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Atrial-Selective Effects of Chronic Amiodarone in the Management of Atrial Fibrillation

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Abstract

Background—Although amiodarone is one of the most effective pharmacologic agents used in clinical management of atrial fibrillation (AF), little is known about its differential effects in atrial and ventricular myocardium.

Objectives—To compare the electrophysiological effects of chronic amiodarone in atria and ventricles.

Methods—We compared the electrophysiological characteristics of coronary-perfused atrial and ventricular wedge preparations isolated from untreated and chronic amiodarone-treated dogs (Amiodarone, 40 mg/kg/day for 6 weeks, n=12).

Results—Chronic amiodarone prolonged action potential duration (APD₉₀) predominantly in atria compared to ventricles and prolonged the effective refractory period (ERP) more than APD₉₀ in both ventricular and atrial preparations (particularly in the latter), due to the development of post-repolarization refractoriness. Amiodarone reduced dispersion of APD₉₀ in both atria and ventricles. Although maximum rate of rise of the action potential upstroke ($V_{\max}$) was significantly lower in both atria and ventricles of amiodarone-treated hearts vs. untreated controls, the reduction of $V_{\max}$ was much more pronounced in atria. Amiodarone prolonged P wave duration more significantly than QRS duration, reflecting greater slowing of conduction in atria vs. ventricles. These atrioventricular distinctions were significantly accentuated at faster activation rates. Persistent acetylcholine-mediated AF could be induced in only 1/6 atria from amiodarone-treated vs. 10/10 untreated dogs.

Conclusions—Our results indicate that, under the conditions studied, chronic amiodarone has potent atrial-predominant effects to depress sodium channel-mediated parameters and that this action of the drug is greatly potentiated by its ability to prolong APD predominantly in the atria, thus contributing to its effectiveness to suppress AF.

Keywords

Atrial fibrillation; arrhythmias; pharmacology; antiarrhythmic drugs; supraventricular

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INTRODUCTION

The risk of developing severe ventricular arrhythmias and/or organ toxicity by currently available drugs used to treat atrial fibrillation (AF) has prompted the development of atrial-specific and selective antiarrhythmic agents. The principal focus has been on the development of agents that selectively inhibit the ultra-rapid delayed rectifier outward potassium channels (I_{Kur}), taking advantage of the presence of these channels in atria, but not ventricles.¹ Recent experimental studies have suggested another approach using atrial selective/predominant sodium channel blockers, such as ranolazine, which are effective in suppressing AF.² This atrial selectivity is due to atrioventricular differences in the action potential characteristics and differences in biophysical properties of atrial and ventricular sodium channels.²

Amiodarone is a multi-ion channel blocker widely used in the management of both atrial and ventricular arrhythmias, although associated with both cardiac and extra-cardiac toxicity, it is likely the most effective agent available for the long-term treatment of AF.³⁻⁵ A unique characteristic of amiodarone is its delayed electrophysiological actions, which generally take weeks to reach a full effect.^{3,4} Because the ion channel block profile and kinetics of interaction of amiodarone with the sodium channel are similar to those of ranolazine,^{2,4,6} we hypothesized that the effects of chronic amiodarone, like those of ranolazine, may be atrial selective. The present study was designed to test this hypothesis using coronary-perfused atrial and ventricular preparations isolated from dogs chronically treated with amiodarone for 6 weeks.

METHODS

This investigation conforms to the Guide for Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication No 85-23, Revised 1996) and was approved by the Animal Care and Use Committee (ACUC) of the Masonic Medical Research Laboratory.

Dogs were chronically administered amiodarone orally at a dose of 40 mg/kg/day for a period of 6 weeks. Electrocardiographic measurements were obtained from conscious dogs at baseline and after 6 weeks of drug administration (Table 1).

