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Effects of Isoflurane on Ouabain Toxicity in Canine Purkinje Fibers

Comparison with Halothane

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Background: **Although halothane reduces digitalis toxicity, other anesthetics, notably cyclopropane, increase toxicity. This study determined the effects of isoflurane on digitalis toxicity in isolated cardiac tissue and compared these effects with those of halothane.**

Methods: **Standard microelectrode techniques were used to record action potentials from excised canine Purkinje fibers. Fibers were paced at cycle lengths between 1,000 and 250 ms for 20 beats to induce delayed afterdepolarizations, which are membrane potential oscillations indicative of intracellular Na^+ and Ca^{2+} overload, produced in these experiments by digitalis toxicity. The digitalis glycoside ouabain, 2×10^{-7} M, was added to the Tyrode's solution superfusate to induce delayed afterdepolarizations. Action potential variables and the coupling interval and amplitude of afterdepolarizations were then measured. Isoflurane (0.5%, 1%, or 2%) was added with a calibrated vaporizer (n = 8). In a second set of experiments (n = 10), isoflurane 1.25% or halothane 0.75% was added to the superfusate. After measurements had been made, the other agent was substituted.**

Results: **Ouabain produced primary and secondary delayed afterdepolarizations, which were reduced in amplitude by isoflurane in a dose-related manner ($P = 0.0002$). Action potential duration to 90% repolarization was shortened by ouabain ($P = 0.009$) and remained shortened during isoflurane administration. Action potential duration to 50% repolarization was shortened by isoflurane 2%. Halothane and isoflurane were equally effective in reducing the amplitude of delayed afterdepolarizations (both $P = 0.0002$). In three fibers, triggered extrasystoles appeared. Halothane and isoflurane each abolished extrasystoles. In two fibers, sustained triggered activity appeared. Isoflurane abolished the arrhythmia in each fiber.**

Conclusions: **Isoflurane and halothane are equally effective in reducing delayed afterdepolarizations induced by ouabain toxicity. (Key words: Anesthetics, volatile: halothane; isoflurane. Heart: arrhythmias; conduction; Purkinje fibers. Heart, electrophysiology: delayed afterdepolarizations; triggered activity. Pharmacology: cardiac glycosides; ouabain.)**

DESPITE the development of newer drugs to enhance myocardial performance and control atrial arrhythmias, clinical use of cardiac glycosides remains common. Cardiac glycosides possess a variety of arrhythmogenic actions that can lead to problems during anesthesia. Abnormal automaticity due to acceleration of diastolic (phase 4) depolarization may occur.[1–3] Decreases in conduction velocity, due in part to Na^+ current inactivation by reduced resting membrane potential, predispose to reentrant arrhythmias.[2] A major cause of arrhythmias, however, is triggered activity.[2,4]

Digitalis glycosides inhibit Na^+,K^+–adenosine triphosphatase (Na^+,K^+-ATPase), which causes intracellular Na^+ concentration to increase and subsequently decreases Ca^{2+} elimination by Na^+–Ca^{2+} exchange. In turn, the intracellular Ca^{2+} concentration increases.[5] Excess Ca^{2+} is taken up into the sarcoplasmic reticulum, but these stores are eventually overloaded, resulting in oscillatory release of Ca^{2+}.[6] This Ca^{2+} release then appears to activate two depolarizing processes.[6] The increase in cytosolic Ca^{2+} resulting from sarcoplasmic reticulum release causes a net depolarizing current when three Na^+ ions enter the cell to eliminate one Ca^{2+} ion by Na^+–Ca^{2+} exchange.[7] Second, there may be activation of a transient cationic inward current. These oscillatory depolarizing currents produce oscillations in membrane potential that occur after full repolarization from a preceding beat.[5,6] Termed "delayed afterdepolarizations," these oscillations increase in amplitude with increasing levels of digitalis toxicity and at faster paced rates.[6,8] If delayed afterdepolarizations reach sufficient amplitude, they can reach threshold potential and trigger repetitive extrasystoles.[5,6,9]

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Although interest has focused recently on the potential exacerbation by digitalis glycosides of cardiotoxicity induced by bupivacaine,[10] arrhythmogenic interactions between digitalis glycosides and general anesthetics may occur.[11,12] Halothane and cyclopropane appear to have opposite effects in this regard. Halothane increases the dose of cardiac glycosides required to produce arrhythmias in isolated cardiac tissue and in intact animals.[13,14] Cyclopropane, on the other hand, increases cardiac glycoside toxicity,[15] probably by increasing sympathetic outflow[16] with a resultant enhancement of Ca^{2+} entry and consequent Ca^{2+} overload.[17]

