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The Electrophysiologic Effects of Amiodarone and Halothane on Canine Purkinje Fibers

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Amiodarone may cause serious complications in patients receiving general anesthetics. Potentially adverse electrophysiologic interactions between amiodarone and halothane were studied with the use of standard microelectrode techniques to record intracellular action potentials (APs) from excised canine Purkinje fibers. A second dog (support dog) was anesthetized and a femoral arteriovenous bypass circuit created in which arterial blood from the support dog superfused the Purkinje fiber in a tissue bath. The applicability of this model was established by first comparing the AP effects of halothane during blood perfusion with those in Tyrode's solution. Halothane reduced AP duration (APD; $P < 0.05$) during Tyrode's solution superfusion and blood cross-perfusion. After the blood perfusion–Purkinje fiber model was validated, the interaction between halothane and amiodarone was studied using Purkinje fibers from dogs chronically treated with oral amiodarone, superfused with blood from chronically amiodarone-treated support dogs. Amiodarone reduced resting membrane potential and prolonged APD. Depression of AP amplitude and reduction of the maximum rate of increase of phase 0 of the AP ($\dot{V}_{max}$) by halothane (both $P < 0.05$) suggested risk of conduction defects if halothane is administered to patients receiving chronic amiodarone therapy. (Key words: Anesthetics, volatile: halothane. Antiarrhythmics: amiodarone. Heart arrhythmias: Purkinje fibers.)

AMIODARONE is a potent Class 3 antiarrhythmic[1] that has been associated with serious adverse hemodynamic and electrophysiologic complications in patients receiving general anesthetics.[2–4] The goal of the current investigation was to evaluate the potential for adverse electrophysiologic interactions between amiodarone and halothane.

Amiodarone has several properties that complicate the application of standard electrophysiologic methods, in which drugs are added to a physiologic salt buffer superfusing excised cardiac tissue. These include the poor solubility of amiodarone in buffer solutions,[5] slow formation of active metabolites,[1,6] slow equilibration with cardiac tissues,[7] and possible *in vivo* interaction with triiodothyronine.[8–10] In addition, the electrophysiologic effects of amiodarone when acutely administered to intact subjects or excised tissue differ from those observed after chronic administration.[1,7,10–12]

The blood cross-perfusion technique devised by Rosen *et al.*,[13] in which blood from a heparinized support dog is used to superfuse Purkinje fibers excised from another dog, allows observation of the cellular electrophysiologic effects of drugs in a situation that more closely mimics the *in vivo* milieu. The tissue bath containing the Purkinje fibers is included in a femoral artery–to–femoral vein bypass circuit using the support dog. Drugs can be administered into the physiologic salt solution bathing the excised Purkinje fiber, or, with the turn of a stopcock, blood from the support dog can be made to superfuse the Purkinje fiber. The drugs in question can be administered to the support dog acutely, or the support dog can be treated chronically before the experiment.

To accomplish the objectives of the current study, Purkinje fibers obtained from dogs chronically treated with amiodarone were superfused with blood from support dogs that also had received amiodarone chronically. First, however, studies were performed to verify that the effects of halothane on canine Purkinje fibers were similar whether the superfusate consisted of buffer solution or blood.

Materials and Methods

This study was approved by the institutional Animal Care and Use Committee. The procedures conformed with the standards described in the "Guide for Care and Use of Laboratory Animals," Public Health Services, National Institutes of Health publication no. 85-23 (rev. 1985).

Preparation of Amiodarone-treated Dogs

Mongrel dogs of either sex were given amiodarone hydrochloride orally at a daily dose of 25 mg/kg for 7 days, followed by 15 mg/kg for 14–18 days.