In vitro experiments were performed using isolated arterially-perfused canine right atrial (RA) preparations and left ventricular (LV) arterially-perfused wedge preparations ($\approx 3.0 \times 1.2 \times 1.2$ cm). The methods used for isolation and perfusion of these preparations have been described in previous publications.^{2,6,7} Briefly, the preparations were dissected from hearts removed from anesthetized (sodium pentobarbital) adult mongrel dogs (20 to 25 kg), untreated or treated with chronic amiodarone. Unfolded RA with a rim of the right ventricle attached was cannulated and perfused through the ostium of the right coronary artery and the LV wedge was perfused through a branch of the left anterior descending coronary artery. Unperfused tissue was removed with a razor blade or scissors. The cut ventricular and atrial branches were ligated using silk thread. After these procedures (performed in cold cardioplegic solution, 4 to 8° C), the preparations were transferred to a temperature-controlled bath and arterially-perfused with Tyrode's solution by use of a roller pump. The composition of the Tyrode's solution was (in mM): NaCl 129, KCl 4, NaH_2PO_4 0.9, NaHCO_3 20, CaCl_2 1.8, MgSO_4 0.5, and D-glucose 5.5, buffered with 95% O_2 and 5% CO_2 ($37 \pm 0.5^\circ \text{C}$, pH=7.35).

Transmembrane action potential (AP) recordings were obtained using standard or floating glass microelectrodes. A pseudo-electrocardiogram (ECG) was recorded using two electrodes consisting of Ag/AgCl half cells placed in the Tyrode's solution bathing the preparation, 1.0 to 1.2 cm from the two opposite sides of the atrial or ventricular coronary-perfused preparations. Effective refractory period (ERP) was measured by delivering premature stimuli at progressively shorter S1-S2 intervals after every 10th basic beat applied at a pacing cycle length

(CL) of 500 ms (5 ms steps with $2 \times$ diastolic threshold of excitation). Post-repolarization refractoriness (PRR) was recognized when ERP exceeded APD₉₀ in the ventricle and APD₇₅ in atria. Ventricular ERP coincided with APD₉₀, whereas atrial ERP generally coincided with APD₇₅.² Stable action potential recordings and the maximum rate of rise of the AP upstroke ($V_{\max}$) measurements could not be readily obtained in vigorously contracting perfused preparations. The largest recorded $V_{\max}$ values per condition were taken for statistical comparison. Due to a substantial inter-preparation variability, $V_{\max}$ values were normalized for each experiment and then averaged. Changes in conduction velocity (CV) were approximated by measuring the duration of the “P wave” complex in atria and the “QRS” complex in ventricles on the ECG at a level representing 10% of “P wave” or “QRS” amplitude. APD₉₀ dispersion in atria was measured as the difference between endocardial crista terminalis (CT) and pectinate muscle (PM) regions (juxtaposed regions giving rise the largest APD dispersion in canine RA⁷) and in ventricles as the difference between M cell and epicardial regions.

Experimental Protocols

The equilibration period for the preparations was 30 to 120 min. The electrical parameters described above were measured at a pacing CL of 500 and 300 ms. Changes in $V_{\max}$, QRS, and P wave were determined on the 15-25th beat upon accelerations from a CL of 500 to 300 ms (the changes reached a steady or nearly steady state in 5-12 beats). To assess the antiarrhythmic potential of chronic amiodarone in atria, we used acetylcholine ((ACh), 0.5-1.0 μ M) together with burst pacing in an attempt to induce persistent AF in coronary-perfused right atria.^{2, 8}

Drugs

Amiodarone (Cordarone[®], 200 mg TAB, Wyeth Pharmaceuticals, Vonore, TN) was chronically administered orally at a dose of 40 mg/kg/day for a period of 6 weeks. Acetylcholine (SIGMA, MO) and E-4031 (Eisai Co Ltd, Japan) were dissolved in distilled water and prepared fresh as a stock of 1 mM before each experiment.

Statistics

Statistical analysis was performed using paired or unpaired Student's t test and one way repeated measures or multiple comparison analysis of variance (ANOVA) followed by Bonferroni's test, as appropriate. All data are expressed as mean $\pm$ SD. Statistical significance was assumed at $p < 0.05$.

RESULTS

Chronic amiodarone treatment significantly slowed the heart rate and prolonged the QT and QTc intervals of conscious dogs (Table 1). The QRS duration was unchanged, but P wave duration was significantly prolonged.

