2:30

EXISTENCE OF SODIUM CURRENTS DURING EARLY VENTRICULAR FIBRILLATION IN DOGS

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It has been shown that sodium channels are inactive after 5 to 10 min of ventricular fibrillation (VF) and that the sodium channels are specifically supressed by TTX or by depolarization of the takeoff potential (ΔTOP). However, the state of sodium channels during early VF, when implantable defibrillator shocks are given, is unknown. In open-chest dogs, a floating glass microelectrode was used to record intracellular action potentials from the right ventricle before and during electrically induced VF. In 5 test dogs, an epsiode of VF was recorded in the absence of drug and after superfusion for 15 min around the microelectrode site by low ($2.8x10^{-6}$ M) and high (10^{-4} M) concentrations of TTX. The maximum phase zero dv/dt (V_{max}) and (ΔTOP) were determined for the sinus beat just before VF and for 10 successive cycles during the 1st, 10th and 20th sec of VF. For the test dogs, the data were as follows:

	VF type	sinus beat	1st sec VF	10th sec VF	20th sec VF
Δ TOP (mV)	no drug	0±0	18±9	22±8	22±7
	low TTX	0±0	15±10*	20±11*	24±11*
	high TTX	0±0	14±9*	17±8*†	18±10*†
$\dot{V}_{max}$ (V/sec)	no drug	104±14	55±32	39±29	37±23
	low TTX	86±15	39±20*	18±12*	18±11*
	high TTX	55±14*†	18±13*†	14±10*†	12±7*†

* = p<0.05 vs no drug VF; † = p<0.05 vs low TTX VF

In three control dogs, which received three successive applications of Tyrode's solution, there were no significant differences in ΔTOP and V_{max} between the three VF episodes. In the test dogs, ΔTOP was increased less than the 25-30 mV reported to cause 50% inactivation of sodium channels while $\dot{V}_{max}$ was decreased after the superfusion of TTX. These two findings indicate that some sodium channel activity continues during the first 20 sec of VF. Thus, sodium channel activity cannot be excluded in proposed mechanisms of defibrillation.

3:00

ELECTROPHYSIOLOGIC RESPONSE OF PURKINJE TISSUE IN THE INTACT CANINE LEFT VENTRICLE TO ALPHA-1 ADRENERGIC ANTAGONISTS

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Previous in vitro studies of alpha-1 adrenergic antagonists revealed multiple mechanisms of electrophysiologic effect. The ability to measure Purkinje relative refractory period (PRRP) allowed investigation of these antagonists in vivo. Eleven dogs were studied after chloralose anesthesia, sinoaortic denervation, vagotomy, and beta blockade with metoprolol (1 mg/kg). Changes in mean arterial pressure (MAP) and His Purkinje interval (HPI), PRRP and muscle effective refractory period (MERP) were measured in response to repeated infusions of phenylephrine 25 μg/kg/min with incremental doses (0.0025-2.5 mg/kg) of two alpha-1 blockers: prazosin or WB4101. Results: The EC50 of the MAP response for prazosin was 0.07 mg/kg and 0.26 mg/kg for WB4101 (p<0.05). Plots for both antagonists were linear and parallel. HPI, PRRP, and MERP were unchanged at all doses of both antagonists. The EC50 of the PRRP prolongation with phenylephrine was similar for both prazosin (0.009 mg/kg) and WB4101 (0.015 mg/kg, NS). However the WB4101 dose response curve was bimodal. Conclusions: 1) Alpha-1 blockade with prazosin or WB4101 occurred without evidence of sodium channel blockade in vivo; 2) the purkinje response to alpha-1 blockers occurred at a 10-fold lesser dose than response of MAP; 3) a 2-component functional response to WB4101 supports the view that 2 distinct alpha-1 adrenergic receptor populations may regulate Purkinje refractoriness.

