PHOSPHOLIPASE INHIBITION BY AMIODARONE IS ASSOCIATED WITH MODULATION OF THE EARLY ELECTROPHYSIOLOGIC CHANGES OF ACUTE MYOCARDIAL ISCHEMIA

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The effects of amiodarone (A), a known phospholipase inhibitor (PI), were studied in an isolated porcine heart model to determine whether this inhibition could preserve electrophysiologic (EP) integrity during reversible ischemia (MI). In untreated hearts (n=5), LAD occlusion (20 mins.) resulted in rapid onset of ST elevation in < 1 min., plateauing at 8 mins. Lysophosphatidycholine (LPC) levels increased by 26% & 52% at 5-7 and 20 mins. MI.

	LPC		ST ↑	
	5-7 min	20 min	6 min	20 min
Untreated	n moles/g wet weight		mV	
Normal	35.4±4.3	36.5±3.9	--	--
Ischemic	44.8±4.1	57.2±5.6*	9.9±4.0	8.6±6.0
Treated		*p<0.02		
Normal	35.9±3.8	33.1±5.3	--	--
Ischemic	38.5±1.9	36.7±8.1	2.9±1.1*	5.4±4.8

In A treated hearts, (n=5, 40 mins. perfusion with 5μM A prior to MI), sinus rate decreased 20% but MAP recordings revealed no change in ventricular effective refractory period (240 vs 245ms), APD (225 vs 230ms) or amplitude (23 vs 26 mV). In these hearts, there was significant attenuation (p<0.02) of the onset of ST elevation during the first 8 mins. ischemia with concomitant suppression of LPC elevation. (LPC increase 7% vs 26% at 5-7 mins. MI) These EP differences were not significant at 20 mins. (LPC increase 11%). The delay in onset of the EP injury in association with attenuation of phospholipid catabolism during MI by A, suggests that myocardial PI may in part be responsible for the preservation of EP integrity observed in the first minutes of ischemia.

EXERCISE-INDUCED INCREASES IN FIBRINOLYTIC POTENTIAL EXCEED THOSE PRODUCED BY EPINEPHRINE INFUSION

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The increased risk of myocardial infarction (MI) after awakening may be triggered by activities associated with adrenergic activation. However, the potential harmful hemodynamic effects of such activation may be offset by adrenergic stimulation of fibrinolysis. To study the contribution of adrenergic activation to fibrinolysis, we compared the effect of epinephrine infusion (0.05 mcg/Kg/min) and bicycle exercise on fibrinolytic potential (euglobulin clot lysis time [ECLT]) and t-PA antigen), systolic arterial pressure (SAP), and heart rate (HR) in 11 normal subjects. Plasma vasopressin (pl AVP), a previously reported mediator of fibrinolysis, was also measured. Values are mean ± SEM. * = p < 0.05

	EPI INFUSION			EXERCISE		
	BEFORE		AFTER	BEFORE		AFTER
t-PA ag (ng/ml)	7.1±1.8	*	11.3±2.9	7.6±2.7	*	18.8±3.1
ECLT (min)	169±41	*	116±30	150±28	*	49±9.7
pl Epi (pg/ml)	41±7	*	349±54	40±5	*	166±28
pl AVP (ng/ml)	1.0±0.2		0.9±0.2	0.9±2	*	9.9±2.9
SAP (mm Hg)	118±3	*	123±1	124±2	*	179±9
HR (bpm)	64±2	*	74±3	70±3	*	167±10

Although Epi infusion produced a greater rise in pl Epi than did exercise, exercise produced a greater increase in fibrinolytic potential. There was no significant correlation between fibrinolytic potential and Epi or AVP. Exercise increased AVP 10-fold; however, lack of correlation with fibrinolysis suggests that other factors, including hemodynamic, contribute to exercise-induced increases in fibrinolytic potential. Further study of the regulation of fibrinolysis and its role in offsetting potentially adverse effects of triggers of occlusive thrombosis may lead to improved prevention.