APD₉₀ and ERP were significantly longer in both atrial and ventricular preparations isolated from chronic amiodarone-treated dogs, compared to the respective tissues isolated from untreated animals (Fig. 1 and 2). Amiodarone-induced APD₉₀ and ERP prolongation were greater in atria vs. ventricles. ERP increased to a greater degree than APD₉₀ in both atria and ventricles, particularly in the atria, due to development of PRR (Fig. 2). The greater ERP prolongation in atria is in part due to the predominant prolongation of atrial APD (Fig. 1) and in large part due to the development of PRR (Fig. 2). Atrial dispersion of APD₉₀ was smaller in chronic amiodarone-treated dogs than in untreated dogs (10 ± 7 vs. 23 ± 8 ms, $p < 0.05$, $n = 7-16$; CL = 500 ms). Ventricular APD₉₀ dispersion was also smaller in chronic amiodarone-treated dogs (20 ± 12 vs. 35 ± 21 ms, $p = 0.056$, $n = 8-12$).

In another series of experiments, we examined the cellular mechanism(s) responsible for the predominant prolongation of atrial APD₉₀ by chronic amiodarone. In our previous study, acutely administrated ranolazine and propafenone prolonged atrial, but not ventricular APD₉₀.^{2, 9} In that amiodarone, ranolazine, and propafenone all inhibit I_{Kr} (along with other currents),^{4, 6, 10} we compared the effects of the specific I_{Kr} blocker E-4031 in atrial and ventricular preparations isolated from untreated dogs. E-4031 induced a predominant prolongation of APD₉₀ in the atrial preparations (Fig. 3). E-4031 prolonged atrial ERP and APD₇₀ proportionally (from 154±16 to 207±21 ms and from 151±12 to 208±17 ms, respectively).

Chronic amiodarone depressed V_{max} in both atrial and ventricular preparations, but more markedly in the former (Fig. 4). At a pacing CL of 500 ms, V_{max} was 42% lower in atria from chronic amiodarone vs. untreated controls, but only 9% lower in the ventricles. Atrioventricular differences in V_{max} were still more exaggerated at rapid pacing rates in the amiodarone-treated group. Figure 4 shows that in preparations isolated from chronic amiodarone-treated dogs, acceleration of the stimulation rate from a CL of 500 to 300 ms leads to marked rate-dependent depression of V_{max} in atrial, but not in ventricular tissue. At a CL of 300 ms, V_{max} was 65% lower in atria from amiodarone vs. untreated controls, but only 16% lower in ventricles (Fig. 4). This rate-dependent predominant depression of V_{max} in atria vs. ventricles by chronic amiodarone is in part due to a more pronounced prolongation of the APD in atria (Fig. 4C). In addition, chronic amiodarone prolonged the “P wave” duration much more than the “QRS” duration and did so in a rate-dependent fashion, reflecting a much greater slowing of conduction in atria (Fig. 5). There was no washout of the electrophysiologic effects of chronic amiodarone in *in vitro* experiments with time. Atrial ERP measured 90 and 300 minutes after the start of coronary-perfusion was 237±31 and 234±27 ms, respectively (CL = 500 ms, PM, n=4).

In atria isolated from untreated dogs, ACh dramatically abbreviated APD and ERP permitting very rapid pacing and precipitation of persistent AF in 10/10 atria (Fig. 6 and Table 2). However, persistent ACh-mediated AF could be induced in only 1/6 atria isolated from chronic amiodarone-treated dogs (Table 2). This anti-AF effect of chronic amiodarone was associated with a smaller ACh-induced APD₇₅ abbreviation and the development of a greater PRR (Table 2). At rapid activation rates, PRR was much longer resulting in 2:1 activation failure at a pacing CL of 136±22 ms in chronic amiodarone vs. 56±15 ms in untreated controls.

DISCUSSION

Our findings show that chronic amiodarone therapy is capable of exerting profound rate-dependent depression of sodium channel-dependent parameters in atrial but not ventricular preparations and that this action of the drug contributes prominently to its effectiveness in preventing the induction of AF. Our results suggest that the effect of chronic amiodarone to produce a predominant prolongation of the atrial action potential potentiates the depression of sodium channel-dependent parameters, thus contributing to its antiarrhythmic efficacy. The combination of Class I and Class III actions likely accounts for the high efficacy of chronic amiodarone in the management of AF.