Electrophysiologic Studies

On the day of the experiment, the Purkinje fiber donor dog (amiodarone treated or nontreated, depending on the specific protocol) was anesthetized with pentobarbital, 30 mg/kg, intravenously (iv). The trachea was intubated, and the lungs were ventilated mechanically with room air. The heart was removed rapidly through a left thoracotomy and placed in cold, oxygenated Tyrode's solution. Free-running Purkinje fibers were excised from either ventricle and placed in a Plexiglas® tissue bath with a 4-ml internal volume similar to that described by Rosen *et al.*[13] The surface upon which the Purkinje fiber rested

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was slanted to prevent stagnation of blood during cross-perfusion, and multiple perfusate inlets were present to allow continuous superfusion while minimizing turbulence, which could dislodge intracellular microelectrodes.

Tyrode's solution was pumped through a heat exchanger into the tissue bath at 25 ml/min with a peristaltic pump. The Tyrode's solution contained 137 mM NaCl, 18 mM $NaHCO_3$, 1.8 mM NaH_2PO_4, 0.5 mM $MgCl_2$, 2.7 mM $CaCl_2$, and 5.5 mM dextrose. The KCl concentration of the Tyrode's solution was matched to the blood potassium concentration of the support dog, which was determined at the start of the experiment. Tyrode's solution was equilibrated with a gas mixture of 95% O_2 and 5% CO_2 and heated to 37° C, and had a *p*H of 7.40 ± 0.05.

Fibers were stimulated from one end, with the use of a bipolar Teflon®-coated silver wire electrode, a stimulator pulse duration of 1 ms, and a current of twice threshold. Intracellular action potentials (APs) were recorded with the use of standard microelectrode techniques. The midportion of false tendons were impaled with glass microelectrodes filled with 3 M KCl (resistance 10–30 Mohms) and connected through a silver–silver chloride junction to the input of a WPI KS-700® dual-microprobe amplifier (World Precision Instruments, New Haven, CT). The first derivative of the transmembrane potential was obtained with the use of an electronic differentiator, which was linear between 50 and 1,000 V/s.

The recordings were photographed from an oscilloscope display, and the following measurements were made: resting membrane potential (RMP; transmembrane potential at the onset of phase 0), AP amplitude (AP_{amp}), AP duration (APD) at 50% and 90% repolarization (APD_{50} and APD_{90}, respectively), and the maximum rate of increase of phase 0 of the AP ($\dot{V}_{max}$). Data were used when a single cell impalement was maintained for the entire experiment.

After measurements were obtained in Tyrode's solution, blood cross-perfusion was instituted.[13] A second dog (support dog) was anesthetized with pentobarbital, 30 mg/kg, iv. The trachea was intubated and the lungs mechanically ventilated with O_2 (fractional inspired O_2 concentration = 1.0) to maintain arterial CO_2 tension between 35 and 40 mmHg. Arterial blood gases were obtained at 30-min intervals and bicarbonate given as needed for metabolic acidosis. The temperature of the donor dog was maintained between 37° C and 37.5° C with the aid of a heating lamp and heating blankets. A femoral artery and vein were cannulated, and the donor received heparin (300 units/kg, iv) in preparation for institution of blood cross-perfusion. Blood was pumped from the femoral artery, through the heat exchanger (37° C bath temperature maintained) into the bath, thus superfusing the Purkinje fiber. The effluent from the bath was collected, passed through an air trap and particle filter, and returned to the donor dog. Measurements then were obtained during blood cross-perfusion.

Experimental Protocols

The Effects of Halothane on Purkinje Fibers during Blood Cross-perfusion in Contrast to Tyrode's Solution Superfusion

Purkinje fibers obtained from dogs not treated with amiodarone were paced at a 500-ms cycle length (120 beats per min) and superfused with Tyrode's solution; after a 1-h equilibration period, control measurements were obtained. Halothane 1% was added to the gas mixture that was bubbled through the Tyrode's solution with a calibrated vaporizer (calibrated with mass spectroscopy). After 1 h, measurements were repeated. Blood cross-perfusion then was initiated with the use of a nontreated support dog, and measurements were repeated in half of the experiments after 1 h to allow for washout of halothane and equilibration in blood. Halothane 1% then was administered to the support dog, and through its blood to the Purkinje fibers. After 1 h, measurements were repeated. The order was reversed in the other half of the experiments involving untreated support dogs in blood cross-perfusion studies with halothane.

