Anesthesiology
73:1158–1168, 1990

A Comparison of the Effects of Halothane and Tetrodotoxin on the Regional Repolarization Characteristics of Canine Purkinje Fibers

Lawrence A. Turner, M.D., Jure Marijic, M.D.,† John P. Kampine, M.D., Ph.D.,‡ Zeljko J. Bosnjak, Ph.D.§*

The effects of halothane, tetrodotoxin (TTX), veratridine (VTD), and alterations of extracellular calcium ion concentration ($[Ca^{++}]_o$) on regional differences of canine Purkinje fiber action potential duration (APD_{50} and APD_{90}) were investigated *in vitro* at a paced rate of 75 beats per min. Under control conditions (n = 15 hearts) APD_{90} of proximal (false tendon) fibers (289 ± 6 ms) always exceeded ($P \leq 0.01$) that of distal (apical) fibers (213 ± 4 ms). Halothane (0.35–1.07 mM) reduced regional differences of APD_{90} by producing dose-dependent decreases of proximal APD_{90} without decreases of distal APD_{90}. The regional actions of halothane were similar to those of low (0.33–1.0 μM) concentrations of the Na^+ channel antagonist TTX, which also decreased proximal APD_{90} more than distal APD_{90}. The actions of halothane in combination with TTX further decreased proximal APD_{90}, whereas the Na^+ channel agonist VTD, which increased proximal APD_{90} more than distal APD_{90}, reversed the regional actions of halothane. Decreasing Ca^{++} influx by reducing $[Ca^{++}]_o$ from 1.8 to 0.6 mM increased proximal APD_{90} more than distal APD_{90} in a manner opposite to the regional actions of halothane. Although there was no difference between the values of APD_{90} obtained for each region in the presence of halothane at 0.6, 1.8, and 3.6 mM $[Ca^{++}]_o$, the action of halothane decreasing APD_{90} of proximal fibers was more prominent at 0.6 mM $[Ca^{++}]_o$ because of the increased APD_{90} of fibers under this condition. The findings are consistent with, but do not definitively prove, the hypothesis that halothane may decrease APD_{90} of proximal Purkinje fibers by a mechanism similar to that of TTX involving inhibition of plateau-phase inward Na^+ current. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmias. Purkinje fibers: tetrodotoxin; veratridine. Ions: calcium; sodium.)

HALOTHANE alters Purkinje fiber action potentials by increasing the slope of the plateau phase and decreasing its duration.[1] These actions may produce either no change[1,2] or a decrease[3,4] of action potential duration (APD) measured at 90% repolarization (APD_{90}). A possible explanation for these different responses was suggested by the finding that halothane decreases APD_{90} of fibers located in a region of longer control duration (the false tendon–papillary muscle junction, referred to as proximal fibers) without decreasing APD_{90} of fibers located in a region of shorter duration (the apex, referred to as distal fibers).[4] However, the electrophysiologic basis for regional differences in the actions of halothane on Purkinje fiber APD_{90} is not known.

The transmembrane ionic mechanisms underlying generation of the cardiac action potential are exceedingly complex[5,6] but may be oversimplified to include a sequence of depolarizing inward Na^+ and Ca^{++} ion fluxes, the latter associated with triggering of the intracellular Ca^{++} transient derived largely from sarcoplasmic reticulum Ca^{++} stores, followed by remission of inward currents and the onset of repolarizing outward K^+ efflux. Halothane may affect each of these major ionic mechanisms and intracellular processes associated with excitation-contraction coupling. Halothane has been reported to inhibit the slow inward current (I_{si}) and outward K^+ currents (I_K) in atrial myocytes,[7] as well as I_{si}, I_K, and inward Na^+ current (I_{Na}) in ventricular myocytes.[8–11] The actions of halothane depressing I_{si}[8] and specific Ca^{++} channel current (I_{Ca}) in ventricular muscle fibers[12] have been linked to inhibition of the intracellular Ca^{++} transient and the negative inotropic effects of halothane.[8,13] However little is known about the possible influence of depression of inward Na^+ and Ca^{++} ion fluxes by halothane on the Purkinje fiber action potential.

Coraboeuf *et al.*[14] first reported that the basis for regional differences of Purkinje fiber APD involves a relatively increased contribution of I_{Na} to the generation of the prolonged plateau of fibers exhibiting longer APD. These authors demonstrated that very low concentrations of the Na^+ channel blocker tetrodotoxin (TTX) produced a greater decrease of APD in false tendon (proximal) fibers than in fibers from other endocardial regions. It was suggested[4] that halothane may also decrease proximal Purkinje fiber APD_{90} by inhibition of plateau phase I_{Na}, based on its actions inhibiting both I_{Na} and I_{si} in ventricular myocytes[9,10] and the similarity of its effects on proximal and distal fibers to those reported for TTX and lidocaine.[15] On the other hand, the actions of halothane depressing the plateau and decreasing APD of ventricular muscle fibers has been attributed to inhibition of I_{si}.[8] Al-

* Assistant Professor of Anesthesiology.

† Research Associate.

‡ Professor and Chairman of Anesthesiology, Professor of Physiology.

§ Professor of Anesthesiology and Physiology.

Received from the Department of Anesthesiology, The Medical College of Wisconsin, Milwaukee. Accepted for publication July 3, 1990. Supported in part by NIH grants HL01901 and HL39776 (Z.J.B.), Anesthesiology Research Training Grant GM 08377, and by the Veterans Administration Medical Center, Milwaukee, Wisconsin. Presented in part at the 9th World Congress of Anaesthesiologists, Washington, D.C., 1988.

Address reprint requests to Dr. Turner: Medical College of Wisconsin, MFRC, Room A1000, 8701 West Watertown Plank Road, Milwaukee, Wisconsin 53226.

though halothane also inhibits I_{Ca} in Purkinje fibers,[12] an action making the plateau more negative, inhibition of I_{si} by halothane may not decrease APD_{90} for several reasons. First, reduction of extracellular Ca^{++} ion concentration ($[Ca^{++}]_0$), which reduces I_{si}, Ca^{++} influx, and intracellular Ca^{++} ion activity,[16] usually prolongs APD by decreasing outward K^+ current.[17] Second, the shortening of APD_{90} produced by halothane in ventricular myocytes is accompanied by inhibition of I_K, which tends to offset the decrease of plateau duration produced by reduction of I_{si}.[11] A relatively greater effect of inhibition of I_K, tending to increase APD, than reduction of I_{si}, depressing the plateau, may be responsible for the increase of APD_{90} produced by halothane in atrial tissues.[3,7] Therefore, although halothane inhibits I_{Ca} and I_K in ventricular tissues, it is possible that an additional effect on plateau phase I_{Na} may contribute to its actions decreasing Purkinje fiber APD.

The current study was designed to examine the relationship between the effects of halothane and those of interventions designed to alter I_{Na} and I_{si} on regional differences of Purkinje fiber APD_{90}. The hypothesis tested was that the effects of halothane on regional differences of Purkinje fiber APD_{90} are more similar to those of an agent that reduces Na^+ influx, such as TTX, than to those of an intervention that reduces Ca^{++} influx, like decreasing $[Ca^{++}]_0$.[16] The interactions between halothane, TTX, and veratridine (VTD), a Na^+ channel agonist,[18] were studied to assess the role of changes in Na^+ influx. In addition, the regional effects of small changes of $[Ca^{++}]_0$ and the actions of halothane at altered $[Ca^{++}]_0$ were determined to evaluate the influence of changes in Ca^{++} influx.