In recent years, isoflurane has become a commonly used inhalation anesthetic. During rapid increases in isoflurane concentration, tachycardia and hypertension may occur.[18] An early study using isoflurane described hemodynamic responses due to increased sympathetic nervous system activity.[19] Furthermore, using another model for triggered activity (partially depolarized Purkinje fibers from infarcted hearts), Laszlo and colleagues[20] found that halothane but not isoflurane opposed triggered activity. It is possible that isoflurane has no effect or even increases the toxicity of cardiac glycosides. Thus, the goal of the current study was to determine the effects of isoflurane on cardiac glycoside–induced toxicity in isolated cardiac tissue and to compare these effects to the known effects of halothane.

Materials and Methods

This research was approved by the Institutional Animal Care and Use Committee. Mongrel dogs of either sex were anesthetized with intravenous pentobarbital, 30 mg/kg. The heart was rapidly removed through a left thoracotomy and placed in cold oxygenated Tyrode's solution. The buffer contained NaCl 137 mM, KCl 4 mM, $NaHCO_3$ 12 mM, NaH_2PO_4 1.8 mM, $MgCl_2$ 0.5 mM, $CaCl_2$ 2.7 mM, and dextrose 5.5 mM, and was equilibrated with a gas mixture of 95% O_2 and 5% CO_2. Free running Purkinje fibers were excised from the left ventricle with a small piece of muscle at each end, were placed in a tissue bath of internal volume 4 ml, and were superfused at a rate of 15–25 ml/min with the buffer. Temperature was maintained at 37°C throughout the experiment, and the *p*H of the buffer was 7.40 ± 0.05. Individual Purkinje fiber cells from the midportions of the Purkinje fibers were impaled with glass electrodes filled with 3 M KCl and having tip resistances of 10–30 Mohm. These were coupled *via* Ag–AgCl junctions to the inputs of a KS700 dual microprobe amplifier (WPI, New Haven, CT), and action potentials were recorded on a chart recorder. Purkinje fibers were paced using bipolar Teflon-coated Ag wire electrodes at cycle lengths described below, a pulse duration of 2 ms, and an amplitude of twice threshold.

For each experimental condition, at a paced cycle length of 500 ms, the following action potential characteristics were measured: maximum diastolic potential (MDP), action potential amplitude, and action potential duration to 50% and 90% repolarization (APD_{50} and APD_{90}, respectively). The maximum rate of rise of phase 0 of the action potential ($\dot{V}_{max}$) was determined by electronic differentiation.

Delayed afterdepolarization amplitude and coupling interval were determined as shown in figure 1. Delayed afterdepolarization amplitude was measured from the point of maximum repolarization of the previous action potential (MDP) to the peak of the delayed afterdepolarization, and delayed afterdepolarization coupling interval from the onset of the previous action potential to the peak of the delayed afterdepolarization. At faster paced rates, a secondary delayed afterdepolarization (DAD2) often appeared. Amplitude of DAD2 was measured from the MDP achieved after the primary delayed afterdepolarization (DAD1) to the peak of DAD2, while coupling interval for DAD2 was measured from the preceding action potential. At the fastest paced rates,

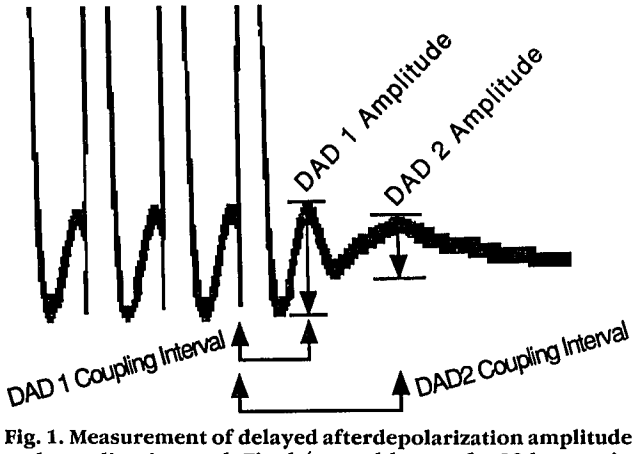

Fig. 1. Measurement of delayed afterdepolarization amplitude and coupling interval. Final 4 paced beats of a 20-beat train at a 500-ms cycle length. After termination of pacing, membrane potential oscillations form primary (DAD1) and secondary (DAD2) delayed afterdepolarizations. Methods for measuring amplitude and coupling intervals of delayed afterdepolarizations are shown.