Effects of Amiodarone and Halothane on Canine Purkinje Fibers

Purkinje fibers were obtained from an amiodarone-treated dog and were superfused with blood from a second amiodarone-treated support dog. After AP measurements were obtained, halothane concentrations of 0.5%, 1%, and 2% were administered in a random order to the support dog and through the blood perfusate to the Purkinje fiber. After 40 min at each halothane concentration, AP measurements were recorded. A control group in which neither the Purkinje fiber donor nor the support dog had received amiodarone was subjected to the same blood cross-perfusion protocol. Serum amiodarone concentrations were obtained from both the Purkinje fiber donor and support dogs. Purkinje fiber amiodarone concentrations were measured in excised Purkinje fibers not used in the electrophysiologic studies.

Serum potassium levels were determined with an IL443 flame photometer (Instrument Laboratories, Lexington, MA). Serum and Purkinje fiber amiodarone concentrations were determined by high-performance liquid chromatography with the use of a modification of the technique of Brien *et al.*[14] This technique showed 4% variability with the use of a 1 μg/ml standard.

Data contrasting blood cross-perfusion with Tyrode's solution superfusion were analyzed with the use of repeated-measures analysis of variance (ANOVA) with two

TABLE 1. Effects of Halothane on Purkinje Fiber Action Potentials during Superfusion with Tyrode's Solution or Blood Cross Perfusion

	Tyrode's Solution		Blood Perfusion	
	Control	Halothane 1%	Control	Halothane 1%
RMP (mV)	−89 ± 2	−88 ± 2	−91 ± 2	−91 ± 2
AP_{amp} (mV)*	118 ± 2	116 ± 2	121 ± 2	121 ± 2
APD_{50} (ms)	137 ± 7	126 ± 6†	143 ± 8	128 ± 7‡
APD_{90} (ms)	205 ± 8	197 ± 7	215 ± 10	211 ± 8
$\dot{V}_{max}$ (V/s)	501 ± 48	477 ± 51	473 ± 50	489 ± 47

Mean ± SEM, n = 14.

RMP = resting membrane potential; AP_{amp} = action potential amplitude; APD_{50} and APD_{90} = AP duration to 50 and 90% repolarization, respectively; $\dot{V}_{max}$ = maximum rate of increase of phase 0. Paced cycle length 500 ms.

* $P = 0.031$, blood perfusion > Tyrode's superfusion by two-factor ANOVA.

† $P = 0.012$, Tyrode's with halothane 1% < Tyrode's superfusion.

‡ $P = 0.003$, blood perfusion > blood perfusion with halothane 1%.

trial factors.† Two-way ANOVA for repeated measures was used for other comparisons.† Significant F ratios were evaluated with the use of Bonferroni's modification of the *t* test. A value of $P < 0.05$ was considered significant. All results are reported as mean ± SEM.

Results

The Effects of Halothane on Purkinje Fibers during Blood Cross-perfusion in Contrast to Tyrode's Solution Superfusion

The effects of halothane during blood cross-perfusion were determined in 14 preparations. The results are summarized in table 1. Blood cross-perfusion significantly increased AP_{amp} ($P = 0.031$), as compared to Tyrode's solution superfusion. Addition of halothane 1% to either perfusate decreased APD_{50} ($P = 0.012$ in Tyrode's solution and $P = 0.003$ in blood). RMP, APD_{90}, and $\dot{V}_{max}$ did not change.

Potassium concentration in the blood of blood perfusion support dogs was 4.1 ± 0.3 mM and was matched in each experiment by the potassium concentration of the Tyrode's solution (4.1 ± 0.3 mM).

Figure 1 displays the results from a typical experiment. The normal canine Purkinje fiber AP and $\dot{V}_{max}$ recorded during superfusion with Tyrode's solution were altered little by the institution of blood cross-perfusion. Addition of halothane 1% to either perfusate shortened the plateau phase and caused the transition from phase 2 (plateau) to phase 3 (rapid repolarization) to become more gradual.

