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Hall F, West Concourse
Regional Vasoconstrictors and Vasodilators

HEMOGLOBIN INHIBITS ENDOTHELIUM-DEPENDENT RELAXATION IN HUMAN CORONARY ARTERIES IN VIVO

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The importance of Endothelium-derived relaxing factor (EDRF) in the control of coronary vasomotor tone has recently been recognised. We investigated the role of EDRF in the maintenance of coronary vasomotor tone at rest, using the specific inhibitor free hemoglobin (Hb). We report for the first time the inhibition of ACh induced coronary vasodilation by free Hb in seven patients with angiographically normal coronary arteries. Following a diagnostic cardiac catheter, three minute infusions were given as follows: ACh 0.1 μM, ACh 0.1 μM + Hb 1 μM, ACh 0.1 μM + Hb 10 μM and 1000 μg isosorbide dinitrate. These substances were infused into the left anterior descending coronary artery via a 2 French infusion catheter. Quantitative coronary angiography was performed after each infusion. ACh 0.1 μM increased left anterior descending coronary artery diameter from (Mean±S.E.M, Student's t test) 2.32±0.12 mm to 2.78±0.20 mm (p<0.01). Hb 1 μM and 10 μM reversed this effect to 2.11±0.18 mm (p<0.001) and 2.29±0.14 (p<0.05) respectively. Isosorbide dinitrate (an endothelium-independent vasodilator) overcame the inhibitory effect of free Hb (1 μM and 10 μM) causing vasodilation (3.04±0.24 mm, p<0.001).

CONCLUSION:
Hb is an inhibitor of EDRF in vivo, at levels that have been recorded in some pathological states. It may provide a useful tool for further investigation of EDRF in this and other vascular beds in man.

THE ACTION OF INTRARENAL ENDOTHELIN IN THE DOG

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The kidney plays an important role in the pathophysiology of congestive heart failure (CHF) with avid sodium retention. Endothelin (ET), a newly described potent vasoactive peptide, has recently been reported to be elevated in CHF. To date, reports of the action of intrarenal ET upon renal hemodynamic function and sodium excretion in the absence of its potent systemic cardiovascular action conflict. In this study we proposed to characterize the renal effects of ET in the absence of systemic effects by the intrarenal infusion of ET (n=4). After baseline equilibration, an intrarenal arterial low dose infusion of ET (2.0ng/kg/min) was initiated (ETK). Normal saline was infused in the contralateral kidney which served as a control (NSK). Heart rate, mean arterial pressure, renal blood flow (RBF), renal vascular resistance (RVR), glomerular filtration rate (GFR), and fractional excretion of sodium (FeNa) were measured before (baseline) and during ET infusion. No significant changes in the heart rate or mean arterial pressure were noted.

	ETK		NSK	
	Baseline	ET infusion	Baseline	NS infusion
GFR(ml/min)	27.2±5.6	15.7±3.7	31.6±3.3	30.8±2.8*
RBF(ml/min)	196.8±20.1	98.8±16.2†	196.2±38.5	206.2±55.6
RVR§	0.64±0.06	1.26±0.24†	0.71±0.14	0.75±0.18
FeNa(%)	1.45±0.40	0.39±0.13†	2.02±0.64	1.06±0.28

†p<0.05 vs baseline *p<0.05 ETK vs NSK §(mmHg/ml/min)

Conclusion: The current studies demonstrate that low dose intrarenally confined ET is a potent renal vasoconstrictor which decreases GFR and sodium excretion independent of systemic hemodynamic actions. These findings are consistent with a potential role for ET in the pathophysiology of congestive heart failure.

ENHANCED LOCAL ENDOTHELIN RELEASE CONTRIBUTES TO NO-REFLOW PHENOMENON IN THE CANINE MODEL

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Myocardial salvage after regional ischemia is limited by a progressive reduction in regional blood flow during the peri-reperfusion period [no-reflow phenomenon (NRF)]. To investigate the role of endothelin (ET) in the pathogenesis of the NRF, 8 closed chest dogs underwent 90 minutes of proximal LAD occlusion and 3½ hrs of reperfusion (R). Serial ET levels were obtained from the coronary sinus (CS) and AO and measured by radioimmunoassay. Area at risk and area of necrosis were measured with Monastral blue and triphenyltetrazolium. NRF was determined with radioactive microspheres and semi-quantitated by light microscopy utilizing fluoroscent beads. Neutrophil infiltration was assessed by myeloperoxidase (MPO) content and ultra-structural changes by electron microscopy.

	Baseline	Occlusion	Pre-R	R-30	R-60	R-210
ET-Cs	7.9±1	14.2±2*	15.5±3*	24.4±5*	21.5±6*	22.6±5*
ET-AO	6.4±1	11.3±2*	14.7±3*	17.1±6	17.5±4*	16.4±4*
Endo	0.56±.2	0.07±.1	---	1.93±.9	0.67±.3	0.40±.1

Endo=Endocardial flow; R=Reperfusion; *p<0.05 vs. baseline

ET in CS progressively increased during the first 3 hrs of reperfusion. An inverse relationship was noted between ET, MPO activity, and the NRF. Conclusion: This study demonstrates that ischemia followed by reperfusion enhances local ET release which contributes to a progressive reduction in microvascular flow in the reperfused myocardium.

TEMPORAL ALTERATION IN ENDOTHELIUM-DEPENDENT RESPONSES OF CANINE CORONARY ARTERIES IN CONGESTIVE HEART FAILURE.

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Experiments were designed to determine if coronary artery responses alter with duration of congestive heart failure (CHF). CHF of equal hemodynamic severity was produced in dogs by rapid ventricular pacing for 15 (15d) and 30 (30d) days. Left circumflex arteries were removed and rings, with and without endothelium, suspended in organ chambers for measurement of isometric force.

In rings with endothelium, relaxations to acetylcholine (ACh) and the alpha$_2$-adrenergic agonist BHT 920 were enhanced at 15d compared to control. In contrast, at 30d the enhancement to ACh was lost (ED_{50} [-log M]: 15d 8.0±0.1 vs 30d 7.7±0.1; n=6, p<0.05), while the response to BHT 920, which acts through a pertussis toxin-sensitive mechanism, remained enhanced at 30d compared to control (maximal relaxation [%]: control -14.7±9.0 vs 30d -86.3±6.5; n=5-6; p<0.05). Endothelium-dependent relaxations to the calcium ionophore A23187 and adenosine diphosphate were unchanged at 15d and 30d compared to control. Endothelium-independent relaxations to nitric oxide, while unchanged at 15d, were enhanced at 30d (ED_{50} [-log M]: control 7.2±0.1 vs 30d 7.7±0.1[n=5-6]; p<0.05).

Thus, relaxations to ACh are transiently enhanced in early CHF, while enhancement of relaxations mediated through a pertussis toxin-sensitive mechanism persist. This is accompanied by increased sensitivity of the vascular smooth muscle to an endothelium-derived relaxing factor.These studies demonstrate that coronary vascular reactivity is variable in CHF and modulated by the duration, independent of the severity, of the syndrome.