often only a single DAD was observed. Evaluation of the coupling interval and amplitude of this DAD usually indicated that DAD2 persisted.[8]

Study Protocol

After a 45-min equilibration period, action potential characteristics were recorded during stable pacing at a 500-ms cycle length. Fibers were then paced for 20 beat trains at cycle lengths of 1,000, 800, 600, 500, 400, 350, 300, and 250 ms. The period immediately following the last paced beat of the train was examined for the presence of afterdepolarizations. Purkinje fibers were then made ouabain toxic by superfusion for 20–30 min with 2×10^{-7} M ouabain in Tyrode's solution. This treatment has been shown to induce delayed afterdepolarizations of approximately 5-mV amplitudes.[8,21] The ouabain was discontinued when afterdepolarizations appeared and superfusion with Tyrode's solution was resumed. Delayed afterdepolarizations produced in this way were stable for at least 1 h.[8,14]

The first set of experiments evaluated the dose-related effects of isoflurane on delayed afterdepolarizations. Eight fibers were subjected to the pacing protocol described above after induction of ouabain toxicity. Isoflurane 0.5%, 1.0%, or 2.0% was then added to the gas mixture bubbling through the Tyrode's solution superfusate by using a vaporizer calibrated by mass spectroscopy. Isoflurane concentrations were administered in random order. Ten minutes was allowed at each concentration before action potentials were recorded during stable pacing (cycle length 500 ms). Twenty beat trains at decreasing cycle lengths were then applied and delayed afterdepolarizations measured.

In another group of ten fibers, the effects of "equipotent" concentrations of isoflurane and halothane on delayed afterdepolarizations were compared. After induction of ouabain toxicity, halothane 0.75% or isoflurane 1.25% was added in random order to the superfusate for 15 min, and measurements were made. The alternate agent was then added, and after 15 min, measurements were repeated. In several fibers, pacing at shorter cycle lengths induced single triggered extrasystoles. When these occurred, the effects of halothane and isoflurane on the inducibility of triggered extrasystoles were documented.

In two additional fibers, during induction of ouabain toxicity, pacing induced sustained triggered activity. When this rhythm persisted for several minutes, isoflurane 1.25% was added to the superfusate, and the effects on the triggered activity were examined. If the arrhythmia did not terminate, isoflurane concentration was increased to 2.5% and effects examined.

Data were analyzed by one- and two-way analysis of variance for repeated measurements and Tukey's HSD (honestly significant difference) test for range testing. $P \leq 0.05$ was considered statistically significant. All results are reported as means ± standard error.

Results

Effects of Isoflurane on Ouabain-toxic Purkinje Fibers

The effects of increasing concentrations of isoflurane on delayed afterdepolarizations in eight ouabain-toxic Purkinje fibers are summarized in figures 2 and 3. In no fiber did pacing induce delayed afterdepolarizations before superfusion with ouabain. Figure 2 shows that isoflurane decreases the amplitude of both DAD1 and, at shorter cycle lengths, the amplitude of the larger DAD2 ($P \leq 0.0001$ for isoflurane effect on both DAD1 and DAD2 amplitudes). Figure 2 also shows a significant