Effects of Amiodarone and Halothane on Canine Purkinje Fibers

Twenty-four Purkinje fibers obtained from 20 amiodarone-treated dogs were studied. The serum amiodarone concentration in amiodarone-treated dogs was 1.42×10^{-6} M (0.91 ± 0.09 μg/ml). In treated dogs supplying Purkinje fibers, the amiodarone concentration was 0.86 ± 0.15 μg/ml, and in treated blood perfusion support dogs, 0.96 ± 0.09 μg/ml ($P > 0.05$). AP characteristics of fibers from amiodarone-treated dogs superfused with blood from amiodarone-treated dogs were compared with results obtained with the use of six fibers acquired from untreated dogs, superfused with blood from untreated dogs. Table 2 summarizes these data. Compared with untreated fibers before administration of halothane, amiodarone-treated fibers displayed reduced RMP ($P = 0.002$) and increased APD_{90} ($P = 0.05$). The reduction of RMP in amiodarone-treated fibers compared with untreated fibers persisted at all halothane concentrations ($P \leq 0.05$). In the amiodarone-treated group, AP_{amp} was reduced by halothane 1% and 2% ($P < 0.05$) and $\dot{V}_{max}$ was reduced by halothane 2% ($P = 0.05$). APD_{50} was reduced by halothane 2% in both groups ($P < 0.001$). The serum potassium concentration was similar in untreated support dogs (4.1 ± 0.3 mM) and amiodarone-treated support dogs (4.2 ± 0.4 mM) ($P > 0.05$).

Figure 2 depicts the effects of halothane on APs and $\dot{V}_{max}$ of a Purkinje fiber obtained from an amiodarone-treated dog superfused with blood from an amiodarone-treated support dog. Progressive shortening of APDs, both APD_{50} and APD_{90}, after administration of increasing concentrations of halothane are the only changes observed.

Comparison of the 14 fibers exposed to halothane 1% during blood cross-perfusion during experiment 1 with the halothane 1% exposure of 24 amiodarone-treated fibers during experiment 2 allows additional comparison of the effects of halothane on amiodarone-treated Purkinje fibers. RMP was significantly lower in amiodarone-treated fibers ($P = 0.008$), and APD_{90} was longer ($P = 0.001$). Halothane 1% shortened APD_{50} in control fibers ($P = 0.003$) and reduced AP_{amp} in amiodarone-treated fibers ($P = 0.004$). These changes are consonant with those described in table 2.

