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Thursday, March 22, 1990
8:30AM–10:00AM, Room 16
Antiarrhythmic Drugs: Clinical and Basic Electrophysiologic Studies

ELECTROPHYSIOLOGIC EFFECTS OF LEFT VENTRICULAR HYPERTROPHY IN VIVO: EFFECT OF PHARMACOLOGIC INTERVENTION.

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In order to define the arrhythmogenic effects of left ventricular hypertrophy (LVH) in the intact heart, we carried out a detailed electrophysiologic assessment in our previously validated feline aortic banding model. Intraventricular conduction times, as well as excitability thresholds (ET), ventricular refractory periods (VRP), and mean monophasic action potential durations (MAPD) measured at several ventricular sites were similar in animals with LVH (n=24), and sham-operated controls (n=12). However, cats with LVH were significantly more vulnerable to ventricular fibrillation occurring either spontaneously, or induced with programmed stimulation. Compared to the sham controls, LVH animals also had a greater dispersion of VRP (35 ± 11 vs 12.4 ± 4 msec; p<0.001), and $MAPD_{90}$ (69 ± 25 vs 39 ± 7 msec; p<0.02). Verapamil (0.30 mg/kg IV then infusion of 10 mcg/kg/min) had no significant effect on these electrophysiologic properties, nor did it affect VF thresholds or inducibility by programmed stimulation. However, Risotilide (5 mg/kg) an inhibitor of the voltage-dependent postassium channel narrowed dispersion of VRP and MAPD concomitant with a marked reduction in ventricular vulnerability. Thus, LVH has a pronounced effect on dispersion of refractoriness and repolarization. Blockade of the voltage-dependent potassium channel, but not the slow calcium channel, narrows the dispersion of recovery of excitability and protects against ventricular fibrillation.

INFLUENCE OF CALCIUM ON THE HEMODYNAMIC AND ANTI-ISCHEMIC EFFECTS OF NIFEDIPINE OBSERVED DURING TREADMILL EXERCISE TESTING.

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To determine whether calcium (Ca) would attenuate the hypotensive effect and reduce the anti-ischemic action of nifedipine (Nifed), we studied 12 pts with ischemic heart disease who were prospectively recruited after undergoing a baseline treadmill exercise test (TET) that revealed diagnostic ST depression within 2 weeks of the protocol. All subjects underwent 2 more TETs in a randomized double-blind crossover fashion. These tests were preceded by 10 mg of bite and swallow Nifed given after either 10 ml of 10% Ca chloride (13.6 mEq) in 50 ml of D5W or D5W alone infused over 25 minutes. Resting systolic blood pressure fell significantly more (135 ± 20 mmHg to 119 ± 18 mm Hg, (p < .05) 25 minutes after Nifed + placebo than following Nifed + Ca (140 ± 20 mmHg to 130 ± 16 mmHg). Peak exercise systolic blood pressure was reduced after Nifed + placebo (173 ± 35 mmHg) compared to that on the baseline treadmill test (182 ± 38 mmHg, p < .05) but not after Nifed + Ca. Exercise duration was longer (p <.05) than baseline (398 ± 96 sec) after Nifed and placebo (450 ± 124 sec) but was unchanged after Nifed and Ca (428 ± 146 sec). Maximum ST depression at baseline (1.33 ± .45 mm) was significantly reduced (p <.05) after either Nifed alone (.71 ± .48 mm) or Nifed + Ca (.67 ± .69 mm). All 12 pts had ST depression on baseline TET but only 6 of 12 pts had ST depression on TET after either Nifed alone or Nifed + Ca.
Conclusion: Ca blunted the hypotensive response to Nifed at rest and during exercise in patients with ischemic heart disease but had little effect on the anti-ischemic action of Nifed observed during TET.

The New Calcium Channel Blocker Ro-236152 (Roche) Prevents Reperfusion Arrhythmias in Dogs.

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Does increased cardiac Ca^{2+} current play a role in the genesis of reperfusion arrhythmias? This was tested in an awake instrumented dog model of coronary occlusion due to spontaneous in vivo thrombus formation in the circumflex artery (LCX) by current application. LCX blood flow by Doppler, ECG, myocardial contractility by length-segment crystals, and coronary sinus norepinephrine release (NE) were measured through out the study. After 45 min of occlusion (no LCX blood flow, marked ST elevation, marked impairment in posterior wall contractility, and more than 2 fold increase in coronary sinus NE), reperfusion was established with 10^6 units of streptokinase and 5000 units of heparin IV. Just prior to thrombolysis, control dogs received the vehicle (normal saline) and experimental group received 0.3mg/kg of RO-236152 IV (napthothiazepinone type Ca^{2+} channel blocker, Roche) followed by a 30µg/kg/min infusion for 60 min.

The incidence of ventricular ectopy including tachycardia < 7 beats long (VPB) or tachycardia (VT) or fibrillation (VF) was:

Type	VPB	VT	VF
Control (n=18)	0/18	12/18	6/18
Treated(n=20)	15/20*	4/20**	1/20+

*p<0.001; **p<0.02; +p<0.005, compared to controls

In this model, reperfusion-induced ventricular arrhythmias and fibrillation may be partially mediated by cardiac Ca^{2+} current.

EFFECTS OF ADENOSINE ON TRIGGERED ACTIVITY IN ISOLATED RABBIT RIGHT VENTRICLE

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Adenosine (Ado) has been shown to suppress certain ventricular tachycardias believed due to triggered activity (TA). This study assessed the hypothesis that this Ado effect is due to inhibition of cyclic AMP (cAMP). Pacing-induced TAs were recorded from isolated rabbit right ventricle (N=15) superfused with K^+ free, high Ca^{++} (5.4 mM) solution. In each study TA-induction frequency was determined using 30 pacing trains (8 beat duration), decrementing cycle length between trains. The TA 'induction percentage' was calculated as TA-induction frequency/30x100. TA-induction percentage was assessed during superfusion of the preparation with either isoproterenol (Iso, 10^{-8}M) to stimulate intracellular cAMP, or dibutyryl cyclic AMP (DBcAMP, 10^{-4}M, $5x10^{-4}$M) to supplement intracellular cAMP. Ado effect on TA induction percentage is tabulated for each treatment group (mean±SD, *p<.01).

	Iso10^{-8}M	DBcAMP10^{-4}M	DBcAMP$5x10^{-4}$M
Control	54±25%	47±23%	63±23%
Ado $5x10^{-4}$M	25±30%*	5±5%	58±27%
Washout	33±30%	45±50%	64±2%

Ado inhibited TA induction in the presence of Iso consistent with inhibition of intracellular cAMP. However, TA inhibition by Ado in the presence of 10^{-4}M DBcAMP suggests that Ado may also exert effects not dependent on cAMP inhibition. Nonetheless, the latter actions can be overcome by high dose ($5x10^{-5}$M) DBcAMP. Thus, TA suppression by Ado appears to be primarily effected by intracellular cAMP inhibition.