The pharmacologic and electrophysiological profile of amiodarone

Amiodarone has been shown to inhibit multiple cardiac ionic currents (I_{Kr}, I_{Ks}, I_{Na}, late I_{Na}, I_{to}, I_{Ca-L}, I_{Ca-T}, I_{K1}, I_{K(ACh)}, I_{K(ATP)}) as well as to block α- and β-adrenoceptors.⁴ Although possessing the properties of all four Vaughan Williams classes of antiarrhythmic agents, amiodarone is still often classified as a Class III antiarrhythmic.^{3,4} Amiodarone is a predominantly inactivated-state sodium channel blocker with rapid binding and unbinding kinetics (similar to a Class IB agent).⁴ However, there are important differences in the electrophysiological actions of acute and chronic amiodarone in the heart. With respect to

effects on the delayed rectifier potassium currents, acute amiodarone has been shown to primarily inhibit I_{Kr} , whereas chronic amiodarone also leads to a reduction of I_{Ks} .¹¹ Whereas the effects of acute amiodarone on ventricular APD are controversial with prolongation, abbreviation and no effect being reported,⁴ chronic amiodarone consistently prolongs ventricular APD and the QT interval.⁴ Both acute and chronic amiodarone prolong ERP more than APD, due to development of PRR.^{12,13} While acute amiodarone reduces V_{max} and blocks I_{Na} in practically all studies,⁴ chronic amiodarone was reported to either depress V_{max} ^{14, 15} or, in most studies, to cause no or little changes in V_{max} in superfused ventricular muscle and Purkinje fibers.^{4,16} Ventricular CV is slowed and QRS duration is prolonged in both acutely and chronically amiodarone-treated humans and animals *in vivo*.¹⁶⁻¹⁸ However, the QRS interval was significantly prolonged only at relatively rapid pacing rates (e.g., at CL of ≤ 500 ms in humans), displaying a non-statistically significant prolongation at normal or slow heart rates,¹⁸ consistent with our results in the dog. In rabbit atrial superfused tissue preparations, acute amiodarone produces an abbreviation of APD and a reduction in V_{max} , while chronic amiodarone prolongs APD and causes little changes in V_{max} .¹⁹ In studies in which direct atrial and ventricular comparisons were made, acute amiodarone produced similar prolongation of ERP in atria and ventricles in *in vivo* dogs (without QTc prolongation)²⁰ and chronic amiodarone caused similar prolongation of APD and a small V_{max} reduction in rabbit superfused atrial and ventricular preparations.²¹

Predominant prolongation of APD₉₀ in atria

Our results indicate that chronic amiodarone predominantly prolongs APD in atrial preparations (Fig. 1), similar to that previously reported for acute ranolazine² and propafenone,⁹ all of which are I_{Kr} blockers.^{4,6,10} Our demonstration of an atrial-predominant effect of E-4031, a selective I_{Kr} blocker (Fig. 3), suggests that I_{Kr} blockade produces a predominant prolongation of atrial APD, which likely contributes to the atrial specific/predominant APD₉₀ prolongation by chronic amiodarone, ranolazine and propafenone. Note that I_{Ks} block, another potential candidate, has been reported to prolong ERP predominantly in canine ventricles vs. atria.²² Our data are consistent with those of previously reported results, showing that I_{Kr} blockers predominantly prolong the atrial ERP at normal pacing rates.²³ At slow pacing/heart rates, however, ventricles, but not atria, develop significant APD prolongation, early afterdepolarizations, and Torsade de Pointes under conditions of reduced I_{Kr} .²⁴⁻²⁶

Block of late I_{Na} by amiodarone²⁷ serves to oppose the effect of I_{Kr} inhibition to prolong APD and thus may contribute to the different effects of the drug to prolong APD in atria vs. ventricles. This would be the case if amiodarone block of late I_{Na} was greater in ventricles vs. atria, thus attenuating the amiodarone-induced APD prolongation in the ventricle but not (or less so) in the atria. However, no data are available regarding atrioventricular differences in late I_{Na} and it is not known if the effect of amiodarone to inhibit late I_{Na} is different in atria vs. ventricles. It is also unclear whether alterations in I_{Ca-L} , $I_{Ca(T)}$, I_{to} , I_{K1} , or $I_{K(ACh)}$ participate in the atrioventricular differences in response to chronic amiodarone. Amiodarone appears to only weakly inhibit I_{Kur} .²⁸ It is noteworthy that block of I_{Kur} in canine non-remodeled atria abbreviates APD₉₀,^{7,29} so that I_{Kur} reduction cannot explain our results.