Materials and Methods

This study was reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. Adult mongrel dogs were anesthetized with halothane in oxygen and their hearts were removed. The left ventricle was dissected to yield two small (5 × 6 mm) endocardial preparations from specific regions of the conduction system (see below). These were mounted in a single low-volume, high-flow chamber (1.0 ml vol, 3 ml/min flow, approximately a 20-s time constant) incorporating a slide valve for rapid switching of the superfusate. The tissues were superfused at 37° C with Tyrode's solution equilibrated with 97% O_2/3% CO_2 (*p*H 7.4–7.45). This solution contained the following (mM): NaCl 137, KCl 4.0, $CaCl_2$ 1.8, $MgCl_2$ 0.5, NaH_2PO_4 0.9, $NaHCO_3$ 18, and dextrose 5.5. Each preparation was stimulated at a constant rate of 75 beats per min, with the use of bipolar endocardial surface electrodes for an initial equilibration period of 1–2 h after isolation. Halothane was introduced by switching to perfusate preequilibrated with the agent with the use of a calibrated vaporizer. Action potential changes stabilized within 5–8 min, and the halothane concentration obtained after 10 min was determined by direct sampling and measurement by gas chromotography. Under the conditions of these experiments, equilibration of the superfusate with halothane at vaporizer settings ranging from 1 to 3 vol% yielded tissue chamber concentrations of halothane ranging from 0.3 to 1.1 mM. TTX and VTD (Sigma, St. Louis, MO) were prepared as stock solutions (1 mg/ml) and were added to measured volumes to achieve the desired concentrations. Low- (0.6 mM) and high- (3.6 mM) calcium Tyrode's solutions were prepared without compensation for changes in ionic strength. In preliminary studies, the effects of halothane and TTX on APD stabilized within 5–8 min, whereas exposure to VDT or changing $[Ca^{++}]_0$ required 30 min for stabilization.

Action potentials were obtained under each condition from subendocardial Purkinje's fibers located at the same two specific sites previously designated[4] as proximal fibers, located at the false tendon–anterior papillary muscle junction, and distal fibers, located over the apical endocardium. Fibers from these regions are well known to exhibit characteristic differences of APD.[19] The action potentials were recorded with standard microelectrode techniques, sampled at a rate of 2 kHz, and analyzed by use of a Hewlett Packard (Sunnyvale, CA) 9000/S300® computer. The values measured for each action potential included the maximum diastolic potential (MDP), overshoot (OS), amplitude (Amp), and APD measured at 50% and 90% of complete repolarization. The rate of phase 0 depolarization (V_{max}) was determined with a differentiator exhibiting a linear response from 100–1,000 V/s and a sample and hold amplifier.

The action potential characteristics of proximal and distal Purkinje's fibers were compared in three experimental groups (n = 5 hearts each group) to determine the dose-dependent effects of halothane, TTX, and VTD. A multifiber technique was used to develop average values for each measured characteristic for each region by pooling the values obtained from five proximal fiber impalements and five distal fiber impalements under each condition. Following control measurements, the preparations were exposed to successively higher drug concentrations and a final control was obtained after washout. The values obtained, summarized by the mean ± standard error of the mean (SEM) in the tables, were evaluated by analysis of variance (ANOVA) and compared with the use of the least significant difference (LSD) procedure.[20]

The interactions between halothane and TTX or VTD were studied in two other experiments (n = 8 hearts each group) using continuous impalements of fibers in both regions maintained throughout all interventions. For each experiment the drug (TTX or VTD) was added to a vol-

ume of preequilibrated halothane–Tyrode's solution and the vaporizer stream was split to assure equal halothane concentrations in the anesthetic and anesthetic-plus-drug solution. The values obtained under different conditions were evaluated by ANOVA and the LSD procedure. The actions of halothane on fibers at 0.6, 1.8, and 3.6 mM $[Ca^{++}]_0$ were evaluated in a additional experiment (n = 5 hearts). Small amounts of concentrated $CaCl_2$ were added to volumes derived from control and halothane-equilibrated calcium-free Tyrode's solution to achieve the desired $[Ca^{++}]_0$ and equal anesthetic concentrations at each level. Changes in the action potential characteristics on altering $[Ca^{++}]_0$ and adding halothane were compared by paired and unpaired *t* tests. A probability value (*P*) less than 0.05 was considered statistically significant.

Results

Changes in the action potentials of single proximal (false tendon) and distal (apical) Purkinje fibers recorded continuously during the specific interventions are shown at the top of each figure, and the mean values of APD_{90} are additionally shown as bar graphs at the bottom of each figure, as in figure 1. Qualitatively, the regional effects of halothane, illustrated to the left in figure 1, were characterized by a greater decrease of APD in the proximal fiber, which exhibited intrinsically longer control duration, than in the distal fiber, which exhibited relatively short control duration. This regional action of halothane was analogous to that of the Na^+ channel antagonist TTX, shown to the right in figure 1, which also decreased proximal fiber APD more than distal fiber APD. The dose-dependent effects of halothane, TTX, and VTD are summarized in table 1, which represents the mean values for each action potential characteristic based on the pooled values obtained by the multiple fiber technique in three groups of five hearts. Comparison of the pooled action potential characteristics obtained under control conditions from 15 hearts indicated that proximal fibers exhibited slightly greater ($P \leq 0.01$) MDP (−87.6 ± 0.7 *vs.* −84.2 ± 0.9 mV), Amp (122.4 ± 0.9 *vs.* 118.7 ± 1.0 mV), and V_{max} (622 ± 26 *vs.* 509 ± 27 V/s) than distal fibers, as well as substantially prolonged APD_{90} (proximal: 289 ± 6 *vs.* distal: 213 ± 4 ms, $P \leq 0.01$).

The effects of 0.65 and 1.07 mM halothane on proximal APD measured at 50% repolarization (APD_{50}) and APD_{90} (table 1) were greater than those of 0.35 mM halothane, indicating that its effects on the plateau and terminal repolarization of proximal fibers were dose dependent. There was also a decrease in distal APD_{50} at the highest halothane dose, whereas APD_{90} of fibers in this region did not change significantly. The decreases of APD_{50} and APD_{90} were greater ($P \leq 0.01$) in proximal than distal fibers at each halothane concentration such that the intermediate and highest concentrations abolished the differences of APD_{90} between the two regions. In the presence of 1.07 mM halothane, proximal APD_{50} was reduced to less than distal APD_{50}. There were also slight decreases in the MDP, OS, and Amp at higher concentrations, which were not consistent between the fibers from the two regions, and there was no change in V_{max}.

Tetrodotoxin produced dose-dependent decreases in

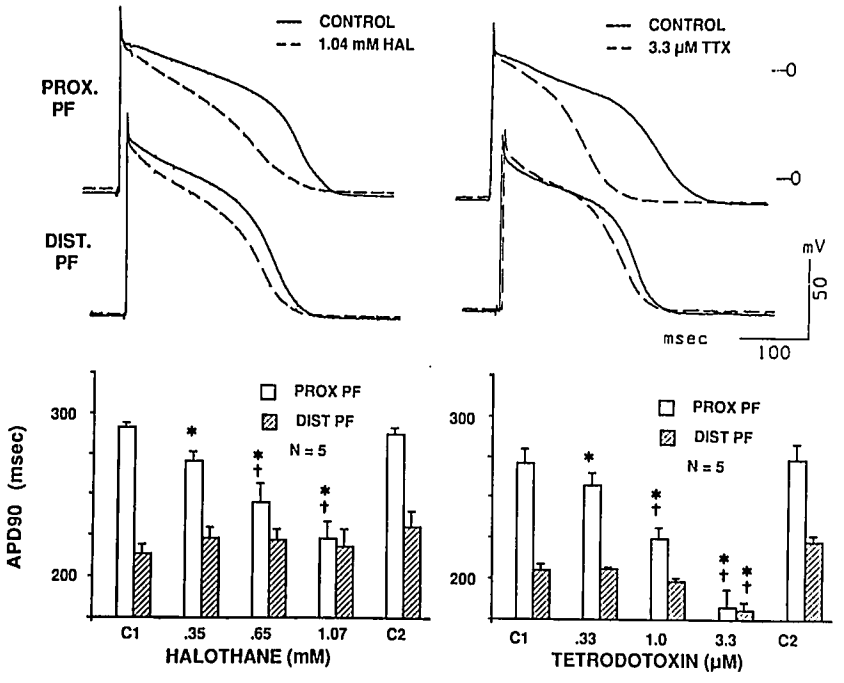

FIG. 1. Effects of halothane (HAL) and tetrodotoxin (TTX) on continuously recorded proximal and distal Purkinje fiber action potentials (tracings, *top*) and mean values of APD_{90} (bar graphs, *bottom*) found in two groups of five hearts during the sequence of interventions shown from left to right along the x-axis. Both halothane and TTX decreased proximal APD_{90} more than distal APD_{90}. C1, C2 = initial and final control. *$P < 0.05$ *versus* C1; †$P < 0.05$ *versus* lowest dose (ANOVA, LSD).

