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Atrial-selective Inhibition of Sodium Channel Current by Wenxin Keli is Effective in Suppressing Atrial Fibrillation

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Abstract

BACKGROUND—Wenxin Keli is a Chinese herb extract reported to be of benefit in the treatment of cardiac arrhythmias, cardiac inflammation and heart failure.

METHODS AND RESULTS—We evaluated the electrophysiologic effects of Wenxin Keli in isolated canine arterially-perfused right atrial preparations with a rim of right ventricular tissue (n=11). Transmembrane action potentials and a pseudo-electrocardiogram were simultaneously recorded. Acetylcholine (ACh, 1 μ M) was used to induce atrial fibrillation (AF) and to test the anti-AF potential of Wenxin Keli (5 g/L). Wenxin Keli produced preferential abbreviation of action potential duration (APD₉₀) in atria, but caused atrial-selective prolongation of effective refractory period, due to development of post-repolarization refractoriness. The maximum rate of rise of the action potential upstroke ($V_{\max}$) was preferentially reduced in atria. Diastolic threshold of excitation increased in both atria and ventricles, but much more in atria. The duration of the “P wave” (index of atrial conduction time) was prolonged to a much greater extent than the duration of the “QRS complex” (index of ventricular conduction time). Wenxin Keli significantly reduced I_{Na} and shifted steady-state inactivation to more negative potentials in HEK293 cells stably expressing *SCN5A*. Wenxin Keli prevented induction of persistent AF in 100% atria (6/6) and, in another experimental series was found to terminate persistent ACh-mediated AF in 100% of atria (3/3).

CONCLUSION—Wenxin Keli produces atrial-selective depression of I_{Na} -dependent parameters in canine isolated coronary perfused preparations via a unique mechanism and is effective in suppressing AF and preventing its induction, with minimal effects on ventricular electrophysiology.

Keywords

Antiarrhythmic drugs; atrial fibrillation; arrhythmias; electrophysiology; pharmacology

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Introduction

Effective and safe treatment of atrial fibrillation (AF) remains a major unmet medical need and the problem is growing as the prevalence of AF continues to increase with the aging of the population. AF is the most prevalent sustained clinical arrhythmia associated with increased morbidity and mortality. Its prevalence is 0.4-1% in the general population and greater than 8% in individuals >80 years of age. An estimated 2.5 million individuals in North America and 4.5 million in Europe are affected by AF. These numbers are projected to increase to up to 15 million in North America alone by 2050, largely due to aging of the population.

Despite significant progress in radiofrequency and cryoablation therapy, antiarrhythmic drugs (AADs) remain first-line therapy for rhythm control of AF.¹ However, the effectiveness and/or safety of agents available for the treatment of AF is less than optimal. Currently available pharmacologic strategies for the rhythm control of AF include: 1) sodium channel blockers, such as propafenone and flecainide; 2) potassium channel blockers (largely I_{Kr}), such as sotalol and dofetilide and 3) mixed ion channel blockers, such as amiodarone and dronedarone.

The development of safe and effective drugs for the management of AF remains a high priority.¹ A major disadvantage of most of the drugs in current use is the risk of induction of ventricular arrhythmias. This risk can be reduced with the use of agents that selectively affect atrial electrophysiological parameters. Inhibition of the ultra-rapid delayed rectifier potassium current, I_{Kur} , present in atria, but not in the ventricles, is an example of an atrial-selective approach that has attracted much of the focus of the pharmaceutical industry in recent years.² Recent studies have introduced the concept of atrial-selective block of peak sodium channel current as a novel approach for the management of AF, taking advantage of the electrophysiological distinctions between sodium channels of atrial and ventricular cells.³ A number of experimental studies have demonstrated the ability of sodium channel blockers like ranolazine, amiodarone and dronedarone to produce atrial-selective electrophysiological effects capable of effectively suppressing AF with minimal effects in the ventricle.³⁻¹⁰

Wenxin Keli is a Chinese herb extract reported to be of benefit in the treatment of cardiac arrhythmias, cardiac inflammation and heart failure. The extract is comprised of 5 components: *Nardostachys chinensis* batall extract (NcBe), *Codonopsis*, *Notoginseng*, *Amber*, and *Rhizoma polygonati*.