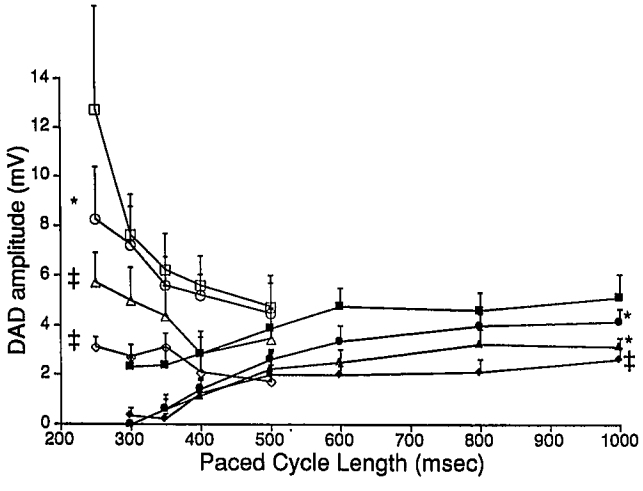

Fig. 2. Isoflurane reduced the amplitude of ouabain-induced delayed afterdepolarizations (n = 8). Delayed afterdepolarization amplitudes, for both primary and secondary delayed afterdepolarizations, at paced cycle lengths from 1,000 to 250 ms are shown. Increasing concentrations of isoflurane decreased the amplitude of delayed afterdepolarizations in a dose-related manner. Data for isoflurane 0% (squares), isoflurane 0.5% (circles), isoflurane 1.0% (triangles), and isoflurane 2.0% (diamonds) are shown for primary delayed afterdepolarizations (filled symbols) and secondary delayed afterdepolarizations (open symbols). *$P \leq 0.05$ *versus* isoflurane 0%; ‡$P \leq 0.05$ *versus* isoflurane 0% and 0.5%.

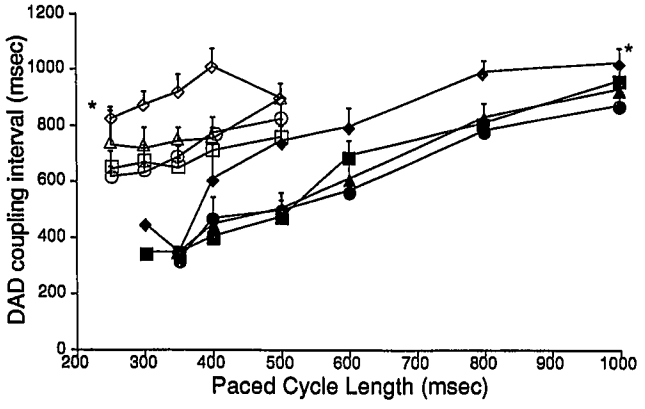

Fig. 3. Isoflurane 2% increased the coupling interval of ouabain-induced delayed afterdepolarizations (n = 8). The coupling intervals of delayed afterdepolarizations at paced cycle lengths from 250 to 1,000 ms are shown for isoflurane 0% (ouabain-toxic) (squares), isoflurane 0.5% (circles), isoflurane 1.0% (triangles), and isoflurane 2.0% (diamonds). Filled symbols = coupling intervals for primary delayed afterdepolarizations; open symbols = coupling intervals for secondary delayed afterdepolarizations. Isoflurane 2% prolonged the coupling intervals of primary and secondary delayed afterdepolarizations. *$P \leq 0.05$ *versus* all other conditions.

effect of paced cycle length on delayed afterdepolarization amplitude ($P \leq 0.0001$). There was no significant interaction between paced cycle length and isoflurane concentration ($P = 0.66$ for DAD1 amplitude; $P = 0.15$ for DAD2 amplitude). By multiple-range analysis, for DAD1, each concentration of isoflurane reduced amplitude *versus* ouabain toxicity without isoflurane ($P \leq 0.05$), whereas isoflurane 2.0% also reduced DAD1 amplitude relative to isoflurane 0.5% ($P \leq 0.05$). For DAD2, all isoflurane concentrations reduced DAD2 amplitude *versus* isoflurane 0% (*i.e.*, ouabain toxicity). In addition, isoflurane 1% and 2% decreased DAD2 amplitude *versus* isoflurane 0.5% (all $P \leq 0.05$).

Figure 3 depicts the effects of isoflurane on the coupling intervals of DAD1 and DAD2 induced by ouabain superfusion. The effects of paced cycle length on coupling interval were highly significant ($P \leq 0.0001$ for DAD1 coupling interval; $P = 0.0063$ for DAD2 coupling interval). Of interest, isoflurane also produced a significant effect on coupling interval for both DAD1 and DAD2 ($P \leq 0.0001$). This effect was explained by significant prolongation by isoflurane 2% of the coupling interval of both DAD1 and DAD2 *versus* all other conditions ($P \leq 0.05$).