TABLE 1. Dose-dependent Actions of Halothane, Tetrodotoxin, and Veratridine on Proximal and Distal Purkinje Fibers

	Action Potential Characteristics					
	MDP (mV)	OS (mV)	Amp (mV)	V_{max} (V/s)	APD_{50} (ms)	APD_{90} (ms)
Halothane						
Proximal PF						
Control 1	−88.8 ± 0.7	35.4 ± 1.1	124.2 ± 1.0	649 ± 39	233 ± 3	291 ± 3
0.35 ± 0.04 mM H	−86.9 ± 1.0*	34.7 ± 0.9	121.5 ± 1.2	623 ± 42	196 ± 3**	271 ± 6*
0.65 ± 0.04 mM H	−86.2 ± 1.4**	33.2 ± 1.2	119.4 ± 1.8**	680 ± 32	153 ± 8**,††	246 ± 11**,††
1.07 ± 0.1 mM H	−84.5 ± 0.8**,†	31.8 ± 2.8	116.3 ± 3.2**,††	620 ± 52	113 ± 7**,††	223 ± 11**,††
Control 2	−87.3 ± 0.5	36.1 ± 0.7	123.3 ± 0.6	647 ± 35	221 ± 4	288 ± 4
Distal PF						
Control 1	−84.4 ± 1.3	34.9 ± 1.6	119.3 ± 1.5	528 ± 40	160 ± 5	214 ± 6
0.35 ± 0.04 mM H	−84.8 ± 1.5	33.2 ± 1.3	118.0 ± 1.8	510 ± 33	164 ± 7	223 ± 7
0.65 ± 0.04 mM H	−83.7 ± 1.3	32.0 ± 1.7*	115.7 ± 2.5	484 ± 46	155 ± 9	222 ± 7
1.07 ± 0.1 mM H	−83.5 ± 1.3	31.0 ± 1.7**	114.5 ± 2.7	467 ± 45	145 ± 7*,††	219 ± 10
Control 2	−84.2 ± 1.7	32.8 ± 1.9	117.0 ± 2.9	502 ± 39	174 ± 10*	231 ± 10
Tetrodotoxin						
Proximal PF						
Control 1	−85.9 ± 0.6	37.5 ± 1.1	123.4 ± 1.5	640 ± 59	207 ± 10	271 ± 9
0.33 μM TTX	−87.5 ± 1.0	36.3 ± 1.2	123.8 ± 1.8	649 ± 59	196 ± 9	257 ± 8*
1.0 μM TTX	−87.6 ± 0.9	36.2 ± 1.3	123.8 ± 1.6	631 ± 47	161 ± 8**,††	224 ± 7**,††
3.3 μM TTX	−86.6 ± 1.3	32.4 ± 1.4**,††	119.0 ± 2.3	500 ± 49**,††	113 ± 9**,††	183 ± 10**,††
Control 2	−87.7 ± 0.9	35.2 ± 0.6	122.9 ± 0.5	564 ± 38	209 ± 9	273 ± 9
Distal PF						
Control 1	−82.2 ± 1.8	35.4 ± 1.4	117.8 ± 2.5	521 ± 68	150 ± 6	205 ± 4
0.33 μM TTX	−83.0 ± 1.3	36.3 ± 1.5	119.3 ± 2.0	524 ± 52	148 ± 3	206 ± 1
1.0 μM TTX	−83.8 ± 1.7	33.8 ± 1.6†	117.7 ± 2.1	444 ± 52	138 ± 7	198 ± 2
3.3 μM TTX	−82.1 ± 1.1	31.1 ± 1.9*,††	113.1 ± 2.6	429 ± 53	111 ± 11**,††	181 ± 5**,††
Control 2	−82.9 ± 1.3	34.8 ± 1.7	117.7 ± 2.1	446 ± 56	163 ± 4	222 ± 4*
Veratridine						
Proximal PF						
Control 1	−88.1 ± 1.8	31.5 ± 1.7	119.7 ± 1.5	579 ± 38	243 ± 17	303 ± 14
10 nM VTD	−89.6 ± 0.7	32.3 ± 2.3	121.9 ± 1.9	569 ± 46	253 ± 18	321 ± 19
30 nM VTD	−87.9 ± 1.4	32.3 ± 0.8	120.2 ± 1.0	509 ± 45	278 ± 28*	369 ± 29**,††
60 nM VTD	−87.2 ± 1.5	34.4 ± 0.9	121.7 ± 1.6	546 ± 57	316 ± 36**,††	436 ± 35**,††
Control 2	−87.1 ± 1.1	33.9 ± 1.1	121.0 ± 1.1	549 ± 68	246 ± 19	315 ± 16
Distal PF						
Control 1	−86.1 ± 1.0	32.9 ± 0.8	119.0 ± 1.1	480 ± 32	170 ± 10	220 ± 11
10 nM VTD	−85.8 ± 1.1	33.0 ± 1.4	118.8 ± 2.2	459 ± 37	179 ± 10	237 ± 12
30 nM VTD	−85.8 ± 1.3	31.9 ± 1.8	117.8 ± 2.8	426 ± 48	191 ± 13**	264 ± 18**,†
60 nM VTD	−85.6 ± 0.9	33.4 ± 1.3	119.0 ± 1.4	476 ± 32	214 ± 18**,††	310 ± 26**,††
Control 2	−84.5 ± 0.8	33.9 ± 2.2	118.8 ± 2.8	462 ± 39	190 ± 9*	247 ± 10*

MDP = maximum diastolic potential; OS = overshoot; Amp = amplitude; V_{max} = maximum rate of phase-0 depolarization; APD_{50}, APD_{90} = action potential duration at 50 and 90% repolarization. H = halothane; TTX = tetrodotoxin; VTD = veratridine; PF = Purkinje fibers.

All values represent means ± SEM for five hearts of pooled values from five fibers of each type under each condition.

* $P \leq 0.05$, ** $P \leq 0.01$ compared to control 1 (ANOVA, LSD).

† $P \leq 0.05$, †† $P \leq 0.01$ compared to lowest concentration (ANOVA, LSD).

APD_{50} and APD_{90} of fibers in both regions (fig. 1, table 1). Similar to the effect of halothane, the decreases of APD_{50} and APD_{90} resulting from TTX were greater ($P \leq 0.05$) in proximal than distal fibers and the difference between APD_{90} of fibers in the two regions was abolished by exposure to 1.0 and 3.3 μM TTX. At the highest concentration, 3.3 μM TTX decreased distal APD_{90}, unlike halothane, whereas the OS decreased in both regions and the proximal fibers exhibited a moderate reduction of V_{max}. For the similar degrees of proximal fiber APD_{90} shortening produced by 0.65 mM halothane (a reduction to 85% of control, approximately 291–246 ms) and by 1 μM TTX (to 83% of control, approximately 271–224 ms), halothane tended to produce greater reduction of APD_{50} (to 66% of control, approximately 233–153 ms) than TTX (to 78% of control, approximately 207–161 ms). However, a similar tendency cannot be identified in the distal fiber responses because of time-dependent changes.