The present study was designed to evaluate the electrophysiologic effects and antiarrhythmic potential of Wenxin Keli in isolated canine arterially-perfused right atrial and ventricular preparations. We demonstrate an effect of Wenxin Keli to produce atrial-selective depression of I_{Na} -dependent parameters and to be effective in suppressing AF and preventing its induction, with minimal effects on ventricular electrophysiology.

Methods

Coronary-perfused canine right atrial preparations were used to study the effects of Wenxin Keli on electrophysiology of atrial and right ventricular parameters and on termination and induction of AF. Detailed methods are provided in the ONLINE SUPPLEMENT.

Effect of Wenxin Keli on acetylcholine (ACh)-induced AF

In the presence of 1 μ M ACh, persistent AF is induced in 100% of coronary-perfused atrial preparations. We tested the ability of Wenxin Keli to terminate AF and prevent its re-

induction in two separate series of experiments. In the first set, ACh was added to the perfusate 30-60 min after the start of Wenxin Keli (5 g/L) and followed by attempts to induce arrhythmias electrically (these experiments were performed in 6 preparations in which electrophysiological parameters were measured first). In the second set, Wenxin Keli was added to the perfusate during ACh-mediated persistent AF (on the 5-6th minutes after the start of the arrhythmia). In cases in which the drug successfully terminated AF, we attempted to re-induce AF with electrical stimulation.

Effect of Wenxin Keli on I_{Na} in HEK293 Cells

HEK 293 cells stably expressing WT-*SCN5A* and transiently transfected with WT-*SCN1B* using fucose were used to study the effect of Wenxin Keli on I_{Na} characteristics. Detailed methods are presented in the ONLINE SUPPLEMENT.

Statistics—Statistical analysis was performed using paired, unpaired t test as well as one way repeated measures or multiple comparison analysis of variance (ANOVA) followed by Bonferroni's test, as appropriate. All data are expressed as mean±SD. $p<0.05$ will be considered significant.

Results

Electrophysiological effects of Wenxin Keli in atria and ventricles

Wenxin Keli preferentially abbreviated APD₉₀ in atria, but caused atrial-selective prolongation of ERP (Figures 1 and 2). ERP prolongation in atria was rate-dependent, i.e., greater at a CL of 300 vs. 500 ms. This was due to development of rate-dependent PRR selectively in atria (Figure 2). At CLs of 300 and 500 ms Wenxin Keli induced on average 196±38 and 155±31 ms of PRR in atria, respectively, but little or no PRR in the ventricle. Thus, Wenxin Keli very significantly prolonged ERP and induced PRR selectively in atria despite producing a prominent abbreviation of APD. Wenxin Keli reduced V_{max} preferentially in atria vs. ventricles, decreasing V_{max} to 46±31 vs. 89±14% of control at a CL of 500 ms and to 24±21 vs. 76±17% of control at a CL of 300 ms, respectively (Figure 3). The rapid onset of use-dependent block and rapid recovery upon return to the slower rate suggest that the drug has rapid binding and unbinding kinetics in its association with the sodium channel. Wenxin Keli (5 g/L) also produced atrial-selective depression of excitability (approximated as an increase in DTE, Figure 4). Wenxin Keli prolonged the duration of the “P wave” in atria to a much greater degree than the duration of the “QRS complex” in the ventricles indicating a much greater slowing of conduction in atria vs. ventricles (Figure 4). The shortest S₁-S₁ permitting 1:1 activation was significantly increased by the drug in atria but not in the ventricles (Figure 5). Thus, all measured sodium channel current-dependent parameters (PRR, V_{max} , DTE, and conduction velocity) were preferentially depressed in atria by Wenxin Keli in a rate-dependent fashion.

Anti-atrial fibrillatory effect of Wenxin Keli—Persistent AF was inducible in 100% atria pre-treated with ACh (0.5 – 1.0 μM).^{3, 13} Wenxin Keli (5 g/L) prevented the induction of persistent AF in 100% of preparations tested (6/6 atria) (Fig. 6). In two atria, self-terminating atrial tachycardia (lasting up to 2 min) was induced and in one atrium a brief episode of AF (lasting < 3 sec) was induced by PES. Wenxin Keli (5 g/L) terminated persistent ACh-mediated AF in 100% atria (3/3 atria). No arrhythmia could be re-induced in these three atria. APD₉₀, ERP, and the shortest S₁-S₁ permitting 1:1 activation were significantly prolonged by Wenxin Keli in the presence of ACh (Figure 7, Table). The prime anti-arrhythmic mechanism of Wenxin Keli appears to be a significant rate-dependent depression of excitability, resulting in a prolonged PRR that does not permit rapid activation of the atria (Table, Figure 6).

