L-type Ca^{2+} channel since EADs could be induced with the Ca^{2+} current agonist Bay K8644 in voltage-clamped sheep Purkinje fibers.[56] Analysis of current traces identified an inward Ca^{2+} transient present at voltages where EADs appeared and showed that nitrendipine, but not tetrodotoxin, abolished the observed current.[56] Clearly, further studies are needed to elucidate the etiology of EADs.

Although halothane blocks the inward Ca^{2+} current, fast Na^+ current, and the window Na^+ current suggested by various authors to be responsible for EADs,[35–37,57,58] halothane also blocks repolarizing outward K^+ currents[59] and prolongs the QT interval.[60,61] In the present study, the prolongation of QT interval by cesium[17] and possibly also by halothane[60,61] may have offset any potentially beneficial effects of halothane on EADs through Na^+- or Ca^{2+}-channel blockade.

Limitations

We acknowledge several study limitations that affect interpretation of results. First, hemodynamic measurements were not obtained during this study, to minimize the risk of problems inducing arrhythmias with intracardiac catheters. Since both halothane and ventricular arrhythmias can adversely affect hemodynamics, resulting hemodynamic changes could have influenced the generation of arrhythmias in the present studies. Therefore, it is not absolutely certain that electrophysiologic changes caused by halothane rather than indirect effects of halothane[62,63] or hemodynamic changes were most responsible for observations of this study. Second, since end-tidal or blood concentrations of halothane were not measured, these may not be clinically relevant. Finally, a large body of evidence supports the mechanisms for VT in each model used. However, since we did not perform the required additional electrophysiologic testing to confirm the presumed VT mechanism in each model, one must view the present findings as indirect evidence for an effect of halothane on specific mechanisms for VT.

Significance

With the use of four distinct models of VT, the present data demonstrate that the proarrhythmic or antiarrhythmic effects of halothane vary according to the presumed mechanisms causing VT. Halothane antagonized those mechanisms dependent primarily upon Ca^{2+} influx, such as abnormal automaticity[9,32] and DAD triggered activity.[22] In the particular model studied for reentrant extrasystoles, halothane had mixed effects depending on the degree of prolongation of ERP. Finally, halothane had little effect on EAD-dependent triggered automaticity. If clinically applicable, our results suggest that the effects of halothane on a given ventricular arrhythmia will vary depending upon the etiology of the arrhythmia. In humans the majority of ventricular arrhythmias are presumably reentrant in origin.[4] Halothane may be beneficial in reentrant VT but, as all other antiarrhythmic agents studied,[64] can be proarrhythmic. Avoidance of halothane when VT induction during intraoperative mapping of VT or automatic defibrillator implantation, for example, would seem prudent.

References

1. Johnston RR, Eger EI, Wilson C: A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man. Anesth Analg 55:709–712, 1976
2. Morrow DH: Anesthesia and digitalis toxicity: IV. Relationship