Atrial predominant depression of sodium channel-dependent parameters

The present results show that chronic amiodarone produces rate-dependent depression of V_{max} , excitability and CV and induces PRR (sodium channel-dependent parameters) predominantly in atrial vs. ventricular preparations (Figs. 2, 4, and 5). Factors contributing to these atrial-predominant rate-dependent effects of chronic amiodarone include: 1) the fact that half inactivation voltage ($V_{0.5}$) in canine atrial myocytes is 16 mV more negative than that of ventricular myocytes (LV, Epicardial and Endocardial cells combined);² 2) resting membrane potential (RMP) in atria is more depolarized than in ventricles (approx. -83 vs. -87 mV); 3) a

slower phase 3 repolarization in atria leads to disappearance of the diastolic interval and depolarization of take-off potential at rapid rates. These factors contribute to a larger fractional inactivation of sodium channels in atria vs. ventricles and, because amiodarone is a predominantly inactivated-state sodium channel blocker,^{4,10} facilitate its binding and slow its unbinding (which occur during the resting state) in atria vs. ventricles.¹⁰ Hence, greater APD prolongation in atria vs. ventricles by chronic amiodarone promotes atrial-predominant sodium channel blockade due to a more pronounced reduction, or even elimination, of the diastolic interval at rapid rates (Fig. 4).

A tentative mechanism of the development of atrial-selective prolongation of ERP due to PRR in the presence of I_{Na} blockers is illustrated in figure 2. Under control conditions, ERP is largely determined by the recovery from inactivation of Na^+ channels responsible for early I_{Na} . In the presence of an I_{Na} blocker, the recovery from Na^+ channel block largely determines ERP. Both effects are voltage-dependent. Recovery from Na^+ channel block in atria displaying a shallow phase 3 repolarization within the -57 to -83 mV range is expected to be much slower than is ventricles displaying a steep phase 3 repolarization within the -75 to -86 mV range, thus contributing to predominant prolongation of ERP in atria following chronic amiodarone.

Amiodarone as an antiarrhythmic agent

In the clinic, acute and chronic amiodarone are widely used in the management of atrial and ventricular arrhythmias.^{3,5} Chronic amiodarone is considered to be one of the best, if not the best, pharmacological agent currently available for the maintenance of sinus rhythm after AF termination.³ The anti-arrhythmic efficacy of chronic amiodarone has been related to a number of factors including APD/ERP prolongation, reduction of dispersion of repolarization, induction of PRR, prolongation of excitable gap, suppression of triggered activity and inhibition of atrial electrical and structural remodeling.^{3,5,13,15,30} The results of our study suggest that the primary mechanism responsible for the anti-AF effect of chronic amiodarone in the canine ACh-mediated AF model is via blockade of sodium channel activity. Indeed, prolongation of refractoriness at rapid rates, secondary to development of PRR, was much greater than the prolongation of atrial APD (Table 2). The ability of amiodarone to directly block I_{KACH} may be involved in its anti-AF action as well.

Atrial-selective approaches for the management of AF

Atrial-selective agents currently being developed for the management of AF are designed to target I_{Kur} , I_{KACH} , or connexin 40.¹ Our group recently introduced the concept of atrial-selective sodium channel block for the treatment of AF,² based on the finding that the biophysical characteristics of sodium channels as well as action potential characteristics differ between atrial and ventricular myocytes.^{2,9} Ranolazine, and less so lidocaine, suppressed sodium channel-dependent parameters (V_{max} , CV, and diastolic threshold of excitation) and produced PRR predominantly in atria vs. ventricles. In contrast, propafenone was not chamber-selective in suppressing these parameters. Ranolazine and propafenone were effective, and lidocaine less so, in suppressing and preventing the induction of ACh-mediated AF.^{2,9}