Effect of Wenxin Keli on I_{Na} in HEK293 Cells

The effects of Wenxin Keli on cardiac sodium channels were functionally characterized in HEK293 cells. The electrophysiological study showed significant alteration in steady-state inactivation after exposure to Wenxin Keli ($n=4$ for each group; $V_{1/2}=-85.74\pm3.62$ mV and $k=7.16\pm0.53$ mV for control, $V_{1/2}=-98.48\pm2.74$ mV and $k=7.96\pm0.40$ mV for 5g/L Wenxin Keli, and $V_{1/2}=-102.92\pm2.61$ mV and $k=7.43\pm0.48$ mV for 10 g/L Wenxin Keli; $P<0.05$ for differences in $V_{1/2}$ compared with control, but $P>0.05$ in k compared with control; Figures 8A and B). Figure 8C shows use-dependent block (UDB) of I_{Na} elicited by a 20-ms pulse before and after exposure to Wenxin Keli. Figure 8D depicts the onset of the UDB caused by Wenxin Keli at stimulus frequencies of 1 and 10 Hz. Compared with control condition, 5 g/L Wenxin Keli caused significant use-dependent block at the higher frequency, which was accentuated when 10 g/L Wenxin Keli was applied ($n=4-6$ for each group).

Discussion

AF is a growing clinical problem associated with increased morbidity and mortality. Pharmacological agents remain first line therapy for rhythm control management of AF.¹ Agents that can effectively suppress AF and prevent its recurrence without substantial risk of adverse actions are highly desirable. The search for new anti-AF agents has largely been focused on the delineation of atrial-specific or selective targets/agents, in order to avoid or reduce the risk of induction of ventricular proarrhythmia. The most investigated atrial-selective target is the I_{Kur} , which is present in atria but not ventricles.¹⁴ Until recently, I_{Kur} was widely considered to be the most promising target for the treatment of AF.² It is becoming increasingly clear that I_{Kur} block alone is unlikely to be sufficient to effectively suppress AF.^{5, 7, 15-17}

Recent experimental studies have identified sodium channel blockers capable of producing atrial-selective electrophysiological effects and thus effectively suppressing AF.^{3, 4, 6, 8, 18} Ranolazine, chronic amiodarone, and AZD1305 reduce V_{max} , prolong conduction time and the shortest S_1 - S_1 permitting 1:1 activation, increase DTE, and induce PRR selectively or predominantly in atrial preparations when studied in experimental models such as coronary-perfused atrial and ventricular preparations.^{3, 4, 6, 18, 19} These agents are thus able to suppress AF without exerting significant depression of electrophysiological parameters in the ventricles. Mechanisms of atrial selectivity of I_{Na} blockers include a more depolarized resting membrane potential and more negative half-inactivation voltage in atrial vs. ventricular cells (discussed in detail elsewhere^{5, 10, 20}) both of which reduce the availability of sodium channels. Differences in AP morphology, particularly the more gradual phase 3 repolarization in atrial cells, contribute to atrial-selectivity of sodium channel blockade. This characteristic of the atrial action potential leads to progressive diminution or disappearance of the diastolic interval at rapid rates of activation, which reduces the ability of sodium channel blockers to dissociate from the sodium channel, thus leading to accumulation of sodium channel block. These distinctions between atrial and ventricular cell electrophysiology have fostered the emergence of a novel strategy for AF suppression, namely the atrial-selective sodium channel block.^{3, 7, 10}

Ranolazine, amiodarone, and AZD1305 have been shown to be capable of effectively suppressing AF, without or with minimal risk of induction of ventricular pro-arrhythmia in the clinic.²¹⁻²⁵ Recent experimental studies conducted in canine atrial and ventricular preparations have demonstrated that the combinations of chronic amiodarone and acute ranolazine as well as acute dronedarone and ranolazine (at a relatively low ranolazine concentration: 5 μ M) cause a potent synergistic atrial-selective depression of sodium channel-mediated parameters, causing the development of marked post-repolarization refractoriness.^{8, 26} Both combinations were shown to very effectively suppress and prevent

the induction of AF, while exerting little to no electrophysiological influence in the ventricles.^{8, 26}