† Wilkinson L: SYSTAT: The System for Statistics. Evanston, Systat, 1989

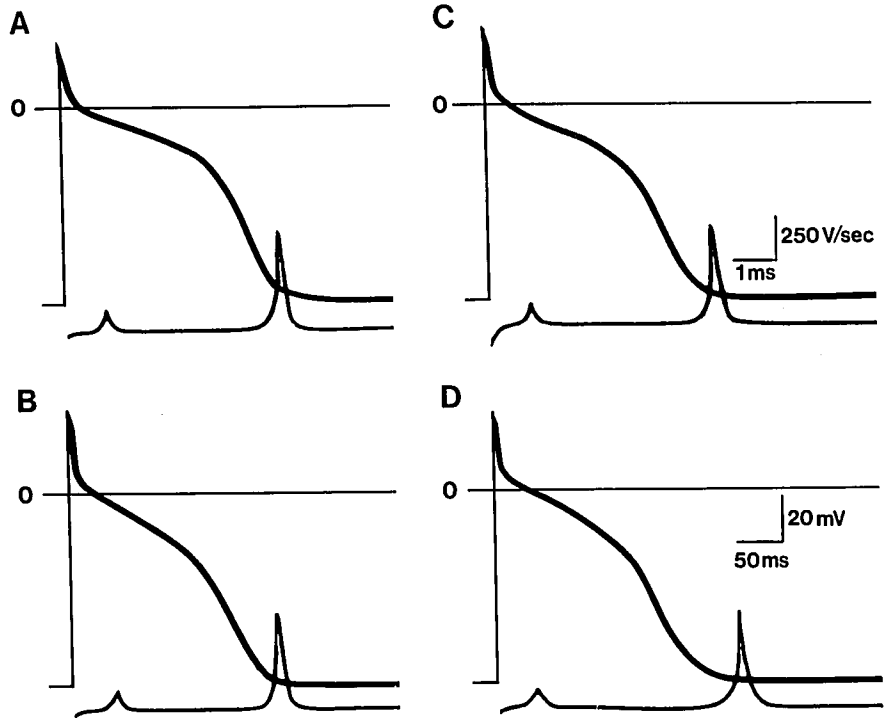

FIG. 1. Effect of halothane of Purkinje fiber action potentials during superfusion with Tyrode's solution or blood cross perfusion. The top trace in each panel shows a canine Purkinje fiber action potential at at paced cycle length of 500 ms. The bottom trace shows $\dot{V}_{max}$ for each action potential at a different oscilloscope sweep speed. The amplitude of the spike is proportional to $\dot{V}_{max}$ of phase 0. The 0-mV potential line is shown in each panel. *C*: Time and amplitude calibrations for $\dot{V}_{max}$; *D*: time and amplitude calibrations for the action potential. *A*: A normal action potential superfused with Tyrode's solution. *B*: Halothane 1% has been added; the plateau is shortened; and the transition from phase 2 (plateau) to phase 3 (rapid repolarization) is more gradual than in *A*. *C*: Blood cross perfusion has been instituted, with little change in action potential contour. *D*: The effects of halothane 1% during blood cross perfusion are shown. The plateau phase is again shortened, as in *B*. $\dot{V}_{max}$ is similar in each panel.

Discussion

Blood is a heterogeneous suspension that contains many components with electrophysiologic effects that could alter the response to halothane. These include epinephrine,[15] adenine nucleotides such as adenosine,[16] and thyroid hormone.[17] Rosen *et al.*[13] have shown that blood cross-perfusion of canine Purkinje fibers does not produce significant changes in AP_{amp}, RMP, $\dot{V}_{max}$, or APD. In the current investigation, transfer of the Purkinje fiber from Tyrode's solution to blood perfusate increased AP_{amp}. However, the increase, from 118 ± 2 to 121 ± 2 mV, although statistically significant, is of minor magnitude. Other measured variables were unchanged.

Halothane 1% in Tyrode's solution significantly reduced APD_{50} without changing other measured variables. APD_{90} was reduced from 205 ± 8 to 197 ± 7 ms, although this change was not significant. These results are consonant with previously published data that APD_{50} is the AP variable most affected by halothane.[18–20] During blood superfusion, halothane shortened APD_{50}. In not shortening APD_{90}, however, it differs from other reports[19] and may reflect the observation of Reynolds *et al.*[20] that halothane prolonged the terminal components of the AP.

Since the 1981 report of atropine- and isoproterenol-resistant bradycardia, low peripheral resistance, heart block, and significantly depressed myocardial contractility

TABLE 2. Effects of Amiodarone and Halothane on Canine Purkinje Fiber Action Potentials during Blood Cross Perfusion

		Halothane Concentration (%)			
		0	0.5	1.0	2.0
RMP (mV)	C	−93 ± 3.4	−97 ± 1.9	−97 ± 2.4	−95 ± 3.8
	A	−87 ± 1.2*	−88 ± 1.1*	−85 ± 1.0*	−85 ± 1.3*
AP_{amp} (mV)	C	118 ± 1.4	122 ± 3.7	120 ± 2.8	118 ± 2.0
	A	119 ± 1.3	118 ± 1.0	114 ± 1.3†	114 ± 1†
APD_{50} (ms)	C	154 ± 17.9	156 ± 16	156 ± 20	141 ± 16†
	A	147 ± 4.4	149 ± 3.8	144 ± 3.8	132 ± 3†
APD_{90} (ms)	C	223 ± 19	233 ± 12	233 ± 17	235 ± 14
	A	243 ± 4.3*	246 ± 5.2	240 ± 4.7	235 ± 5
$\dot{V}_{max}$ (V/s)	C	363 ± 32	412 ± 24	421 ± 29	425 ± 32
	A	478 ± 24	473 ± 23	444 ± 23	434 ± 22†