The single-fiber recordings at the top of figure 2 illustrate the antagonism between the regional effects of TTX and VDT on Purkinje's fiber APD. In this preparation, 1.0 μM TTX decreased proximal APD more than distal APD, whereas exposure to 60 nM VTD in the continuing presence of TTX reversed the actions of TTX. The dose-

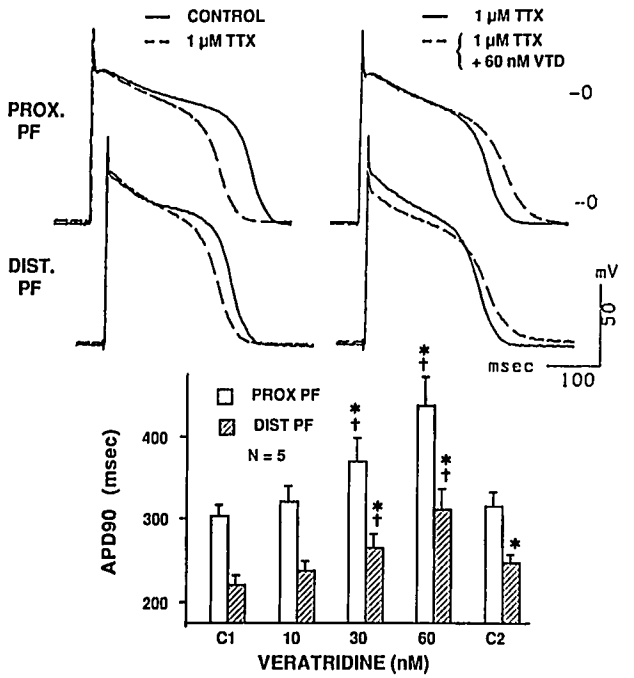

FIG. 2. Antagonism between the regional actions of tetrodotoxin (TTX) and veratridine (VTD) on Purkinje fiber action potentials (upper tracings) and dose-dependent effects of veratridine on APD_{90} (bar graph). *$P < 0.05$ *versus* C1; †$P < 0.05$ *versus* lowest dose (ANOVA, LSD).

dependent effects of VDT (graph fig. 2, table 1) were characterized by greater prolongation of proximal APD_{90} than distal APD_{90}. At higher concentrations (30 and 60 nM), VTD increased APD_{90} in both regions.

The similarity between the regional actions of halothane and TTX suggested that they may have additive regional effects on APD_{90}, whereas the antagonism between the regional actions of VTD and TTX suggested that the Na^+ channel agonist may reverse the actions of halothane in this preparation. The interactions between these agents were therefore studied in additional experiments using continuous impalements of proximal and distal fibers maintained throughout all interventions.

In preliminary studies it was found that 5–10 μM TTX produced a loss of excitability, whereas exposure to high halothane levels (≥0.5 mM) in addition to TTX (≥3.3 μM) often resulted in complete loss of excitability. Therefore, we examined the interaction between approximately 0.5 mM halothane and 2 μM TTX, a concentration reported to produce about one half maximal shortening of Purkinje fiber APD.[21] As shown at the top of figure 3, the responses of single fibers suggested that halothane may produce slightly less shortening of proximal APD in the presence of TTX than in its absence, whereas the distal fiber remained relatively insensitive to halothane under either condition. Quantitatively (table 2), halothane decreased proximal APD_{50} and APD_{90} both in the absence and presence of TTX. Although there was a tendency for the decreases of proximal APD_{50} and APD_{90} to be less ($0.1 \geq P \geq 0.05$) in the presence of TTX than its absence, these differences were not significant by ANOVA and the LSD procedure. In combination, the relatively greater effects of both agents on proximal APD_{90} tended to reverse the control relationship (proximal greater than distal) between the APD_{90} values in the two regions. However, proximal APD_{90} in the presence of both halothane and TTX (191 ± 7 ms) was not significantly shorter ($0.1 \geq P \geq 0.05$) than distal APD_{90} (208 ± 7 ms). V_{max} did not decrease in either region with addition of halothane to TTX.

The actions of VTD on single fibers exposed to halothane are shown in figure 4. The decrease of proximal APD_{90} produced by halothane was readily reversed by simultaneous exposure to 30 nM VTD. For the group (table 2), the initial exposure to 0.58 mM halothane decreased proximal APD_{90} by 39 ± 5 ms, whereas the addition of 30 nM VTD in the continued presence of 0.60 mM halothane increased proximal APD_{90} by 42 ± 5 ms.

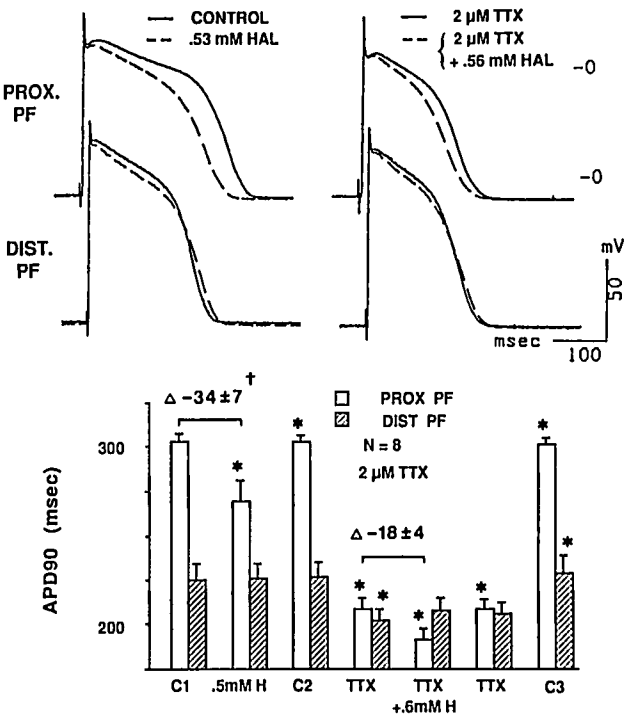

FIG. 3. Effects of halothane on proximal and distal Purkinje fiber action potentials in the absence (*left tracings*) and presence (*right tracings*) of 2 μM TTX. Bar graph: mean values of APD_{90} found during the sequence of interventions shown along the x-axis. C1, C2, C3 = controls. The paired changes (Δ) of proximal APD_{90} due to halothane are given in ms ± SEM above the brackets. *$P < 0.05$ *versus* preceding condition (ANOVA, LSD); †$P < 0.05$ *versus* change due to halothane in the presence of TTX (paired *t* test).

TABLE 2. Interaction Between Halothane, Tetrodotoxin, and Veratridine on Proximal and Distal Purkinje Fibers

