EXTENT OF MYOCARDIAL BETA-1 RECEPTOR DOWN-REGULATION CORRELATES WITH IMPAIRMENT IN NOREPINEPHRINE REUPTAKE IN EXPERIMENTAL RIGHT HEART FAILURE.

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We have previously shown that neuronal norepinephrine (NE) reuptake and total beta-receptor number are both reduced in the failing RV produced by tricuspid avulsion and pulmonary artery constriction in dogs. To further study the relationship between impaired NE reuptake and beta-receptor subtypes, we measured RV NE reuptake activity, and beta-1 and beta-2 receptor density in dogs with right heart failure (RHF) and in sham-operated controls. NE reuptake activity was measured in tissue slices incubated with ^{3}H-NE. Radioiodinated iodocyanopindolol was utilized for measuring total beta-receptor density, and beta-receptor subtyping was performed with the very highly selective compound CGP-20712A (6000 fold beta-1 selective). Results (mean±SE) of beta-receptor density (fmol/mg protein) and NE reuptake (fmol/mg/15 min) were: [a]p<0.01 vs. sham.

	N	Beta-1	Beta-2	NE reuptake
Sham	9	64±7	26±2	82±5
RHF	8	27±5[a]	28±3	47±10[a]

The reduction in beta-1 receptor density in RHF correlated significantly with the extent of impairment in NE reuptake (r=0.82, p<0.01). Thus, RHF was associated with a reduction of NE reuptake activity and a corresponding selective decrease in beta-1 receptor density. The results indicate that impaired NE reuptake in RHF may be functionally linked to the mechanism by which beta-1 receptor down-regulation occurs.

REGIONAL MYOCARDIAL BLOOD FLOW IS HETEROGENEOUS DURING REPERFUSION FOLLOWING TRANSIENT REVERSIBLE ISCHEMIA.

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To quantitate the relative variability in regional myocardial blood flow (RMBF) during reperfusion following brief periods of myocardial ischemia, we measured RMBF with Sr85, Sc46, and Ce141 radioactive microspheres (15u) in 9 open chest dogs at: baseline, 20 min of ischemia due to left anterior descending coronary (LAD) occlusion, and 1 min reperfusion. Transmural myocardial samples (1-1.5g) were excised from within the LAD region of risk defined by post mortem perfusion of the LAD with Evans Blue dye and the anatomical distribution of the coronary arteries. Myocardial samples from sites selected for RMBF < .25cc/g/min (n=84) during ischemia were analyzed for inter-sample variance in RMBF after correction for inter-dog variance by ANOVA, (S^2). To test for significant differences in S^2 at baseline, ischemia and reperfusion the ratio of S^2 for the conditions under consideration was compared using the F distribution.

CONDITION	RMBF(cc/g/min)	S^2	P
baseline	0.89±0.27	.0468	<0.01
ischemia	0.15±0.05	.0022	
reperfusion	3.48±1.88	.2857	<0.01

RMBF at reperfusion had greater inter-sample variance than at baseline or ischemia. Thus during reperfusion following brief periods of ischemia, RMBF to the previously ischemic segment exhibits increased heterogeneity. This finding has implications for the uniformity of tissue recovery.

Monday, March 19, 1990
4:00PM–5:30PM, Room 26
New Aspects of Reperfusion

EFFECT OF PRECONDITIONING ISCHEMIA ON REPERFUSION ARRHYTHMIAS AND HIGH ENERGY PHOSPHATES AFTER CORONARY ARTERY OCCLUSION AND REPERFUSION

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Severe arrhythmias occur predictably upon reperfusion after 5 minutes of coronary occlusion in the rat. There is little data available on whether ischemic preconditioning (PC) of hearts can reduce the incidence of such arrhythmias. We studied the effect of PC (3 cycles of 2 minute coronary occlusion and 5 minute reperfusion) on development of arrhythmias following a subsequent 5 minute coronary artery occlusion and reperfusion. Rats (n=16 each group) underwent 5 minute occlusion and reperfusion alone, or preceded by PC; arrhythmias were monitored during ischemia and for 10 minutes of reperfusion and biopsies taken for creatine phosphate and adenosine triphosphate in ischemic and nonischemic zones of the left ventricle. The incidence of ventricular tachycardia (VT) during occlusion was reduced by PC (81% control vs. 13% PC, P<.001). Upon subsequent reperfusion, ventricular fibrillation (VF) developed in no PC animals vs 13 (81%) of controls (P<.001), and irreversible VF in none of PC vs. 7 (44%) of controls (P=.007). Ventricular tachycardia occurred in 4 (25%) of PC vs. 100% of controls (P<.001). Mean duration of VT plus VF was reduced from 320 ± 54 seconds to 5 ± 1 secs (P<.001) and arrhythmia onset delayed from 8 ± 2 to 85 ± 35 secs after reperfusion by PC. There was no difference in creatine phosphate levels in the ischemic zone at end-reperfusion in PC animals compared to controls without irreversible VF (16.2 ± 4.1 vs 15.5 ± 3.9 nM/mg protein, P =NS). There was no relationship between creatine phosphate levels and occurrence of VT or VF (14 ± 5.6 nM/mg protein VF vs. 16.7 ± 3.3 no VF; 16.4 ± 3.5 VT vs. 15.4 ± 4.5 no VT; P=NS). Adenosine triphosphate levels were unaffected by treatment (15.5 ± 2.1 vs 14.5 ± 1.9 nM/mg protein, PC vs control). When coronary occlusion is preceded by preconditioning, the usually severe reperfusion arrhythmias are virtually eliminated. This protective effect of preconditioning is not likely to be related to alterations in high energy phosphate compounds.

SEGMENTAL SYSTOLIC RESPONSES TO ISCHEMIA AND REPERFUSION IN HYPERTROPHIED HYPERTENSIVE CANINE MYOCARDIUM

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Left ventricular hypertrophy and hypertension (LVHHT) accelerate the rate of myocardial necrosis and increase infarct size during ischemia. The influence of LVHHT on recovery of segmental systolic thickening (ST) after ischemia and reperfusion (R) is unknown. Hypothesis: LVHHT may diminish recovery of ST following transient ischemia. Methods: Awake, unsedated dogs with renovascular LVHHT instrumented with hemodynamic catheters, LAD occluders, and intramyocardial sonomicrometers underwent either (Group A) 15 min coronary occlusion (CAO) and 24 hrs R (n=8) or (Group B) 2 hrs CAO and 4 wks R (n=9). Normotensive, nonhypertrophied controls (C) were studied for each group. Myocardial segments were subdivided by ST (as % control ST) at the end of CAO (Class 1=>67%ST, Class 2=0-67%ST, Class 3=<0%ST). ST, hemodynamics and regional blood flow were measured serially. Results: Heart weight (g) to body weight (kg) ratio (HW:BW) and mean arterial pressure mmHg (AoM) were significantly increased for both LVHHT groups. HW:BW (LVHHT vs C) Group A -5.6 vs 4.2 g/kg, p=.001, Group B -5.8 vs 4.2 g/kg, p<.001. AoM (LVHHT vs C) Group A -136 vs 105, p=.0001, Group B -136 vs 104, p=.0004. Despite significant increases in LV mass and mean arterial pressure, the time course and extent of recovery of ST for all classes of segments did not differ between LVHHT and C in either group A or B. Conclusion: Regardless of level of ischemic dysfunction, reperfusion after ischemia results in recovery of ST despite significant LV hypertrophy and hypertension.