Mean ± SEM. Purkinje fibers paced at 2 Hz.
C = control group (Purkinje fibers from nontreated dogs superfused with blood from nontreated donors; n = 6); A = amiodarone group (Purkinje fibers from amiodarone-treated dogs superfused with blood from amiodarone-treated donors; n = 24).
* $P \leq 0.05$, group A *versus* C.
† $P \leq 0.05$, *versus* halothane 0%.

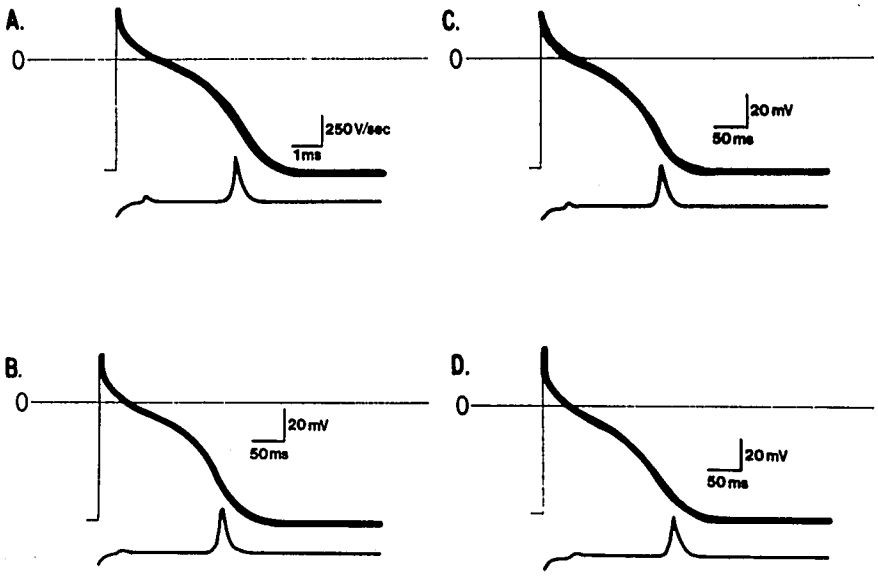

FIG. 2. Effects of halothane on canine Purkinje fibers obtained from chronically amiodarone treated dogs during blood cross perfusion. The top trace in each panel shows a canine Purkinje fiber action potential at a paced cycle length of 500 ms. The bottom trace shows $\dot{V}_{max}$ for each action potential at a different oscilloscope sweep speed. The amplitude of the spike is proportional to $\dot{V}_{max}$ of phase 0. The 0-mV potential line is shown in each panel. *A:* Time and amplitude calibrations for $\dot{V}_{max}$; *B–D:* time and amplitude calibrations for the action potential. *A:* A control action potential from a chronically amiodarone treated dog superfused with blood from a chronically amiodarone treated dog. *B, C,* and *D:* The addition of halothane 0.5, 1, and 2%, respectively. Gradual reduction of RMP and shortening of both APD_{50} and APD_{90} are noted. Though seen in this experiment, the reduction in APD_{90} did not achieve statistical significance.