	Action Potential Characteristics					
	MDP (mV)	OS (mV)	Amp (mV)	V_{max} (V/s)	APD_{50} (ms)	APD_{90} (ms)
H and 2 μM TTX						
Proximal PF						
Control 1	−89.6 ± 0.9	34.9 ± 2.1	124.5 ± 1.9	574 ± 32	250 ± 4	303 ± 5
0.52 ± 0.07 mM H	−88.7 ± 0.9	35.8 ± 1.8	124.6 ± 1.4	596 ± 41	202 ± 5**††	270 ± 11**††
Control 2	−89.0 ± 0.7	36.1 ± 1.2	125.1 ± 0.8	579 ± 33	250 ± 4**	303 ± 4**
TTX	−89.1 ± 0.8	33.3 ± 1.6	122.5 ± 1.3	526 ± 36**†	145 ± 6**††	209 ± 6**††
TTX + 0.57 ± 0.09 mM H	−88.1 ± 0.8	32.5 ± 1.7	120.6 ± 1.6	498 ± 39††	114 ± 8**††	191 ± 7**††
TTX	−89.4 ± 0.5	33.5 ± 2.4	123.0 ± 2.2	511 ± 45††	145 ± 5**††	209 ± 5**††
Control 3	−89.4 ± 0.6	34.3 ± 1.6	123.8 ± 1.5	563 ± 46**	247 ± 5**	301 ± 4**
Distal PF						
Control 1	−88.8 ± 0.8	35.2 ± 1.3	124.0 ± 1.9	457 ± 21	178 ± 8	225 ± 9
0.52 ± 0.07 mM H	−89.1 ± 0.6	33.7 ± 1.4	122.8 ± 1.4	438 ± 33	172 ± 9	226 ± 8
Control 2	−89.1 ± 0.8	35.6 ± 1.1	124.7 ± 1.1	450 ± 40	179 ± 9	227 ± 8
TTX	−88.9 ± 1.1	31.3 ± 1.8**††	120.2 ± 2.0*†	373 ± 29**††	144 ± 6**††	202 ± 7**††
TTX + 0.57 ± 0.09 mM H	−86.7 ± 2.0	31.7 ± 1.8†	118.4 ± 2.7††	354 ± 28††	140 ± 6††	208 ± 7††
TTX	−87.5 ± 1.5	32.3 ± 1.5†	119.8 ± 2.3†	371 ± 30††	142 ± 8††	206 ± 6††
Control 3	−89.2 ± 0.9	33.3 ± 1.3	122.6 ± 1.2	445 ± 40**	181 ± 10**	229 ± 10**
H and 30 nM VTD						
Proximal PF						
Control 1	−88.9 ± 0.8	35.9 ± 1.7	125.8 ± 1.3	623 ± 35	255 ± 12	312 ± 12
0.58 ± 0.06 mM H	−88.7 ± 0.9	34.7 ± 1.1	123.5 ± 1.5	602 ± 39	195 ± 9**††	273 ± 9**††
0.60 ± 0.07 mM H + VTD	−88.9 ± 1.1	31.8 ± 1.2	120.7 ± 1.5††	557 ± 53†	214 ± 11**††	315 ± 11**
0.67 ± 0.07 mM H	−88.3 ± 1.3	33.8 ± 1.0	122.2 ± 1.8	559 ± 46†	184 ± 10**††	268 ± 11**††
Control 2	−88.1 ± 0.6	32.4 ± 1.6	120.5 ± 1.7††	547 ± 43††	251 ± 9**	315 ± 9**
Distal PF						
Control 1	−89.9 ± 0.9	36.1 ± 2.0	126.1 ± 1.3	452 ± 49	181 ± 7	235 ± 8
0.58 ± 0.06 mM H	−89.7 ± 1.2	34.3 ± 2.0	124.0 ± 1.2	407 ± 51*†	170 ± 6	235 ± 5
0.60 ± 0.07 mM H + VTD	−89.1 ± 0.9	33.0 ± 2.2†	122.1 ± 1.7††	380 ± 48††	183 ± 6*	260 ± 7**††
0.67 ± 0.07 mM H	−89.5 ± 1.2	32.5 ± 2.4††	122.0 ± 2.0††	380 ± 47††	174 ± 6	244 ± 5**
Control 2	−89.9 ± 0.9	33.8 ± 2.8	123.7 ± 2.2	385 ± 47††	196 ± 8**†	255 ± 7*††

Abbreviations as in Table 1.

All values represent means ± SEM for eight fibers of each type, continuously impaled throughout all interventions.

* $P \leq 0.05$, ** $P \leq 0.01$ compared to preceding value (ANOVA, LSD).

† $P \leq 0.05$, †† $P \leq 0.01$ compared to control 1 (ANOVA, LSD).

However, although 30 nM VTD reversed the decrease of proximal APD_{90} produced by halothane, the actions of halothane decreasing APD_{50} (to 76% of control, approximately 255–195 ms) were not fully reversed by VTD in the presence of halothane (return to 84% of control, approximately 214 *vs.* 255 ms). In addition, although 0.58 mM halothane alone did not decrease distal APD_{90}, 30 nM VTD in the presence of halothane increased APD_{90} of distal fibers. Despite the latter change, the actions of VTD in the presence of halothane tended to restore the regional differences of APD_{90} present under control conditions.

The influence of changes of Ca^{++} ion influx on regional action potential differences was evaluated by alteration of extracellular Ca^{++} ion concentration. Fibers were initially impaled in control Tyrode's solution (C1, table 3), with subsequent trials of halothane beginning at 0.6 mM $[Ca^{++}]_0$. The initial change to 0.6 mM $[Ca^{++}]_0$ was accompanied by loss of OS, Amp, and V_{max} in both regions, as well as prolongation of APD_{90}, which was greater in proximal than distal fibers. At 0.6 mM $[Ca^{++}]_0$, the addition of halothane resulted in loss of excitability in three of five preparations, and it was necessary to return to 1.8 mM $[Ca^{++}]_0$ without halothane to obtain new impalements. Comparison (unpaired *t* test) of APD_{90} at the three levels of $[Ca^{++}]_0$ before each anesthetic trial indicated that proximal APD_{90} was longer at 0.6 mM $[Ca^{++}]_0$ than at either 1.8 or 3.6 mM $[Ca^{++}]_0$, whereas the durations for distal fibers did not differ significantly. Thus, increasing $[Ca^{++}]_0$ tended to reduce, or, conversely, decreasing $[Ca^{++}]_0$ tended to accentuate, regional differences of APD largely by producing reciprocal changes of proximal APD_{90}.

The actions of halothane as a function of $[Ca^{++}]_0$ are illustrated by single-fiber recordings in figure 5. Qualitatively, the decreases of proximal APD resulting from halothane were similar at 1.8 mM (center) and 3.6 mM $[Ca^{++}]_0$ (right) but were accentuated at 0.6 mM $[Ca^{++}]_0$ (left tracings) in association with the greater control APD of the fibers in low Ca^{++} solution. Quantitatively (table 3), approximately 0.9 mM halothane decreased APD_{50} and APD_{90} of proximal as well as distal fibers (n = 5,

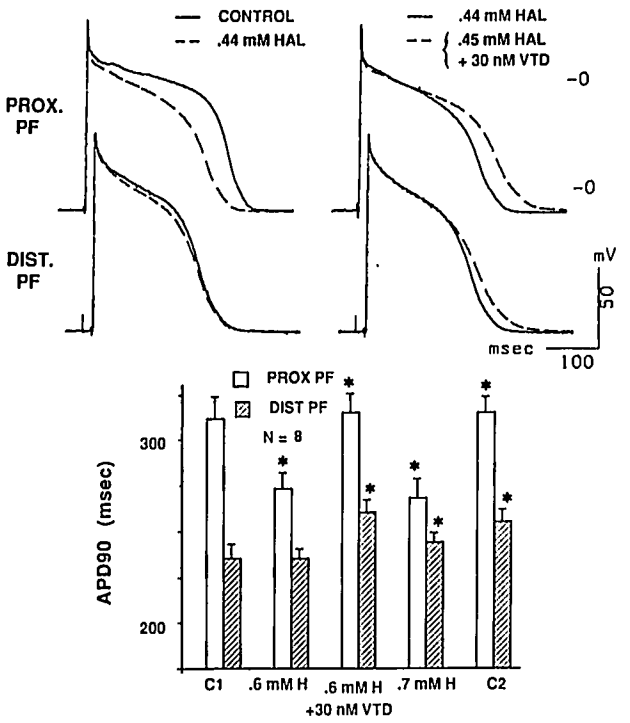

FIG. 4. Antagonism by veratidine (*right tracings*) of the regional actions of halothane (*left tracings*) on proximal and distal Purkinje fiber action potentials. Bar graph: mean values of APD_{90} found during the sequence of interventions shown along the x-axis. C1, C2 = controls. $*P < 0.05$ *versus* preceding condition (ANOVA, LSD).

paired *t* test) at all levels of $[Ca^{++}]_o$ studied. The decrease of distal APD_{90} at 1.8 mM $[Ca^{++}]_o$, representing a small change (-10 ± 2 ms) in five continuously recorded fibers exposed to 0.85 mM halothane, was a different response from the lack of significant effects of halothane on distal APD_{90} found by the multiple-fiber averaging technique (table 1). The changes of APD_{90} resulting from halothane (table 3 and bar graph in fig. 5) were greater ($P \leq 0.05$) in proximal than distal fibers at each level of $[Ca^{++}]_o$, indicating that the regional actions of halothane were present at each Ca^{++} concentration. The decreases of proximal and distal APD_{90} resulting from halothane (graph in fig. 5) were greater ($P \leq 0.05$) at 0.6 mM $[Ca^{++}]_o$ than at either 1.8 or 3.6 mM $[Ca^{++}]_o$. However, there was no difference between the mean values of proximal APD_{90} found in the presence of halothane at the three Ca^{++} levels or between the values of distal APD_{90} obtained in the presence of halothane at the different levels of $[Ca^{++}]_o$.