A number of factors contribute to the anti-AF efficacy and safety of these atrial-selective sodium channel blockers, with block of peak and late I_{Na} as well as I_{Kr} working in concert (for review see^{5, 7, 10}). It is noteworthy that all atrial-selective I_{Na} blockers that have been identified thus far, also inhibit I_{Kr} and preferentially prolong APD in atria. APD prolongation in atria has been shown to potentiate the development of use-dependent block of I_{Na} due to reduction or elimination of diastolic interval, particularly at rapid pacing rates. These observations have led to the hypothesis that the most effective atrial-selective sodium channel blockers are those that dissociate from the sodium channel rapidly and that concomitantly block I_{Kr} or other outward currents responsible for atrial APD prolongation.^{3-5, 10}

The results of the current study demonstrate that Wenxin Keli causes potent atrial-selective depression of I_{Na} -mediated parameters, thus very effectively preventing induction of AF and acting to terminate persistent AF. These electrophysiological and anti-AF effects of Wenxin Keli are similar to those exerted by other atrial selective I_{Na} blockers (ranolazine, amiodarone, and AZD1305) in the canine heart.^{3, 4, 6, 18, 19} An important difference is that Wenxin Keli abbreviates APD₉₀, much more in atrial vs. ventricular cells (Figure 1), whereas ranolazine, amiodarone, and AZD1305 selectively prolong atrial APD₉₀.^{3, 4, 6, 18, 19} Thus, Wenxin Keli is able to induce very potent atrial-selective depression of I_{Na} -mediated parameters despite the fact that it significantly abbreviates the atrial AP (Figure 1). Preferential abbreviation of APD in atria prolongs the diastolic interval in atria preferentially. This is expected to reduce the effectiveness of I_{Na} block because much of the recovery from sodium channel block generally occurs during the diastolic interval. With Wenxin Keli, the opposite is observed - preferential abbreviation of APD in atria is associated with a greater use-dependent block. The mechanism responsible remains unknown. Thus, Wenxin Keli is capable of inducing marked PRR in atria but not ventricles via a mechanism different from that ascribed to the traditional atrial-selective sodium channel blockers. Our data indicate that Wenxin Keli, like ranolazine and amiodarone, displays rapid unbinding kinetics from the sodium channel (Figure 3). The kinetics of unbinding from the sodium channel have been shown to play a critical role in atrial selectivity of the I_{Na} blockers (for review see⁵). All previously described atrial-selective I_{Na} blockers (e.g., ranolazine, and amiodarone) have rapid unbinding kinetics and agents that lack atrial-selectivity (e.g., propafenone and flecainide) display slow unbinding kinetics. Part of the explanation may lie with the potent effect of Wenxin Keli to shift steady-state inactivation of the sodium channels to more negative potentials (Figure 8). This shift is expected to produce a more dramatic reduction in I_{Na} in atria owing to the fact that the half-inactivation voltage is 9-13 mV more negative in atria vs. ventricles.³ The drug-induced shift of steady-state inactivation coupled with the fact that atrial resting membrane potential is more positive, would be expected to result in a much greater decrease in the availability of sodium channel in atria vs. ventricles. Additional studies are clearly warranted to further delineate the unique mechanism(s) by which Wenxin Keli is able to exert such potent atrial-selective depression of sodium channel dependent parameters.

Very limited data are available in the literature concerning the electrophysiological actions of Wenxin Keli or its individual components. One of its components, NcBe, is a traditional Tibetan medicinal compound, extracted from Valerianaceae plants. Liu *et al.* reported that NcBe significantly blocks I_{Na} and I_{to} recorded from rat ventricular myocytes.²⁷ At a concentration of 10 g/L, NcBe produced a 38.2%, and 57.9% inhibition of peak I_{Na} and I_{to} , respectively. Using rabbit ventricular myocytes, Tang and co-workers reported that NcBe blocks I_{Na} , I_{Ca-L} , I_K and I_{to} in a concentration dependent manner, but not I_{K1} .^{28, 29} We have