of digitalis tolerance to catecholamines during cyclopropane or halothane anesthesia. Anesth Analg 46:675–681, 1967
3. Reynolds AK, Horne ML: Studies on the cardiotoxicity of ouabain. Can J Physiol Pharmacol 47:165–170, 1969
4. Mason JW, Stinson EB, Winkle RA, Oyer PE: Mechanisms of ventricular tachycardia: Wide complex ignorance. Am Heart J 102: 1083–1087, 1981
5. Rosen MR, Ilevento JP, Binah O, LeMarec H: The use of matrices of pharmacological agents in the diagnosis of arrhythmogenic mechanisms. J Electrophysiol 1:30–33, 1987
6. LeMarec H, Spinelli W, Rosen MR: The effects of doxorubicin on ventricular tachycardia. Circulation 74:881–889, 1986
7. Harris AS, Rojas AG: Initiation of ventricular fibrillation due to coronary artery occlusion. Exp Med Surg 1:105–122, 1943
8. Harris AS: Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. Circulation 1:1318–1328, 1950
9. Dangman KH, Dresdner DP, Zaim S: Automatic and triggered impulse initiation in canine subepicardial ventricular muscle cells from border zones of 24-hour transmural infarcts: New mechanisms for malignant cardiac arrhythmias? Circulation 78:1020–1030, 1988
10. LeMarec H, Dangman KH, Danilo P, Rosen MR: An evaluation of automaticity and triggered activity in the canine heart one to four days after myocardial infarction. Circulation 71:1224–1236, 1985
11. Josephson ME, Horowitz LN, Farshidi A: Continuous local electrical activity. A mechanism of recurrent ventricular tachycardia. Circulation 57:659–665, 1978
12. Denniss AR, Richards DA, Taylor AT, Uther JB: Halothane anesthesia reduces inducibility of ventricular tachyarrhythmias in chronic canine myocardial infarction. Basic Res Cardiol 84:5–12, 1989
13. Deutsch N, Hantler CB, Tait AR, Uprichard A, Schork MA, Knight PR: Suppression of ventricular arrhythmias by volatile anesthetics in a canine model of chronic myocardial infarction. ANESTHESIOLOGY 72:1012–1021, 1990
14. Hunt GB, Ross DL: Comparison of effects of three anesthetic agents on induction of ventricular tachycardia in a canine model of myocardial infarction. Circulation 78:221–226, 1988
15. Malfatto G, Rosen TS, Rosen MR: The response to overdrive pacing of triggered atrial and ventricular arrhythmias in the canine heart. Circulation 77:1139–1148, 1988
16. Moak JP, Rosen MR: Induction and termination of triggered activity by pacing in isolated canine Purkinje fibers. Circulation 69:149–162, 1984
17. Brachmann J, Scherlag BJ, Rosenshtraukh LV, Lazzara R: Bradycardia-dependent triggered activity: Relevance to drug-induced multiform ventricular tachycardia. Circulation 68:846–856, 1983
18. Bazett HC: An analysis of the time-relations of electrocardiograms. Heart 7:353–370, 1920
19. Wilkinson L: SYSTAT: The System for Statistics. Evanston, Systat, 1989
20. El-Sherif N, Mehra R, Gough WB, Zeiler RH: Reentrant ventricular arrhythmias in the late myocardial infarction period: Interruption of reentrant circuits by cryothermal techniques. Circulation 68:644–656, 1983
21. El-Sherif N, Smith RA, Evans K: Canine ventricular arrhythmias in the late myocardial infarction period: 8. Epicardial mapping of reentrant circuits. Circ Res 49:255–265, 1981
22. Cranefield P: Action potentials, afterpotentials, and arrhythmias. Circ Res 41:415–423, 1977
23. Wit AL, Rosen MR: Afterdepolarizations and triggered activity, The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 1949–1490
24. Lazzara R, El-Sherif N, Scherlag BJ: Electrophysiological properties of canine Purkinje cells in one-day-old myocardial infarction. Circ Res 33:722–734, 1973
25. Dresdner KP, Kline RP, Wit AL: Intracellular K^+ activity, intracellular Na^+ activity and maximum diastolic potential of canine subendocardial Purkinje cells from one-day-old infarcts. Circ Res 60:122–132, 1987
26. Fozzard HA: Cardiac muscle excitability and passive properties. Prog Cardiovasc Dis 19:343–359, 1977
27. Levy MN: Role of calcium in arrhythmogenesis. Circulation 80: IV23–IV30, 1989
28. Elharrar V, Zipes DP: Voltage modulation of automaticity in cardiac Purkinje fibers, Slow Inward Current and Cardiac Arrhythmias. Edited by Zipes DP, Bailey JC, Elharrar V. The Hague, Martinus Nijhoff, 1980, pp 357–373
29. Kass RS, Lederer WJ, Tsien RW, Weingart R: Role of calcium in transient inward currents and aftercontractions induced by strophanthidin in cardiac Purkinje fibers. J Physiol (Lond) 281: 187–208, 1978
30. El-Sherif N, Gough WB, Zeiler RH, Mehra R: Triggered ventricular rhythm in one-day-old myocardial infarction in the dog. Circ Res 52:566–579, 1983
31. Nayler WG, Daly MJ: Calcium and the injured cardiac myocyte, Physiology and Pathophysiology of the Heart. Edited by Sperelakis N. Boston, Martinus Nijhoff, 1984, pp 477–492
32. Escande D, Coraboeuf E, Planche C: Abnormal pacemaking is modulated by sarcoplasmic reticulum in partially-depolarized myocardium from dilated right atria in humans. J Mol Cell Cardiol 19:231–241, 1987
33. Logic JR, Morrow DH, Gatz RN: Idioventricular tachycardia complicating experimental myocardial infarction. Dis Chest 56: 477–480, 1969
34. Turner LA, Bosnjak ZJ, Kampine JP: Actions of halothane on the electrical activity of Purkinje fibers derived from normal and infarcted canine hearts. ANESTHESIOLOGY 67:619–629, 1987
35. Ikemoto Y, Yatani A, Arimura H, Yoshitake J: Reduction of the slow inward current of isolated rat ventricular cells by thiamylal and halothane. Acta Anaesthesiol Scand 29:583–586, 1985
36. Eskinder H, Rusch NJ, Supan FD, Kampine JP, Bosnjak ZJ: The effects of volatile anesthetics on L- and T-type calcium channels in canine cardiac Purkinje cells. ANESTHESIOLOGY 74:919–926, 1991
37. Terrar DA, Victory JG: Effects of halothane on membrane currents associated with contraction in single myocytes isolated from guinea pig ventricle. Br J Pharmacol 94:500–508, 1988
38. Lynch C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
39. Bosnjak ZJ, Kampine JP: Effects of halothane on transmembrane potentials, Ca2+ transients, and papillary muscle tension in the cat. Am J Physiol 251:H374–H381, 1986
40. Komai H, Rusy BF: Direct effect of halothane and isoflurane on the function of the sarcoplasmic reticulum in intact rabbit atria. ANESTHESIOLOGY 72:694–698, 1990
41. Dangman KH, Hoffman BF: Studies on overdrive stimulation of canine Purkinje fibers: Maximal diastolic potential as a determinant of the response. J Am Coll Cardiol 2:1183–1190, 1983
42. Mehra R, Zeiler RH, Gough WB, El-Sherif N: Reentrant ventricular arrhythmias in the late myocardial infarction period. 9. Electrophysiologic-anatomic correlation of reentrant circuits. Circulation 67:11–24, 1983