2:45

EXTRACELLULAR SODIUM CONCENTRATION MODULATES THE SODIUM CHANNEL BLOCKING ACTION OF FLECAINIDE

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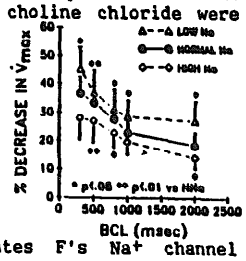
Class IC antiarrhythmic drug toxicity produces severe conduction slowing and arrhythmias, reversible clinically with hypertonic $NaHCO_3$. Recent studies suggest that NaCl also reverses class IC drug toxicity. To evaluate the potential modulation of class IC action by Na^+ per se we studied the effects of flecainide (F) on $\dot{V}_{max}$ of Purkinje fibers at low (116 mM, LNa), normal (141 mM, NNa) and high sodium (166mM, HNa). We used isotonic choline chloride substitution to maintain constant osmolarity and $[Cl^-]$. Results: F 3.2 μM caused a concentration- and rate-dependent reduction of $\dot{V}_{max}$. The actions of F were substantially increased by LNa, and reduced by HNa (graph). The EC50 for F effects on $\dot{V}_{max}$ depended on $[Na^+]$: 8.5 μM (LNa), 13.5 μM (NNa), 19.0 μM (HNa), suggesting that increased $[Na^+]$ decreases the affinity of F for the Na^+ channel. Direct actions of choline chloride were limited to increases in action potential duration (APD): 11±4% at 25 mM, 20±9% at 50 mM; an osmotic effect mimicked by isotonic sucrose and unaltered by 0.1 μM atropine. LNa slightly decreased APD and HNa slightly increased APD: thus, the interaction between F and Na^+ was not due to changes in APD.



We conclude that $[Na^+]$ modulates F's Na^+ channel blocking action, apparently by altering F binding to its receptor. This molecular interaction may account for the beneficial effects of Na^+ salts in IC toxicity.

3:15

INTERACTION BETWEEN PROLONGATION OF REPOLARIZATION AND SODIUM CHANNEL BLOCKADE PRODUCES ENHANCED PROLONGATION OF REFRACTORINESS AND GREATER USE-DEPENDENT BLOCK

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Mexiletine (Mex)-quinidine (Qd) combination produces enhanced antiarrhythmic efficacy. As Qd blocks both potassium (K) and sodium (Na) channels, the Mex-Qd interaction may relate to interactions between K channel blockers and Na channel blockers or interactions between sodium channel blockers with slow (Qd) and fast (Mex) kinetics of onset of use-dependent block (UDB). Since Qd produces multiple electrophysiologic effects, model drugs were combined: Ba^{+2} (10μM) partially inhibits Ik_1 without effects on ICa, Ik or It; o-desmethyl encainide (ODME, 100 ng/mL) produces slow onset UDB with minimal change in APD, Mex (4μM) produces rapid onset of UDB in papillary muscle. Results: x̄±SD; Δ=changes from baseline; *=p<0.05; comparing ODME+Mex to ODME+Mex+Ba; n=11.

	Ba	ODME	ODME+Mex	ODME+Mex+Ba
ΔVmax(V/s)	3 ± 12	-35±11	-49±10	-59±15 *
ΔRMP(mV)	-0.9±2	-0.4±1	-0.2±1	-0.6±2
ΔERP(msec)	17±3	16±9	24±13	50±16 *
UDB(%)	none	5±9	10±3	14±2 *

ODME+Mex+Ba produced significantly greater UDB than did ODME+Mex or other monotherapies. The time constant of onset kinetics of UDB of ODME+Mex+Ba (4.0±2.0 pulses) was faster than ODME (13.0±4.2 pulses) and ODME+Mex (6.6±2.2 pulses). No difference in recovery kinetics from UDB was observed among these groups. In conclusion, the combination of prolongation of APD + simultaneous Na channel block with slow and fast kinetics produced greater prolongation of refractoriness and greater use-dependent block.