A typical experiment in which isoflurane reduced delayed afterdepolarization amplitude in a dose-related manner is shown in figure 4. In this example, at a paced cycle length of 500 ms, only a single delayed afterdepolarization is prominent. Another fiber (fig. 5), paced at a faster rate (200-ms cycle length) displayed a single triggered extrasystole followed by a prominent delayed afterdepolarization after superfusion with ouabain. Addition of isoflurane eliminated the extrasystole and progressively reduced the amplitude of the residual delayed afterdepolarization.

Table 1 summarizes the effects of ouabain and increasing doses of isoflurane on action potentials from Purkinje fibers paced at a cycle length of 500 ms. No significant changes in $\dot{V}_{max}$, action potential amplitude, or MDP were observed. APD_{50} was significantly reduced ($P = 0.036$), from a control value of 148.1 ± 6.68 mV to 111 ± 7.66 mV. APD_{90} was significantly reduced from the control value by ouabain ($P \leq 0.05$). Isoflurane 0.5% restored APD_{90} toward control, but isoflurane

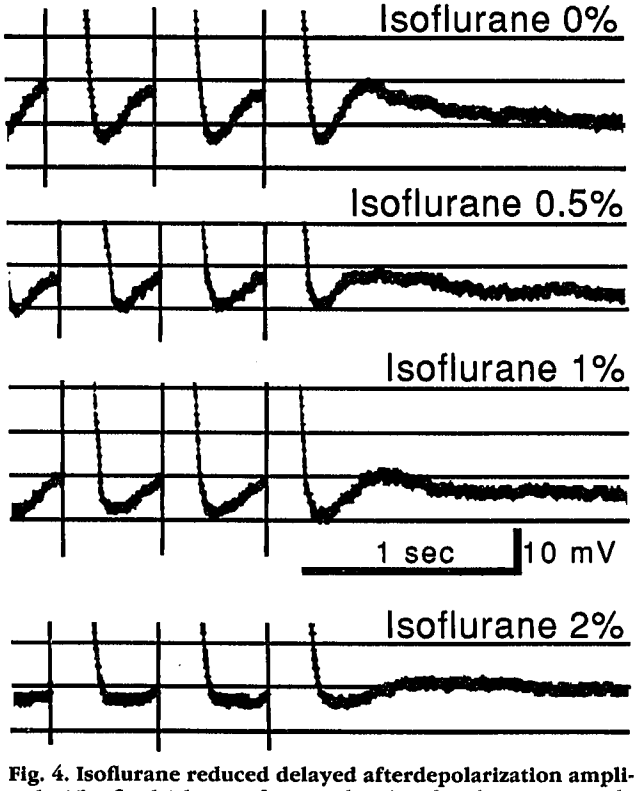

Fig. 4. Isoflurane reduced delayed afterdepolarization amplitude. The final 3 beats of a paced train of 20 beats at a cycle length of 500 ms are shown. After induction of ouabain toxicity (isoflurane 0%), a prominent delayed afterdepolarization appeared after termination of pacing. Isoflurane reduced delayed afterdepolarization amplitude in a dose-dependent manner.

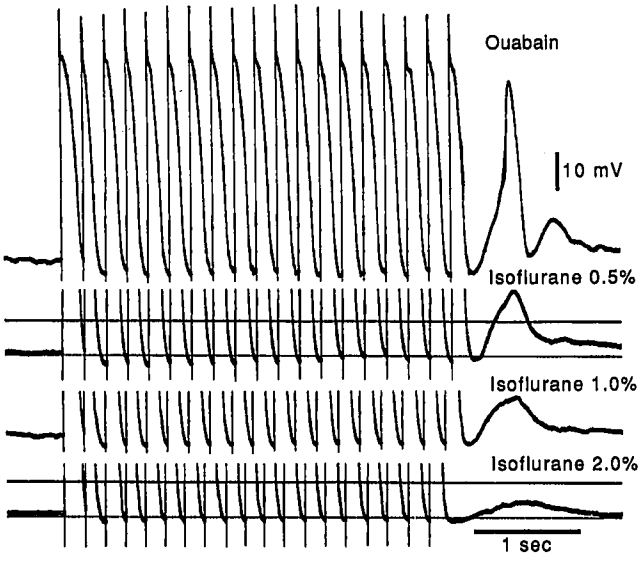

Fig. 5. Isoflurane eliminated triggered extrasystoles and reduced delayed afterdepolarization amplitude. In this example, a paced train of 20 beats at a 200-ms cycle length triggered a single extrasystole followed by a prominent delayed afterdepolarization. Increasing doses of isoflurane abolished the extrasystole and reduced the amplitude of the delayed afterdepolarization.