in a patient treated with amiodarone,[2] there have been several reports of perianesthetic problems in patients treated with amiodarone. Feinberg *et al.*‡ compared 33 patients chronically receiving oral amiodarone with 96 other patients. All underwent left ventricular aneurysmectomy. Patients receiving amiodarone demonstrated poorer baseline ventricular function, a greater requirement for intraoperative and postoperative vasoactive drug support, and a 21% incidence of respiratory complications compared with an incidence of 4% in patients not receiving amiodarone. Liberman and Teasdale[3] reported a significantly greater perioperative incidence of low systemic vascular resistance and cardiac rhythm disturbances, including atropine-resistant bradycardia, slow nodal rhythm, complete heart block, or pacemaker dependency in 16 patients taking amiodarone compared with 30 patients with poor left ventricular function not receiving amiodarone. Fully 50% of patients undergoing cardiopulmonary bypass required intraaortic balloon counterpulsation *versus* 2 of 30 control patients. The authors concluded that dangerous and even fatal interactions may occur in patients taking amiodarone who undergo general anesthesia. Patients receiving amiodarone before operation for obstructive hypertrophic cardiomyopathy had a 50% postoperative incidence of hepatic dysfunction, 25% incidence of pulmonary dysfunction requiring a fourfold increase in duration of ventilatory support, and 19% incidence of low cardiac output.[4] In contrast, liver, lung, and heart dysfunction incidences were 2%, 0%, and 2%, respectively, in patients not receiving amiodarone.[4] Elliot *et al.*,§ described a high incidence of decreased heart rate, cardiac index, and blood pressure in 21 patients receiving amiodarone who underwent surgery. These patients, however, had no greater incidence of problems than a similar group of patients not treated with amiodarone. Despite this report, the bulk of evidence suggests that patients receiving amiodarone are at increased risk of adverse reactions during anesthesia.

In the current investigation, both serum and Purkinje fiber amiodarone concentrations were similar to those reported by others as being therapeutically effective.[1,7,10,21,22] The Purkinje fiber concentration of amiodarone observed (5.98 ± 0.69 μg/g wet tissue weight) is less than that reported in rabbit ventricular muscle by Ikeda *et al.*[7] (11.52 ± 7.2 μg/g). However, during acute administration, the ventricular muscle amiodarone concentration (5.61 ± 4.6 μg/g) exceeds the Purkinje fiber concentration (2.00 ± 0.80 μg/g),[22] suggesting that differences in tissue uptake, rather than species differences, account for the lesser concentration of amiodarone in Purkinje fiber as compared with that in the ventricular muscle. Although desethylamiodarone, the most abundant and pharmacologically active metabolite of amiodarone, was not measured directly, it is reasonable to assume that appropriate levels were present in blood and tissue of treated dogs.[1,6,14,21,22]

Amiodarone and the metabolite desethylamiodarone have multiple cardiac actions, all of which may contribute to the antiarrhythmic mechanism of action. Blockade of cardiac sodium,[23] potassium,[24] and calcium channels[25] has

‡ Feinberg BI, LaMantia KR, Levy WJ: Amiodarone and general anesthesia—A retrospective analysis (abstract). Eighth Annual Meeting of the Society of Cardiovascular Anesthesiologists, 1986, p 137

§ Elliott PL, Schauble JF, Rogers MC, Reid PR: Risk of decompensation during anesthesia in presence of amiodarone (abstract). Circulation 68:III-280, 1983

been reported. Aomine[12] described frequency-dependent inhibition of closed sodium channels and depression of tetrodotoxin-sensitive plateau currents and outward potassium currents. The role of potassium channel block, especially block of the delayed rectifier current, in the action of amiodarone and other Class 3 antiarrhythmic drugs recently has been reviewed by Colatsky *et al.*[26] These authors present experimental data and computer simulations that suggest that Class 3 drugs prolong repolarization by blocking one or more potassium channels.[26] Additionally, Levine *et al.*[27] demonstrated changes in resistance to passive current flow and suggested that these may be responsible for the clinical efficacy of amiodarone.

Alterations in thyroid function caused by the iodinated amiodarone molecule,[1] similarity between the electrophysiologic actions of amiodarone and hypothyroidism,[17] and reversal of the electrophysiologic effects of amiodarone by triiodothyronine[10] suggest that the actions of long-term amiodarone administration may result in part from antagonism of thyroid hormone.