Discussion

The current study compares the effects of halothane on regional differences of Purkinje's fiber APD_{90} with those resulting from reduction of the Na^+ ion influx produced by the specific Na^+ channel antagonist TTX and with those resulting from reduction of the Ca^{++} ion influx produced by decreasing $[Ca^{++}]_o$. The fibers from the two regions selected differ in several important control char-

TABLE 3. Actions of Halothane at Low (0.6 mM), Intermediate (1.8 mM), and High (3.6 mM) Extracellular Ca^{++} Concentrations on Proximal and Distal Purkinje Fibers

			Action Potential Characteristics					
			MDP (mV)	OS (mV)	Amp (mV)	V_{max} (V/s)	APD_{50} (ms)	APD_{90} (ms)
Proximal PF								
	mM Ca	mMH						
C1	1.8		−89.5 ± 1.3	32.3 ± 2.8	121.9 ± 1.9	621 ± 65	233 ± 6	296 ± 7
	0.6		−86.1 ± 2.0	24.7 ± 4.3†	110.7 ± 2.9†‡	406 ± 42†	271 ± 3†‡	344 ± 5†‡
	0.6	0.92 ± 0.06	−84.0 ± 1.9	21.8 ± 3.6	105.8 ± 3.4	380 ± 50	139 ± 10**	236 ± 15**
	1.8		−89.9 ± 1.6	32.8 ± 3.2	122.7 ± 2.7	577 ± 68	223 ± 10	291 ± 8
	1.8	0.85 ± 0.06	−87.2 ± 2.3	31.3 ± 4.7	118.6 ± 3.7	529 ± 77	143 ± 7**	235 ± 12**
	3.6		−88.8 ± 1.1	31.2 ± 1.6	120.0 ± 1.5	519 ± 49	200 ± 8	273 ± 7
	3.6	0.88 ± 0.06	−88.5 ± 1.9	30.5 ± 1.7	119.0 ± 2.2	483 ± 43*	128 ± 10**	224 ± 10**
Distal PF								
	mM Ca	mMH						
C1	1.8		−86.8 ± 1.1	31.7 ± 3.0	118.5 ± 2.7	458 ± 57	165 ± 5	217 ± 5
	0.6		−83.0 ± 1.0‡	22.4 ± 3.4†	105.4 ± 4.0†‡	302 ± 40†	177 ± 6	229 ± 6†
	0.6	0.92 ± 0.06	−80.1 ± 2.1	19.3 ± 3.4	99.4 ± 5.1	262 ± 30	146 ± 9**	202 ± 7**
	1.8		−89.0 ± 1.0	29.5 ± 1.9	118.5 ± 1.9	507 ± 65	171 ± 6	229 ± 5
	1.8	0.85 ± 0.06	−89.9 ± 1.4	27.1 ± 2.5	117.0 ± 2.3	442 ± 68	150 ± 9**	219 ± 7**
	3.6		−89.0 ± 0.6	30.1 ± 2.2	119.2 ± 2.0	421 ± 41	162 ± 5	219 ± 6
	3.6	0.88 ± 0.06	−89.0 ± 1.6	29.1 ± 1.8	118.1 ± 2.0	420 ± 43	140 ± 6**	212 ± 7*

* $P \leq 0.05$, **$P \leq 0.01$ compared to value in absence of halothane at same Ca^{++} (paired *t* test).

† $P \leq 0.05$ compared to initial control value (C1) at 1.8 mM Ca^{++} (paired *t* test).

‡ $P \leq 0.05$ compared to value at either 1.8 or 3.6 mM Ca^{++} in the absence of halothane (Student's *t* test).

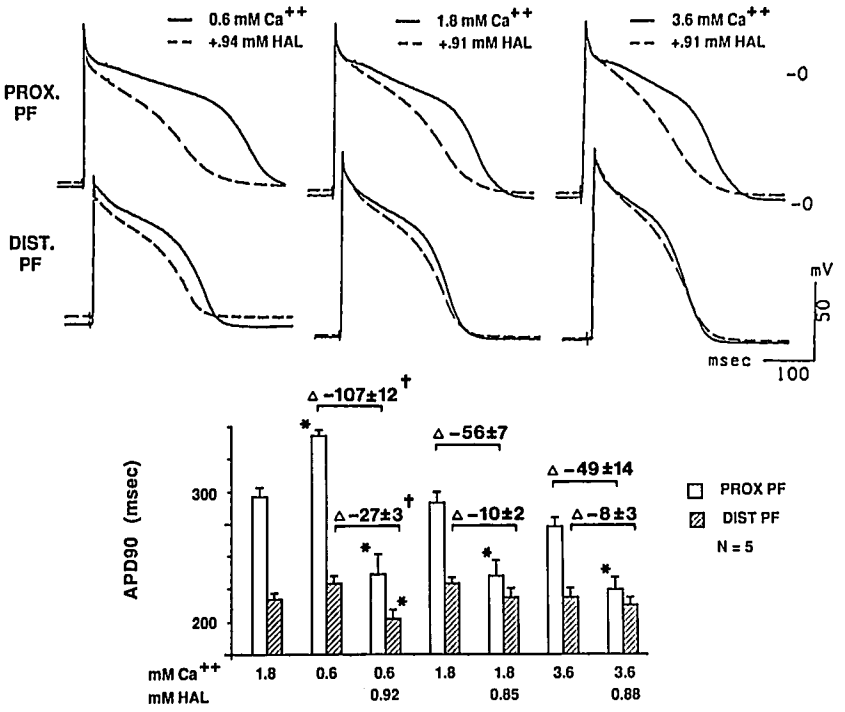

FIG. 5. Actions of halothane at 0.6 mM (*left tracings*), 1.8 mM *center tracings*) and 3.6 mM (*right tracings*) extracellular Ca^{++} ion concentration on proximal and distal Purkinje fiber action potentials. Bar graph: mean values of APD_{90} found during the sequence of interventions shown from left to right along the x-axis. The paired changes (Δ) of proximal and distal APD_{90} due to halothane are given in ms ± SEM above the brackets. $*P < 0.05$ *versus* preceding condition (paired *t* test); $\dagger P < 0.05$ *versus* change due to halothane at 1.8 mM $[Ca^{++}]_0$ (Student's *t* test).

acteristics. Fibers at the terminations of the false tendons (proximal fibers) exhibit relatively high V_{max} and conduction velocity as well as prolonged refractoriness associated with greater APD than fibers located in the upper portions of the bundle branches or the apical (distal) Purkinje fiber network.[19,22] In contrast, distal fibers, which are located close to the Purkinje–ventricular muscle junctions, exhibit "transitional" characteristics intermediate between those of more proximal Purkinje fibers and true ventricular muscle fibers.[23] The short APD of distal fibers may result in part from the electrotonic influence of earlier myocardial repolarization because interrupting their connections to the underlying myocardium increases their APD.[23] On the other hand, the work of Coraboeuf *et al.*[14] demonstrating a greater sensitivity of proximal fibers to the effects of TTX on APD must reflect a relatively greater participation of inward sodium current (I_{Na}) in the generation of the relatively prolonged APD of false tendon fibers than in other fibers exhibiting shorter APD. Voltage clamp studies in Purkinje fibers indicate that a small TTX-[24,25] and lidocaine-sensitive[21] inward Na^+ current persists during the action potential plateau and that Na^+ channel-blocking agents decrease APD during phase 3 repolarization (APD_{90}) by reduction of this "window" or "plateau" component of I_{Na}.[25] The persistence of I_{Na} during the plateau may result from peculiar Na^+ channel phenomena such as delayed opening and reopening or bursting rather than a second type of Na^+ channel distinct from the "fast" Na^+ channel.[26]

The results of the current study support the hypothesis that the electrophysiologic basis underlying regional differences of Purkinje fiber APD is related to differences in the contribution of Na^+ influx and I_{Na} to the plateau phase of fibers exhibiting prolonged APD. The observed responses to TTX were analogous to those reported by Coraboeuf *et al.*,[14] who compared the responses of false tendon fibers with those of fibers exhibiting shorter APD in the upper bundle branches. In addition, the Na^+ channel agonist VTD, which increases Na^+ influx by prolonging the mean open time of Na^+ channels,[18] was found to have regional actions opposite to those of TTX that increased proximal APD_{90} more than distal APD_{90}. Finally, the observation that decreasing $[Ca^{++}]_0$ also increased APD_{90} of the proximal fibers more than distal fibers suggests that these regional differences of APD are probably not related to differences of inward Ca^{++} currents because the reduction of Ca^{++} influx under these conditions would not support the increased plateau duration of the proximal fibers.