observed an effect of Wenxin Keli to block I_{Na} and I_{to} in canine myocytes as well as in HEK293 cells transfected with *SCN5A+SCN1B* or *KCND3+KChIP2* (unpublished observations Barajas-Martinez et al.). Rabbit coronary-perfused left ventricular wedge studies demonstrated that Wenxin Keli can reduce transmural dispersion of repolarization (TDR) under conditions of acute ischemia.³⁰ The effects of NcBe to reduce intracellular sodium and prevent calcium overload is thought to underlie its actions to reduce triggered activity and reentry. NcBe, as well as another component of Wenxin Keli, Notoginseng, are reported to antagonize the effect of acetylcholine on various human organs. As a result of its anticholinergic action, Notoginseng was found to be effective in suppressing atrial fibrillation or flutter induced by acetylcholine.³¹

Study limitations

The atrial selectivity of Wenxin Keli was determined acutely in “healthy” hearts *in vitro*. The presence of autonomic influences and other factors present *in vivo* may modulate the effect of Wenxin Keli, resulting in outcomes different from those observed in the present study. The anti-AF efficacy of Wenxin Keli was also determined in “healthy” atria exposed to ACh. Vagally-mediated AF is not very prevalent in the clinic. Clinical cardiac arrhythmias are normally associated with electrical and structural abnormalities, which may significantly modulate pharmacological responses, anti-arrhythmic efficacy, and safety. Additional studies are clearly needed to characterize the concentration-dependent effects of Wenxin Keli in pathophysiologic models of AF and to assess the degree to which the anticholinergic actions of the drug contribute to its anti-AF efficacy. The mechanism by which Wenxin Keli produces a preferential abbreviation of the atrial action potential, yet a preferential use-dependent prolongation of ERP, remains to be fully elucidated. Although a great deal of work remains to be done to identify and characterize the action of the individual components of Wenxin Keli, the data presented here point to an interesting and potentially novel mechanism for effective management of AF that warrants additional study.

Conclusions

Our data suggest that Wenxin Keli possesses potent anti-AF properties owing to its ability to depress sodium channel-dependent parameters. The atrial selectivity of this action of the drug likely contributes to its usefulness for safe and effective management of AF. The mechanism(s) of atrial selectivity of Wenxin Keli to inhibit I_{Na} appear to be unique and requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AAD	antiarrhythmic drugs
ACh	acetylcholine
ADP	action potential duration

AF	atrial fibrillation
ANOVA	analysis of variance
AP	action potential
CL	cycle lengths cycle lengths
DTE	diastolic threshold of excitation
ERP	effective refractory period
I_{Kur}	ultra-rapid delayed rectifier potassium current
NcBe	Nardostachys chinensis batal extract
PM	pectinate muscle
PRR	post-repolarization refractoriness
TDR	transmural dispersion of repolarization
V_{max}	maximum rate of rise of the AP upstroke

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Figure 1.

Wenxin Keli causes a greater abbreviation of action potential duration (APD₉₀) in atria than in ventricles.

Upper panels: superimposed action potentials recorded from atrial and ventricular muscle under control conditions (C) and after addition of 5 g/L Wenxin Keli (W) to the coronary perfusate. Pacing cycle length (CL) = 500 ms. Bottom panels: Plots depict the average APD₉₀ data recorded at pacing CLs of 500 and 300 ms. * - p < 0.05 vs. control. ** - p < 0.001 vs. control.

Figure 2.

Wenxin Keli prolongs effective refractory period (ERP) selectively in atria due to induction of post-repolarization refractoriness (PRR) in atria but not in the ventricles.

Upper panels: Shown are typical action potentials recorded from atrial and ventricular parts of the coronary-perfused preparation in control and after Wenxin Keli. Each tracing shows a basic beat following by the premature beat with the shortest coupling interval producing an active propagating response, thus depicting the ERP. Bottom panels: Plots show average action potential duration (APD) and ERP data at a cycle length (CL) of 500 and 300 ms. Dashed lines depict the duration of PRR. PRR was approximated by the difference between ERP and APD₇₀ in atria and between ERP and APD₉₀ in ventricles; note that ERP corresponds to APD₇₀₋₇₅ in atria and to APD₉₀ in ventricles. * - p<0.05 vs. control. ** - <0.001 vs. control. † - p<0.001 vs. APD₇₀.