1.0% and 2.0% significantly reduced APD_{90} ($P \leq 0.05$ for both).

Effects of Isoflurane on Sustained Triggered Activity

In two fibers, during superfusion with ouabain, pacing induced sustained triggered activity (fig. 6). Isoflurane 1.25% was added to the superfusate after the arrhythmia had been stable for 8 min. After 49 s of isoflurane exposure, the arrhythmia terminated in a prominent delayed afterdepolarization. A different response was noted in the second fiber (fig. 7). A sustained triggered arrhythmia had persisted for 6 min 18 s when isoflurane 1.25% was added. Exposure to isoflurane 1.25% for 5 min 32 s slowed the cycle length of the arrhythmia but did not terminate the triggered activity. After increasing isoflurane concentration to 2.5% for 50 s, the arrhythmia terminated and displayed a residual delayed afterdepolarization.

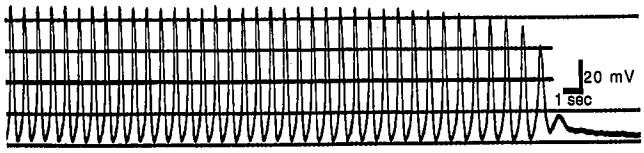

Fig. 6. Isoflurane 1.25% terminated sustained triggered arrhythmia in an ouabain-toxic Purkinje fiber. In this fiber, pacing after superfusion with ouabain triggered a stable arrhythmia that persisted for 8 min before isoflurane 1.25% was added to the superfusate. After 49 s, without changing the cycle length of the arrhythmia, isoflurane terminated the arrhythmia, revealing a prominent afterdepolarization.

Comparison Between Effects of Halothane and Isoflurane on Ouabain-induced Delayed Afterdepolarizations

Figure 8 summarizes the results of ten experiments comparing the effects of halothane and isoflurane on delayed afterdepolarizations induced by ouabain superfusion. Halothane 0.75% and isoflurane 1.25% each reduced the amplitudes of DAD1 ($P = 0.0002$) and DAD2 ($P \leq 0.0001$). There were no differences between halothane and isoflurane. Coupling interval was not affected by either agent. Figure 9 depicts a typical experiment showing both DAD1 and DAD2 after a 20-beat train of pacing at a cycle length of 500 ms. Both halothane 0.75% and isoflurane 1.25% comparably reduced the amplitude of the delayed afterdepolarizations.

In three of these fibers, pacing at shorter cycle lengths triggered extrasystoles after superfusion with ouabain.

Table 1. Effects of Ouabain and Isoflurane on Action Potential Characteristics (n = 8)

	AP_{amp}	MDP	APD_{50}	APD_{90}	$\dot{V}_{max}$
Control	103.0 ± 2.19	−73.8 ± 1.15	148.1 ± 6.68	223.8 ± 4.51	300 ± 32.4
Ouabain	95.0 ± 3.74	−77.5 ± 2.09	121.3 ± 9.34	188.8 ± 5.81*	200 ± 29.1
Isoflurane 0.5%	98.6 ± 1.64	−80.1 ± 2.03	127.5 ± 7.50	196.3 ± 5.65	263 ± 39.5
Isoflurane 1.0%	99.9 ± 2.30	−77.8 ± 1.90	117.5 ± 9.96	188.8 ± 10.43*	269 ± 36.5
Isoflurane 2.0%	102.5 ± 2.22	−77.4 ± 1.93	111.3 ± 7.66*	191.3 ± 9.15*	250 ± 30.3

AP_{amp} = action potential amplitude; MDP = maximum diastolic potential; APD_{50}, APD_{90} = action potential duration to 50% and 90% repolarization, respectively; $\dot{V}_{max}$ = maximum rate of rise of phase 0.

* $P \leq 0.05$ *versus* control.