The regional actions of halothane on Purkinje fiber APD_{90} were similar to those of low (≤1 μM) concentrations of TTX, which suggests that halothane may decrease proximal fiber APD_{90} by the same mechanism involving inhibition of plateau phase I_{Na}. This interpretation of the results is consistent with the findings that halothane produced relatively greater decreases of APD_{90} in proximal fibers, those most sensitive to the actions of TTX, and that the decreases of APD_{90} were readily reversed by the

Na^+ channel agonist VTD. The finding that the decrease of proximal fiber APD_{90} was reversed by VTD is nonspecific in the sense that this agent should prolong APD_{90} by increasing plateau phase I_{Na} regardless of the mechanism or mechanisms by which halothane decreased APD_{90}. However, the observed reversal by VTD of the regional actions of halothane supports the hypothesis that the anesthetic effects may result from "TTX-like" inhibition of plateau phase I_{Na} because of the strong evidence supporting the role of differences of I_{Na} in production of the characteristic regional pattern (proximal greater than distal fiber APD) of Purkinje fiber repolarization. At concentrations of halothane and TTX producing similar degrees of reduction of proximal fiber APD_{90}, halothane tended to produce greater depression of the plateau (APD_{50}), whereas VTD was less effective in reversing the depression of APD_{50} resulting from halothane than in reversing the anesthetic effect on APD_{90}. These additional effects of halothane on the early action potential contour (APD_{50}) of proximal fibers could result from inhibition of I_{si} in addition to inhibition of I_{Na}. In contrast, the relative insensitivity of distal fibers to the effects of TTX and VTD on the action potential contour indicates that I_{Na} contributes less to the plateau of distal than proximal fibers. The finding that higher halothane concentrations either had no effect (table 1) or slightly decreased (table 3) distal APD_{90}, whereas APD_{50} was depressed, may reflect the opposing influences of inhibition of I_{Ca} and I_K by halothane[11] on APD_{90} in fibers in which I_{Na} has a less important role in maintaining the plateau. At moderate concentrations the combination of halothane and TTX produced largely additive regional effects in the sense of decreasing proximal APD_{90} more than either agent alone, whereas at the concentrations used the addition of halothane to TTX did not further reduce V_{max}. It was not possible to evaluate the interaction of halothane and TTX at higher concentrations because of loss of excitability and failure to generate an action potential.

On the other hand, Lynch *et al.*[8] suggested that the reduction in the amplitude and duration of the action potential plateau of ventricular muscle fibers by halothane may reflect inhibition of the slow inward current, and halothane probably inhibits inward Ca^{++} channel currents in both ventricular muscle and Purkinje fibers.[12] The experiments at altered $[Ca^{++}]_0$ were designed to evaluate the potential role of reduction of Ca^{++} influx by halothane on regional differences of Purkinje fiber APD_{90}. The findings indicate that reduction of $[Ca^{++}]_0$, and presumably the Ca^{++} influx, increases proximal fiber APD_{90} more than distal fiber APD_{90}, thereby accentuating regional differences of APD. Conversely, increasing $[Ca^{++}]_0$ has the opposite effect of reducing regional differences of APD, just like halothane. Although the effects of altering $[Ca^{++}]_0$ on regional differences of Purkinje fiber APD have not been previously reported, the observed action potential responses probably include changes resulting from alterations of K^+ and perhaps Na^+ ion conductance in addition to those resulting from changes of Ca^{++} influx. It has been shown by intracellular injection techniques that reduction of the intracellular Ca^{++} ion concentration delays repolarization by reducing outward K^+ current, whereas increases of intracellular Ca^{++} facilitate repolarization by enhancing outward K^+ current.[17] In addition, substantial decreases of $[Ca^{++}]_0$ (from 20 to 0.1 mM) have been reported to increase Na^+ channel conductance[27] and could contribute to an increase of plateau phase I_{Na}. However, it is probable that the sixfold reduction of $[Ca^{++}]_0$ (from 3.6 to 0.6 mM) used in the current study increased proximal APD_{90} and accentuated regional differences of APD largely by reduction of outward I_K, although a minimal effect increasing plateau phase I_{Na} cannot be excluded. Therefore, the regional actions of halothane on Purkinje fiber APD_{90} are not consistent with simple inhibition of Ca^{++} influx during the plateau phase because reductions of $[Ca^{++}]_0$, the Ca^{++} influx, and presumably outward K^+ current produce regional effects opposite to those resulting from halothane.

The actions of halothane at altered $[Ca^{++}]_0$ were characterized by more prominent decreases of proximal fiber APD_{90} than distal fiber APD_{90} at low $[Ca^{++}]_0$ compared with high $[Ca^{++}]_0$. These regional actions were associated with the greater control APD of the fibers under conditions of lower $[Ca^{++}]_0$, whereas the values of proximal fiber APD_{90} obtained in the presence of halothane did not vary significantly over the sixfold range of $[Ca^{++}]_0$. The greater regional response to halothane at low $[Ca^{++}]_0$, in the presence of presumably a reduced contribution of the Ca^{++} influx to the plateau and reduction of outward K^+ current, again supports the hypothesis that halothane decreases APD_{90} of proximal fibers by inhibition of the remaining Na^+ influx under these conditions. This conclusion is limited in that the responses at low $[Ca^{++}]_0$ do not exclude an action of halothane increasing outward K^+ current. However, such an action would not be consistent with the evidence that halothane probably inhibits I_K in other cardiac tissues (atrial and ventricular myocytes).[7,11] At a minimum, the responses to halothane at altered $[Ca^{++}]_0$ suggest that inhibition of I_{si} and the Ca^{++} influx by halothane during the action potential is probably not responsible for its regional effects because its regional actions are more prominent under conditions (low $[Ca^{++}]_0$) in which the prolonged APD_{90} of proximal fibers must result from a relatively greater Na^+ influx.

These observations, indicating that the regional actions of halothane on Purkinje fiber APD_{90} are similar to those of TTX and that they are unlike those resulting from reducing Ca^{++} influx by lowering $[Ca^{++}]_0$, provide only indirect evidence that halothane may decrease proximal

fiber APD_{90} by inhibition of Na^+ influx. Direct demonstration that halothane blocks plateau-phase I_{Na} in Purkinje fibers, as in ventricular muscle fibers,[10] will require voltage clamp techniques and ionic substitution to eliminate overlapping changes in I_{Ca} and I_K and demonstration that halothane blocks the residual TTX-sensitive component of the inward Na^+ current[28] that persists after depolarization. Although identification of the relative contributions of Na^+, Ca^{++}, and K^+ channel blockade by halothane to its actions on Purkinje fiber repolarization is important, it is clear that the net regional effects of low concentrations of halothane on APD_{90} of canine Purkinje fibers are comparable to those resulting from low concentrations of the Na^+ channel antagonist TTX.

The current study of action potential responses cannot discriminate between all the potential actions of halothane on the complex ionic mechanisms underlying Purkinje fiber repolarization. The comparisons made are limited by the lack of specificity of the interventions used to alter plateau phase ionic fluxes and can only suggest in a general way the possible changes of ionic currents responsible for the observed action potential responses. Recent studies indicate that the negative inotropic actions of Na^+ channel-blocking agents such as lidocaine are associated with parallel decreases in intracellular Na^+ and Ca^{++} ion concentrations mediated by Na^+–Ca^{++} exchange.[29,30] "Forward-mode" Na^+–Ca^{++} exchange (three Na^+ in, one Ca^{++} out), which may contribute to depolarizing inward current during the plateau, appears to operate by extrusion of Ca^{++} ions that had entered early during the action potential as I_{Ca} and "reverse-mode" entry of Ca^{++} (one Ca^{++} in, three Na^+ out) in exchange for Na^+.[31] Therefore, it is likely that reduction of either Ca^{++} or Na^+ influx by agents or interventions that reduce I_{Ca} or I_{Na} or both, such as halothane,[9,10,12] could produce changes in the action potential contour resulting from alterations of the intracellular Ca^{++} and Na^+ concentrations and exchange current.[32] Although some studies suggest that general anesthetics may alter Na^+–Ca^{++} exchange,[11,33] the implications of changes in exchange currents on the action potential are as yet uncertain.