43. Gessman LJ, Agarwal JB, Endo T, Helfant RH: Localization and mechanism of ventricular tachycardia by ice mapping 1 week after onset of myocardial infarction in dogs. Circulation 68: 657–666, 1983
44. Levine JH, Morganroth J, Kadish AH: Mechanisms and risk factors for proarrhythmia with type 1a compared with 1c antiarrhythmic drug therapy. Circulation 80:1063–1069, 1989
45. Rinkenberger RL, Prystowsky EN, Jackman WM, Naccarelli GV, Heger JJ, Zipes DP: Drug conversion of nonsustained ventricular tachycardia to sustained ventricular tachycardia during serial electrophysiologic studies: identification of drugs that exacerbate tachycardia and potential mechanisms. Am Heart J 103:177–184, 1982
46. Brody TM, Akera T: The pharmacology of the cardiac glycosides, Physiology and Pathophysiology of the Heart. Edited by Sperelakis N. Boston, Martinus Nijhoff, 1984, pp 405–419
47. Reynolds AK, Chiz JF, Pasquet AF: Halothane and methoxyflurane: A comparison of their effects on cardiac pacemaker fibers. ANESTHESIOLOGY 33:602–610, 1970
48. Gallagher JD, Bianchi JJ, Gessman LJ: Halothane antagonizes digitalis toxicity in canine Purkinje fibers. ANESTHESIOLOGY 71: 695–703, 1989
49. Lederer WJ, Tsien RW: Transient inward current underlying strophanthidin's enhancement of pacemaker activity in Purkinje fibers. J Physiol (Lond) 249:40P–41P, 1975
50. Tsien RW, Kass RS, Weingart R: Calcium ions and membrane current changes induced by digitalis in canine Purkinje fibers. Ann NY Acad Sci 307:483–490, 1978
51. Moss AJ: Prolonged QT-interval syndromes. JAMA 256:2985–2987, 1986
52. Damiano BP, Rosen MR: Effects of pacing on triggered activity induced by early afterdepolarizations. Circulation 69:1013–1025, 1984
53. Levine JH, Spear JF, Guarnieri T, Weisfeldt ML, deLangen CDJ, Becker LC, Moore EN: Cesium chloride-induced long QT syndrome: Demonstration of afterdepolarizations and triggered activity in vivo. Circulation 72:1092–1103, 1985
54. El-Sherif N, Zeiler RH, Craelius W, Gough WB, Henkin R: QTU prolongation and polymorphic ventricular tachyarrhythmias due to bradycardia-dependent early afterdepolarizations. Circ Res 63:286–305, 1988
55. Coulombe A, Coraboeuf E, Malecot C, Deroubaix E: Role of the "Na window" current and other ionic currents in triggering early after-depolarizations and resulting re-excitations in Purkinje fibers, Cardiac Electrophysiology and Arrhythmias. Edited by Zipes DP, Jalife J. Orlando, Grune & Stratton, 1985, pp 43–49
56. January CT, Riddle JM: Early afterdepolarizations: Mechanism of induction and block. Circ Res 64:977–990, 1989
57. Ikemoto Y, Yatani A, Imoto Y, Arimura H: Reduction in the myocardial sodium current by halothane and thiamylal. Jpn J Physiol 36:107–121, 1986
58. Turner LA, Marijic J, Kampine JP, Bosnjak ZJ: A comparison of the effects of halothane and tetrodotoxin on the regional repolarization characteristics of canine Purkinje fibers. ANESTHESIOLOGY 73:1158–1168, 1990
59. Hirota K, Momose Y, Takeda R, Nakanishi S, Ito Y: Prolongation of the action potential and reduction of the delayed outward K+ current by halothane in single frog atrial cells. Eur J Pharmacol 126:293–295, 1986
60. Riley DC, Schmeling WT, Al-Wathiqui MH, Kampine JP, Warltier DC: Prolongation of the QT interval by volatile anesthetics in chronically instrumented dogs. Anesth Analg 67:741–749, 1988
61. Schmeling WT, Warltier DC, McDonald DJ, Madsen KE, Atlee JL, Kampine JP: Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. Anesth Analg 72:137–144, 1991
62. Kono K, Philbin D, Coggins CH, Moss J, Rosow CE, Schneider RC, Slater EE: Renal function and stress response during halothane or fentanyl anesthesia. Anesth Analg 60:552–556, 1981
63. Seagard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP: Halothane and the carotid sinus reflex: Evidence for multiple sites of action. ANESTHESIOLOGY 57:191–202, 1982
64. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB: Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 65:886–894, 1982