Despite a significant abbreviation of APD in atria, Wenxin Keli significantly prolonged ERP in atria. In contrast, Wenxin Keli abbreviated both APD and ERP in ventricles.

Figure 3.

Wenxin Keli (5 g/L) produced a much greater reduction of the maximum rate of rise of the action potential upstroke (V_{max}) in atria vs. ventricles.

Upper panel: Transmembrane action potentials and respective V_{max} values recorded upon abbreviation of cycle length (CL) from 500 to 300 ms and following return to 500 ms

Bottom panels: Summary data of the effects of Wenxin Keli on V_{max} in atrial and ventricular preparations. All data are normalized to control V_{max} the value recorded at a CL of 500 ms. *- $p < 0.05$ vs. control; ** - $p < 0.001$ vs. control.

Figure 4.

Wenxin Keli (5 g/L) increases diastolic threshold of excitation (DTE) and conduction time (CT) preferentially in atria. These atrioventricular differences in response to Wenxin Keli are greater at a cycle length (CL) of 300 vs. 500 ms. * - $p < 0.01$ vs. control. ** - $p < 0.001$ vs. control.

Figure 5.

Wenxin Keli (5 g/L) increases the shortest $S_1 - S_1$ permitting 1:1 activation in atria but not in the ventricles (measured at a DTEx2 at a cycle length (CL) = 500 ms). Upper panel: typical examples of action potential tracings showing failure of 1:1 activation at a CL of 300 ms in an atria but 1:1 capture in the ventricle. Lower panel: summary data. * - $p < 0.001$ vs. control.

Figure 6.

Wenxin Keli (5 g/L) effectively terminates persistent acetylcholine (ACh)-mediated atrial fibrillation and prevents its induction.

Shown are ECG and action potential tracings recorded 1) during persistent atrial fibrillation (AF) induced in the presence of ACh alone (upper panel); at the moment of termination of persistent ACh-mediated AF by Wenxin Keli (bottom left panel); and 3) during a failed attempt to induce AF by rapid pacing in the presence of both ACh and Wenxin Keli.

Figure 7.

Wenxin Keli (5 g/L) prolongs atrial action potential duration in the presence of acetylcholine (1.0 μ M). Shown are superimposed action potentials recorded from pectinate muscle under baseline conditions (control), in the presence of acetylcholine (ACh) and following addition of Wenxin Keli in the continuous presence of ACh. Cycle length = 500 ms.

Figure 8.

The effects of Wenxin Keli on peak I_{Na} measured in HEK293 cells stably expressing SCN5A.

A: Representative currents recorded at -20 mV following a preconditioning pulse to -140 mV, -90 mV and -60 mV (inset) at 0.1 Hz before and after 5 g/L Wenxin Keli. **B:** Steady-state inactivation (availability) relationship in control and after 5 and 10 g/L Wenxin Keli. **C:** Rate-dependence of I_{Na} before and after exposure to 5 g/L or 10 g/L Wenxin Keli. A train of 40 pulses (to -20 mV for 20 ms) was applied at 10 Hz from a holding potential of -120 mV. Numbers indicate the 1^{st} and 40^{th} pulse of the 10 -Hz train. **D:** Use-dependent block (UDB) of I_{Na} following acceleration from 1 to 10 Hz in control and after exposure to 5 and 10 g/L Wenxin Keli.

Table

Effects of Wenxin Keli (5 g/L) on the atrial electrophysiological parameters in the presence of acetylcholine (ACh, 1.0 μ M).

	APD ₉₀ (ms)	ERP (ms)	Shortest S ₁ -S ₁ (ms)
Acetylcholine	50 $\pm$ 7	55 $\pm$ 8	62 $\pm$ 10
Wenxin Keli	92 $\pm$ 24 [*]	202 $\pm$ 75 ^{**}	249 $\pm$ 56 ^{**}

Action potential duration measured at 90% repolarization (APD₉₀) and effective refractory period (ERP) data presented were obtained from the pectinate muscle region of coronary-perfused atria at a cycle length (CL) of 500 ms (n=5-10). Shortest S₁-S₁ = the shortest CL permitting 1:1 activation.

* p <0.05 vs. acetylcholine alone

** p<0.001 vs. acetylcholine alone.