Interestingly, antiarrhythmic agents that block both I_{Na} and I_{Kr} (like propafenone, quinidine, disopyramide, flecainide, etc) have relatively slow unbinding kinetics from the sodium channel (with a τ of ≥ 6 sec),¹⁰ with at least propafenone being not atrial-selective. In contrast, agents like ranolazine and amiodarone, which block both I_{Na} and I_{Kr} ,^{4,6} but which have relatively rapid unbinding kinetics from the sodium channel ($\tau = 1.56 \pm 56$ and 0.3 to 1.6 sec, respectively)^{2,4} are atrial-selective. The combination of rapid dissociation of drug from the sodium channel and an ability to predominantly prolong atrial APD, secondary to I_{Kr} block, appear to be important features for atrial-selective depression of sodium channel dependent parameters and anti-AF efficacy.^{2,31} The present study suggests that these same characteristics are shared by

chronic amiodarone. Interestingly, during initial characterization of ranolazine in ventricular myocytes in 2004, we noted the similarity between the ion channel block profile of ranolazine and that of chronic amiodarone.⁶

Study limitations

Extrapolation of the results of any investigation conducted in *in vitro* animal models, as our study, to the clinic or to the understanding of *in vivo* phenomenon, must be done with due caution. The absence of exogenous autonomic modulators and other hormones absent in isolated Tyrode's perfused preparations may affect the results. A greater lengthening of P wave vs. QRS in both *in vivo* and *in vitro* studies indicates to similarities in these two. The dose of chronic amiodarone used in our study (40 mg/kg/day) was larger than that used in the clinic, where the loading dose of amiodarone ranges from 800 to 1600 mg/day (which is up to 20 to 25 mg/kg/day). However, pharmacokinetic characteristics of amiodarone such as bioavailability, half-life of elimination and partition into slowly equilibrating tissues (e.g., myocardial) may justify different dosing in dogs and man.³² The atrial-selectivity of chronic amiodarone observed in "healthy" preparations studied in the present study may be different under pathophysiologic conditions in which the heart may be electrically or structurally remodeled.

CONCLUSIONS

Our results indicate that the effect of chronic amiodarone to inhibit sodium and potassium channel activity results in more accentuated changes in action potential parameters in "healthy" coronary-perfused canine atria vs. ventricles. Chronic amiodarone effectively prevents AF in "pharmacologically remodeled" (ACh-treated) atria. To our knowledge, this study is the first to demonstrate an atrial-predominant effect of chronic amiodarone.

Our results suggest that the effectiveness of chronic amiodarone to suppress AF is due largely to its effects to depress sodium channel current-mediated parameters, and that these effects of the drug are greatly potentiated by its effect to also prolong action potential duration. Thus, atrial-predominant APD prolongation, due in large part to blockade of I_{K_r} , serves to synergize the other action of the drug, suggesting that inhibition of I_{K_r} in the atria is a desirable quality and may be a key factor in the antiarrhythmic potency of pharmacologic agents. Indeed, "pure" I_{Na} blockers are known to be less effective against AF (like lidocaine), than I_{Na} blockers that also inhibit I_{K_r} (like propafenone).

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ABREVIATION LIST

ACh	acetylcholine
AF	atrial fibrillation
AP	action potential
APD	action potential duration
CL	cycle length
ECG	electrocardiogram
ERP	effective refractory period
LV	left ventricular
PM	pectinate muscle
PRR	post-repolarization refractoriness
RA	right atrium

RMP	resting membrane potential
V_{0.5}	half inactivation voltage
V_{max}	maximum rate of rise of the AP upstroke

Figure 1.

Chronic amiodarone prolongs APD₉₀ predominantly in atria vs. ventricles. Upper panel: Superimposed action potential recorded from pectinate muscle in atrial and ventricular epicardial preparations isolated from untreated control (C) and amiodarone-treated dogs. Dashed lines denote the level of APD₉₀ and the numbers indicate the changes in APD₉₀ induced by chronic amiodarone. Lower panel: Graphs plot the average APD₉₀ data. CT – crista terminalis, PM – pectinate muscle, M cell – M cell region, Epi – epicardium. * $p < 0.05$ - vs. respective controls. N=7-16. CL = 500 ms.

Figure 2.

Chronic amiodarone predominantly prolongs ERP in atria vs. ventricle due to predominant prolongation of atrial APD and the development of PRR primarily in atria. PRR is defined as the difference of APD₇₅ and ERP in atria and APD₉₀ and ERP in ventricles (ERP corresponds to APD₇₅ in atria and APD₉₀ in ventricles,² contributing to a shorter ERP in atria). Upper panel: schematic illustration of the effects of chronic amiodarone to prolong ERP in atria and ventricles, through Na⁺ channel blockade. The arrows denote the position on the action potential corresponding to the end of the ERP in atria and ventricles and the effect of chronic amiodarone (Na⁺ channel block) to shift the end of the ERP predominantly in atria. C – Control. Bottom panel: Summary data from pectinate muscles in atria and epicardial region in ventricles at a CL of 500 ms (n = 3-10). * p<0.05 - vs. respective controls; † p<0.05 vs. APD₇₅. See “Discussion” for details.

