

ULTRA-RAPID DELAYED RECTIFIER CURRENT (I_{Kur}) PLAYS A CONSTITUTIVE ROLE IN CANINE VENTRICULAR ACTION POTENTIAL REPOLARIZATION

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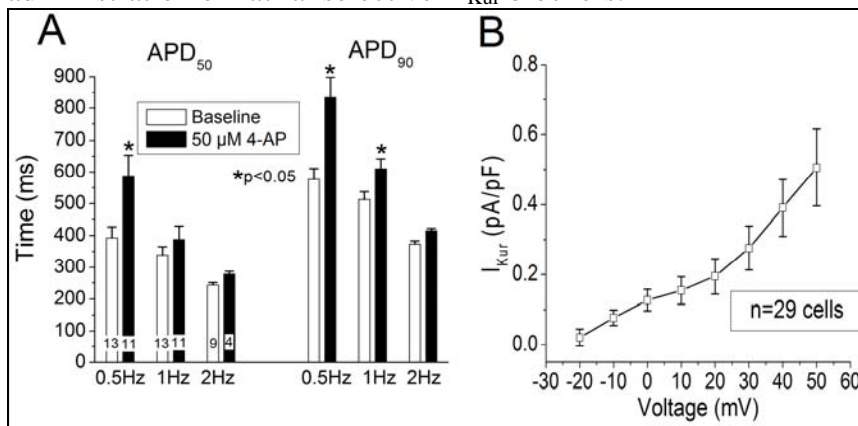
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BACKGROUND: Ultrarapid delayed rectifier current (I_{Kur}) is a major current responsible for repolarization in canine and human atria. The functional current is seen in the atria and not in the ventricles; I_{Kur} is accepted as an “atrial-specific” current. While the protein encoding I_{Kur} (Kv1.5) has been found in normal canine and human ventricles, previous studies failed to elucidate the presence of I_{Kur} in ventricular myocytes. We sought to identify the existence of I_{Kur} and determine its role in modulating the canine ventricular action potential.

METHODS: Canine (Ages 9 months – 3 years) mid-myocardial ventricular myocytes were isolated and amphotericin-B perforated patch clamp experiments were performed. Action potentials were recorded at 0.5, 1 and 2 Hz with and without micromolar concentrations (50, 100 μ M - selective for I_{Kur} blockade) of 4-Aminopyridine (4-AP). I_{Kur} was identified as the 100 μ M 4-AP sensitive steady state current. The dose response relationship describing 4-AP inhibition of I_{Kur} was constructed.

RESULTS: After I_{Kur} blockade, Action Potential Duration at 50% (APD_{50}) and 90% (APD_{90}) repolarization was prolonged significantly, and seen more prominently at slower stimulation rates (Panel A, $p < 0.05$). This effect on APD was reversible upon washout. The 4-AP sensitive current (I_{Kur}) was detectable in 71% of myocytes with a density of 0.51 ± 0.1 pA/pF at +50mV ($n=29$ cells, Panel B). There was no evidence of blockade of other outward K^+ currents.

CONCLUSIONS: I_{Kur} exists in canine midmyocardial myocytes and plays a constitutive role in action potential repolarization. Blockade of I_{Kur} with 50 μ M 4-AP prolongs APD in reverse use dependent manner. The reverse use dependence we observed is consistent with the lack of effect on QTc intervals and ventricular refractory periods at physiologic heart rates during administration of “atrial selective” I_{Kur} blockers.



Panel A: Summary data of APD_{50} and APD_{90} as a function of stimulation frequency measured at baseline and during superfusion with 50 μ M 4-AP. Numbers on each bar indicate the cells tested. Panel B: Summary current-voltage relation of the 100 μ M 4-AP sensitive current.