In agreement with the current study, prolongation of APD after chronic amiodarone administration has been observed in rabbit cardiac tissue,[7] and in canine ventricular muscle during acute superfusion.[5] The reduction in RMP also has been reported previously.[12]

Halothane has a spectrum of action on cardiac ionic channels as diverse as amiodarone. Particularly prominent are effects on myocardial calcium fluxes. Halothane blocks the slow inward Ca^{2+} current,[28] abolishes Ca^{2+}-dependent APs,[29] decreases intracellular Ca^{2+} transients,[30] and inhibits release of Ca^{2+} from sarcoplasmic reticulum.[31] Halothane also blocks the fast Na^+ current,[32] and it has been suggested recently that halothane reduces APD by antagonism of a persistent plateau Na^+ current.[33] Amiodarone also depresses this "window" current.[12] Additionally, halothane blocks outward K^+ currents.[34,35]

The multiple electrophysiologic effects of both drugs make speculation difficult concerning the precise mechanism of interaction between halothane and amiodarone. The effects of this interaction are clear, however. When administered to amiodarone-treated Purkinje fibers, halothane reduced AP_{amp} and $\dot{V}_{max}$. This constellation of actions may impair conduction and increase the risk of heart block and other conduction defects.[36]

The potential for halothane to exacerbate proarrhythmic properties of amiodarone also must be addressed.[37,38] "Proarrhythmia" refers to the creation or exacerbation of supraventricular or ventricular arrhythmias by antiarrhythmic drugs.[38] All currently used antiarrhythmics are potentially proarrhythmic, with an incidence between 5.9% and 15.8%.[37] Levine *et al.*[38] have summarized data describing two specific syndromes of antiarrhythmic-induced ventricular tachycardia: 1) polymorphic ventricular tachycardia or *torsades des pointes* associated with QT interval prolongation, and 2) incessant, wide complex tachycardia. The former, seen most commonly after quinidine, but also after amiodarone, is hypothesized to result from early afterdepolarizations and triggered automaticity caused by the prolongation of the QT interval.[38] The significant prolongation of APD_{90}, the cellular equivalent of QT-interval prolongation, observed when halothane and quinidine were combined,[18] suggests that proarrhythmia may be a concern if these agents are used together intraoperatively. In contrast, the insignificant shortening of APD_{90} after halothane administration to amiodarone-treated Purkinje fibers, if manifested as a reduction in QT interval, could decrease the risk of proarrhythmia with this drug combination.

Certain potentially confounding factors that could affect the results of the current investigation must be addressed. Turner *et al.*[39] have shown that basal pentobarbital anesthesia attenuates the effects of halothane on the ventricular refractory period, and Ikemoto *et al.*[28,32] have described depressant effects of barbiturates on both the sodium and slow inward calcium currents. However, during blood cross-perfusion, Rosen *et al.*[13] have found that pentobarbital transiently (*i.e.*, less than 30 min) prolongs repolarization without affecting other AP characteristics. The absence of APD prolongation after transfer from Tyrode's solution to blood superfusion (table 1) argues against a significant effect of residual pentobarbital in the blood of the support dog.

Because the potassium concentration has a major influence on RMP[40] and, consequently, on $\dot{V}_{max}$ and AP_{amp},[40,41] care was taken to match the potassium concentration of the Tyrode's solution to that of the support dog. The close matching obtained excludes the possibility that differences between blood and Tyrode's solution could depend on potassium concentration.

The data presented concerning the effects of chronically administered amiodarone and halothane in blood-cross-perfused canine Purkinje fibers demonstrate a possible cellular electrophysiologic mechanism for heart block in patients chronically receiving amiodarone who are anesthetized with halothane. Additional experimentation and clinical observation of amiodarone-treated patients who undergo general anesthesia are necessary to determine whether a similar mechanism is responsible for the heart block and bradycardia reported when patients receiving amiodarone are anesthetized with other drugs.[2,3]

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