The regional actions of halothane on Purkinje fiber APD_{90} may produce changes in conduction during the relative refractory period of the ventricular conduction system. In the normal heart, descending premature impulses may undergo conduction block at regions of increased APD and refractoriness in the bundle branches producing functional bundle branch block.[22] The actions of halothane decreasing APD_{90} of proximal (false tendon) fibers in the current study may account for previous observations from this laboratory that halothane decreases the functional refractory period for propagation of His bundle extrastimuli in the canine heart *in vivo*.[34] In addition, in the 1-day-old canine infarction model,[4] the actions of halothane abbreviating repolarization in false tendon fibers contribute to the induction of reentrant activity by increasing the disparity between the repolarization times of fibers located within and outside the ischemic region. Thus, the differential actions of halothane on Purkinje fiber APD_{90} in different regions of the ventricle may have an important influence on the propagation of premature impulses by altering critical differences between the repolarization times of fibers located at specific sites of conduction delay or block.

In summary, the regional actions of halothane on canine left ventricular Purkinje fibers, characterized by greater decrease of APD_{90} in fibers located in a region of longer APD (false tendon fibers) than in fibers from a region exhibiting shorter APD (apical fibers), are comparable to those produced by low concentrations of TTX. Further, the regional actions of halothane on APD_{90}, which may be reversed by the Na^+ channel agonist VTD, are opposite to those obtained by reducing $[Ca^{++}]_0$ and the Ca^{++} influx. The findings, which are consistent with the hypothesis that the regional effects of halothane on APD_{90} may result from blockade of plateau phase I_{Na}, do not prove a Na channel action of halothane on Purkinje fibers or exclude other more complicated actions of halothane on the Ca^{++} influx or K^+ efflux that might explain the TTX-like effects of halothane. However, the results are consistent with the less complicated hypothesis that halothane may decrease APD_{90} of Purkinje fibers located in certain regions of the heart by inhibition of plateau phase inward Na^+ current.

References

1. Reynolds AK, Chiz JF, Pasquet AF: Halothane and methoxyflurane—a comparison of their effects on cardiac pacemaker fibers. ANESTHESIOLOGY 33:602–610, 1970
2. Gallagher JD, Gessman LJ, Moura P, Kerns D: Electrophysiologic effects of halothane and quinidine on cardiac Purkinje fibers: Evidence for a synergistic interaction. ANESTHESIOLOGY 65: 278–285, 1986
3. Hauswirth O: Effects of halothane on single atrial, ventricular and Purkinje fibers. Circ Res 24:745–750, 1969
4. 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
5. Noble D: The surprising heart: A review of recent progress in cardiac electrophysiology. J Physiol (Lond) 353:1–50, 1984
6. DiFrancesco D, Noble D: A model of cardiac electrical activity incorporating ionic pumps and concentration changes. Philos Trans R Soc Lond [Biol] B307:353–398, 1985
7. 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 Pharmcol 126:293–295, 1986
8. Lynch C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
9. 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
10. 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
11. Terrar DA, Victory JGG: Effects of halothane on membrane currents associated with contraction in single myocytes isolated from guinea-pig ventricle. Br J Pharmacol 94:500–508, 1988
12. Bosnjak ZJ, Rusch NJ: Calcium currents are decreased by halothane, enflurane and isoflurane in isolated canine ventricular and Purkinje cells (abstract). ANESTHESIOLOGY 69:A452, 1988
13. Bosnjak ZJ, Kampine JP: Effects of halothane on transmembrane potentials, Ca^{2+} transients and papillary muscle tension in the cat. Am J Physiol 251:H374–H381, 1986
14. Coraboeuf E, Debroubaix E, Coulombe A: Effect of tetrodotoxin on action potentials of the conducting system in the dog heart. Am J Physiol 236:H561–H567, 1979
15. Allen JD, Brennan FJ, Wit AL: Actions of lidocaine on transmembrane potentials of subendocardial Purkinje fibers surviving in infarcted canine hearts. Circ Res 43:470–481, 1978
16. Sheu SS, Fozzard HA: Transmembrane Na^+ and Ca^{++} electrochemical gradients in cardiac muscle and their relationship to force development. J Gen Physiol 80:325–351, 1982
17. Isenberg G: Cardiac Purkinje fibers. Resting, action and pacemaker potential under the influence of $[Ca^{2+}]_i$ as modified by intracellular injection techniques. Pflugers Arch 371:51–59, 1977
18. Brill DM, Wasserstrom JA: Intracellular sodium and the positive inotropic effect of veratridine and cardiac glycoside in sheep Purkinje fibers. Circ Res 58:109–119, 1986
19. Myerburg RJ, Gelband H, Castellanos A, Nilsson K, Sung RJ, Bassett A: Electrophysiology of endocardial intraventricular conduction: The role and function of the specialized conducting system, The Conduction System of the Heart. Edited by Wellens HJJ, Lie KI, Janse MJ. Philadelphia, Lea & Febiger, 1976, pp 336–359
20. Miller RG: Simultaneous Statistical Inference. New York, McGraw-Hill, 1966, pp 90–94
21. Colatsky T: Mechanisms of action of lidocaine and quinidine on action potential duration in rabbit cardiac Purkinje fibers. Circ Res 50:17–27, 1982
22. Myerburg RJ, Stewart JW, Hoffman BF: Electrophysiologic properties of the canine peripheral A-V conducting system. Circ Res 26:361–378, 1970
23. Mendez C, Mueller WJ, Merideth J, Moe GK: Interaction of transmembrane potentials in canine Purkinje fibers and at Purkinje fiber-muscle junctions. Circ Res 24:361–372, 1969
24. Attwell D, Cohen I, Eisner D, Ohba M, Ojeda C: The steady state TTX-sensitive ("window") sodium current in cardiac Purkinje fibers. Pflugers Arch 379:137–142, 1979
25. Gintant GA, Datyner NB, Cohen IS: Slow inactivation of a tetrodotoxin-sensitive current in canine cardiac Purkinje fibers. Biophys J 45:509–512, 1984
26. Grant AO, Starmer CF: Mechanisms of closure of cardiac sodium channels in rabbit ventricular myocytes: Single-channel analysis. Circ Res 60:897–913, 1987
27. Nilius B: Calcium block of guinea-pig heart sodium channels with and without modification by the piperazinylindole DPI-201-106. J Physiol (Lond) 399:537–558, 1988
28. Kiyosue T, Avita M: Late sodium current and its contribution to action potential configuration in guinea pig ventricular myocytes. Circ Res 64:389–397, 1989
29. Sheu SS, Lederer WJ: Lidocaine's negative inotropic and antiarrhythmic actions: Dependence on shortening of action potential duration and reduction of intracellular sodium activity. Circ Res 57:578–590, 1985
30. Fozzard HA, Wasserstrom JA: Voltage dependence of intracellular sodium and control of contraction, Cardiac Electrophysiology and Arrhythmias. Edited by Zipes DP, Jalife J. Orlando, Grune & Stratton, 1985, pp 51–57
31. Noble D: Experimental and theoretical work on excitation and excitation-contraction coupling in the heart. Experientia 43: 1146–1150, 1987
32. Sonn JK, Lee CO: Na^+-Ca^{++} exchange in regulation of contractility in canine cardiac Purkinje fibers. Am J Physiol 255:C278–290, 1988
33. Haworth RA, Goknur AB, Berkoff HA: Inhibition of Na-Ca exchange by general anesthetics. Circ Res 65:1021–1028, 1989
34. Turner LA, Zuperku EJ, Purtock RV, Kampine JP: *In vivo* changes in canine ventricular cardiac conduction during halothane anesthesia. Anesth Analg 59:327–334, 1980