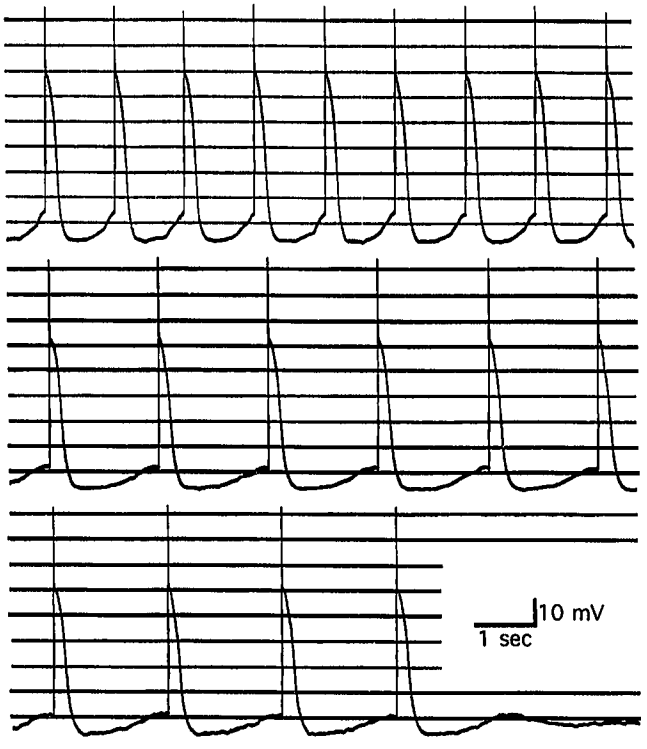

Fig. 7. Progressive slowing and ultimate termination of triggered arrhythmia in an ouabain-toxic Purkinje fiber. Pacing after superfusion with ouabain triggered a sustained arrhythmia that persisted for 6 min 18 s before addition of isoflurane (*top*). Isoflurane 1.25% administered for 5 min 32 s slowed but did not terminate the arrhythmia (*middle*). Addition of 2.5% isoflurane further slowed the triggered activity, and after 50 s the arrhythmia terminated (*bottom*).

Table 2 summarizes the effects of halothane and isoflurane on these extrasystoles. In two of the three fibers, halothane 0.75% and isoflurane 1.25% were equally effective in abolishing triggered extrasystoles as demonstrated in figure 10. In the third fiber, at the fastest paced rate tested (200-ms cycle length), halothane was unable to abolish the extrasystole. After superfusion with ouabain, a triggered extrasystole and large delayed afterdepolarization were seen. Isoflurane, administered before halothane in this case, abolished the triggered activity, leaving a prominent delayed afterdepolarization. Halothane 0.75% was unable to prevent the triggered extrasystole.

Discussion

The data presented demonstrate that isoflurane, in a dose-related manner, reduces the amplitude of delayed afterdepolarizations induced by toxic concentrations of the cardiac glycoside ouabain. Also, at roughly equivalent concentrations, halothane and isoflurane have similar effects. In a few experiments, triggered extrasystoles and sustained arrhythmias, more severe forms of ouabain toxicity, occurred. Isoflurane abolished these arrhythmias, which are perhaps more akin to the clinical situation.

The effects of ouabain and isoflurane on canine Purkinje fiber action potentials were largely consonant with previous reports. Ouabain intoxication depolarizes MDP, shortens action potential duration, and reduces $\dot{V}_{max}$.[22] Inhibition of sarcolemmal Na^+,K^+-ATPase reduces intracellular K^+ concentration, reducing MDP as predicted by the Nernst equation.[21] Na^+,K^+-ATPase also provides 2–6 mV of hyperpolarization to the resting membrane voltage.[23] Loss of this potential contributes to the reduced membrane potential after ouabain.[23] Partial inactivation of the Na^+ current from the decreased membrane potential and increased intracellular Na^+ combine to reduce $\dot{V}_{max}$.[24,25] Increased K^+ conductance during the plateau phase is one mechanism that can lead to a reduction of APD.[26] Activation of Ca^{2+} dependent K^+ currents due to the increase in intracellular Ca^{2+} may also contribute.[27] In the present study, only the shortened APD achieved statistical significance, in contrast to previous studies where only action potential amplitude was significantly reduced