EFFECTS OF CAPTOPRIL ON THE BETA-ADRENERGIC SYSTEM IN NONINFARCTED MYOCARDIUM IN THE RAT HEART FAILURE MODEL.

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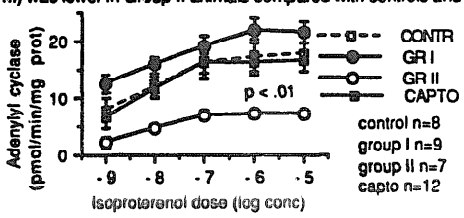
We studied the effects of captopril on the beta-adrenergic receptor (BAR)-adenylyl cyclase (AC) system in noninfarcted myocardium in rats 6 weeks after large anterior myocardial infarction (MI) of >40% of the left ventricle (LV). Captopril treatment, which improves LV hemodynamics in this model, was started 3 weeks after MI.

There are two different populations post-MI with respect to beta-adrenergic responses. Group I demonstrated no difference to sham-operated controls in BAR density (Bmax) or dissociation constant (Kd) and was similar with respect to isoproterenol (ISO)-stimulated AC activity. Group II animals did not differ in Bmax, but Kd was higher than Group I [43.7 ± 3.12 pM vs 30.9 ± 3.34 pM (p<.05)]. ISO-stimulated AC activity (ISO dose-response curves 10-9 M - 10-5 M) was lower in Group II animals compared with controls and Group I.



In contrast, there was no difference in forskolin-stimulated (10-6 M - 10-3 M) or guanyl-5'-imidodiphosphate (GppNHp)-stimulated (10-9 M - 10-4 M) AC activity between Group II and controls. Captopril treatment normalized ISO-stimulated AC activity and had no effect on Bmax or Kd.

Conclusions: 1) Two distinct populations of animals exist after large infarctions with respect to BAR-AC function. 2) Group II animals demonstrate a decreased response to ISO-stimulated AC activity and have a higher antagonist Kd. 3) Treatment of infarcted animals with captopril returns the ISO-stimulated AC activity towards normal.

EFFECT OF AFTERLOAD REDUCTION ON POST-ISCHEMIC SYSTOLIC FUNCTION IN HYPERTROPHIED CANINE MYOCARDIUM.

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Despite increased infarct size when left ventricular hypertrophy and hypertension (LVH-HT) are present, we have shown that recovery of segmental systolic thickening with reperfusion after ischemia in hearts with LVH-HT parallels that of nonhypertrophied-normotensive (C) hearts. Reduction in blood pressure (RBP) in LVH-HT has been shown to decrease infarct size, however, the influence of RBP on recovery of segmental systolic thickening in LVH-HT is unknown. HYPOTHESIS: RBP in canine left ventricles with LVH-HT will improve recovery of segmental systolic thickening after 15 min ischemia and 24 hrs reperfusion. METHODS: 3 groups of conscious dogs (LVH-HT, LVH-RBP, and C) with hemodynamic catheters, coronary artery occluders, and sonomicrometers underwent 15 min ischemia and 24 hrs reperfusion. Myocardial segments were grouped by % of segmental systolic thickening (as % control systolic thickening) at 15 min ischemia (Class 1 ≥ 67%, Class 2, 0-66%, Class 3 < 0% control systolic thickening) and the recovery of each class was measured serially during reperfusion. Hemodynamics and blood flow were also measured. RESULTS: Systolic thickening in class 2 (hypokinetic) segments was significantly depressed in LVH-RBP during early reperfusion (p<0.05 compared to C and LVH-HT) and systolic thickening in class 3 (dyskinetic) segments showed a similar trend. CONCLUSION: In hearts with LVH-HT, reduced blood pressure was associated with significantly greater depression (rather than improvement) of systolic thickening compared to C hearts. In hearts with LVH-HT, RBP may exaggerate rather than ameliorate myocardial stunning.