Figure 3.

Why does amiodarone cause a preferential prolongation of atrial APD? The selective I_{Kr} blocker E-4031 (1 μ M) prolongs APD₉₀ in atria to a much greater extent than in ventricular preparations isolated from untreated control dogs. Atria – pectinate muscle; Ventricles – M cell region. * $p < 0.05$ vs. respective untreated control. † $p < 0.05$ vs. respective ventricles. $n=5-7$.

Figure 4. Chronic amiodarone produces a rate-dependent depression of maximum rate of rise of the action potential upstroke ($V_{\max}$) predominantly in atria vs. ventricles

A: Atrial-predominant rate-dependent depression of $V_{\max}$ following chronic amiodarone. CL = cycle length. **B:** Plot of normalized reduction in $V_{\max}$ ($n = 4-14$). "Atria" represent combined PM and CT data. "Ventricles" represent combined epicardial and M cell data. * $p < 0.05$ vs. untreated control. † $p < 0.001$ vs. control. **C:** Mechanism contributing to atrial selectivity of chronic amiodarone to depress $V_{\max}$ at rapid activation rates: Greater APD prolongation resulting in greater reduction or elimination of diastolic interval (during which recovery from Na^+ channel block primarily occurs) and a more positive take off potential. Dashed line indicates RMP in atria.

Figure 5.

Chronic amiodarone prolongs the duration of “P wave” complex in atrial preparations to a greater extent than the duration of “QRS” complex in ventricular preparations, reflecting a greater and rate-dependent slowing of conduction velocity in atria vs. ventricles. CL – cycle length. * $p < 0.05$ vs. control. † $p < 0.05$ vs respective CL = 500 ms. $n = 6-10$.

Figure 6. Chronic amiodarone prevents induction of AF in the presence of acetylcholine (ACh) by prolonging APD and reducing excitability, preventing rapid 1:1 activation

Upper panel: ECG and action potential (AP) tracings during pacing at CL of 100 and 70 ms in the presence of ACh leads to AF induction in an atrium isolated from an untreated dog.

Bottom panel: ECG and AP tracings during acceleration of pacing rate, leading to activation failure at a CL of 150 ms without arrhythmia induction in an atrial preparation isolated from a chronic amiodarone-treated dog.

TABLE 1
Effects of chronic amiodarone treatment on electrocardiographic parameters in the conscious dog *in vivo* (n= 12).

Heart Rate (bpm)		QRS (ms)		P wave (ms)		QT interval (ms)		QTc interval (ms)	
Pre-tr	Amio	Pre-tr	Amio	Pre-tr	Amio	Pre-tr	Amio	Pre-tr	Amio
140±21	102±16*	54±10	58±9	42±6	49±7*	208±20	248±16*	297±17	314±17*

The QT interval was corrected for changes in heart rate (RR interval) by the method of Bazett ($QT_c = QT / \sqrt{RR}$). Pre-tr – Pre-treatment.

* - p<0.05 vs. Pre-treated.

Electrophysiologic characteristics of atria and the incidence of persistent AF in atria isolated from untreated and amiodarone-treated dogs (AMIO) in the absence or presence of acetylcholine (ACh).

TABLE 2

	APD ₇₅ (ms)	ERP (ms)	PRR (ms)	Shortest S ₁ -S ₁ (ms)	Persistent AF
Untreated atria	149±12	148±15	-1±7	129±8	0/10
AMIO atria	183±6 [*]	232±26 [*]	51±21 [*]	222±39 [*]	0/12
Untreated atria+ACh	38±7	45±7	8±4	56±15	10/10
AMIO atria+ACh	69±13 [*]	105±28 [*]	36±18 [*]	136±22 [*]	1/6

Data were obtained from pectinate muscle region.

^{*} P<0.05 vs. respective untreated atria. N=6-10. CL = 500 ms. Shortest S₁-S₁ – the shortest CL permitting 1:1 activation.