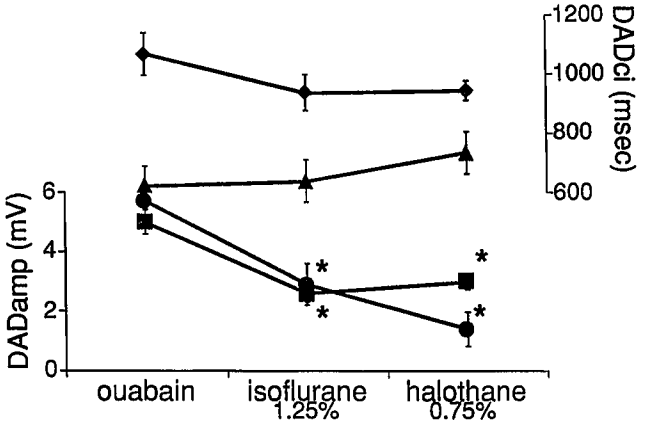

Fig. 8. Effects of halothane and isoflurane on ouabain-induced delayed afterdepolarizations (n = 10). Both halothane 0.75% and isoflurane 1.25% decreased the amplitudes of primary (DAD1) and secondary (DAD2) delayed afterdepolarizations. Neither agent altered delayed afterdepolarization coupling interval. No differences between the two agents were apparent. Paced cycle length 500 ms. Squares = DAD1 amplitude; circles = DAD2 amplitude; triangles = DAD1 coupling interval; and diamonds = DAD2 coupling interval. *$P \leq 0.05$ *versus* ouabain.

and decreased background inward current.[46] Repolarizing currents increased by lidocaine shorten action potential duration and limit influx of Na^+ through the window current. This and lidocaine-induced inhibition of the fast inward current may reduce cellular Na^+ concentration, limiting Ca^{2+} loading through Na^+–Ca^{2+} exchange.[46,47] Reduction of ischemic damage by preventing the increase in intracellular Na^+ by R56865, a compound that blocks noninactivating components of the Na^+ current, corroborates the role of Na^+ influx in Na^+–Ca^{2+} exchange.[44] Adriamycin has been suggested to directly block the transient inward current, but another fascinating possibility is that adriamycin changes membrane resistance.[48] If adriamycin reduced slope resistance, a transient inward current of equal magnitude would produce smaller changes in membrane potential (*i.e.*, a smaller delayed afterdepolarization).[48]

Neither halothane nor isoflurane displayed differential effects on block at short *versus* long paced cycle lengths, as shown by the lack of significant interaction terms in the data analysis of the present results and earlier studies.[14] As with lidocaine, multiple effects on a variety of cell currents may contribute to the reduction in delayed afterdepolarization amplitude.[49–53]

In a previous report of halothane in a ouabain toxicity model, delayed afterdepolarization coupling interval did not change.[14] In the present study 2% isoflurane, the highest dose studied, prolonged coupling interval. The significance of this finding is uncertain, but implies an alteration in the kinetics of delayed afterdepolarizations. Previous studies on the effects of a variety of agents on ouabain-induced delayed afterdepolarizations, including tetrodotoxin, lidocaine, and verapamil,[46] did not note changes in delayed afterdepolarization coupling interval. Adriamycin had no effect on coupling interval while reducing amplitude.[48] Further study will be required to elucidate the cause and significance of this finding.

Whether the findings of this investigation apply to humans can only be determined after verification in intact subjects with functioning autonomic nervous systems. Parasympathetically mediated effects of digitalis typically cause sinus node slowing, sinoatrial block or atrioventricular block.[2] Sympathetic stimulation facilitates digitalis toxicity in atrial and ventricular specialized conducting tissue.[2] Both, for example, increase the rate of phase 4 depolarization.[3] Endogenous catecholamine release or intact cardiac sympathetic nerves facilitate the toxic effects of digitalis.[54]

Isoflurane reduces the chronotropic response to both sympathetic and vagal stimulation.[55] Despite depression of both limbs of the autonomic system, greater depression of parasympathetic than sympathetic tone accounts for the hemodynamic responses to isoflurane.[56] Especially during rapid increases in isoflurane concentration, tachycardia and hypertension may occur.[18] By increasing delayed afterdepolarization amplitude, tachycardia predisposes to triggered activity.[57] Halothane, in contrast, reduces sympathetic outflow by several mechanisms and rarely causes tachycardia.[58] Thus, in the presence of an intact nervous system, isoflurane could conceivably enhance digitalis toxicity. Only studies in intact animals will determine whether isoflurane displays a clinically relevant effect, either increasing or decreasing cardiac glycoside toxicity. Nonetheless, the results of the present study demonstrate that isoflurane, like halothane, antagonizes a major electrophysiologic mechanism of cardiac glycoside toxicity, delayed afterdepolarization induced triggered activity.

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