953-92 Coronary and Contractile Effects of Intracoronary Bradykinin and Their Modulation by ACE Inhibitor in Normal Conscious Dogs

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Inhibition of bradykinin (BK) degradation may contribute to the hemodynamic effects of angiotensin converting enzyme (ACE) inhibitors. In this study, we examined in normal conscious dogs, the coronary and contractile effects of intracoronary (ic) BK and their modulation by ACE inhibitor. To avoid neuroreflex activations low doses of BK were used (0.1, 1, 3, 10 nanogramme/kg ic bolus). The effects of i.c. BK were also examined in the presence of the ACE inhibitor enalaprilat (E) given intracoronarily (0.75 mg) and orally (20 mg). Seven mongrel dogs were chronically instrumented with left ventricular (LV) micromanometer, aortic catheter, coronary flow probe, circumflex coronary catheter and piezoelectic crystals for the measurement of LV posterior regional ventricular function. In absence of systemic hemodynamic changes, low doses of BK increased dose-dependently coronary blood flow (CBF velocity: 30 ± 5, 42 ± 7, 45 ± 8, 48 ± 7 cm/s, respectively, from 19 ± 3 cm/s). The increase in CBF induced by BK was associated with an increase in end-diastolic regional wall thickness (BK 10 ng/kg: from 11.9 ± 1.1 to 12.4 ± 1.1 mm, $p < 0.01$) without change in LV regional wall thickening. Intracoronary enalaprilat extended significantly the duration of the rise in CBF induced by BK (10 ng/kg: from 42 ± 5 to 116 ± 15 sec, $p < 0.01$) without change in peak effect. After enalaprilat a further increase in the end-diastolic wall thickness was observed (E + BK 10 ng/kg: 13.4 ± 1.2 mm, $p < 0.05$) with no change in regional contractility. Similar findings were observed one hour after oral administration of enalapril. Thus, in normal conscious dogs, BK increases coronary blood flow and end-diastolic wall thickness with no effect on myocardial contractility. Intracoronary or oral administration of enalaprilat does not change the contractile response to BK but prolongs the coronary vasodilator effect of bradykinin.

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954-85 Haemodynamic and Endocrine Effects of ANP and BNP in Pulmonary Heart Disease

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We have studied the effects of atrial natriuretic peptide (ANP) and b-type natriuretic peptide (BNP) in eight patients with pulmonary heart disease secondary to hypoxaemic lung disease. Each patient was studied twice in cross-over fashion. After resting to reach baseline haemodynamics, subjects were given a 20 minute placebo infusion, followed by either ANP or BNP (3 pmol/kg/min then 10 pmol/kg/min for 20 mins each). Responses were measured at baseline, after placebo infusion, and following low then high dose ANP or BNP.

Baseline conditions were similar and placebo infusion had no significant effects on either study day. Low dose ANP and BNP significantly reduced mean pulmonary artery pressure (MPAP) from baseline by 3.7 ± 1.1 mmHg and 3.0 ± 1.1 mmHg respectively High dose ANP and BNP further reduced MPAP from baseline by 7.1 ± 1.1 mmHg and 7.1 ± 1.6 mmHg respectively. ANP and BNP had no confounding systemic haemodynamic effects and did not worsen arterial oxygenation. Plasma aldosterone was significantly suppressed by ANP (– 156 ± 48 pmol/l after low dose, – 275 ± 57 pmol/l after high dose) and by BNP (– 92 ± 36 pmol/l after low dose, – 159 ± 55 pmol/l after high dose).

ANP and BNP caused dose-related pulmonary vasodilatation and had favourable neurohormonal effects by suppressing aldosterone, without worsening oxygen saturation or affecting systemic haemodynamics. These actions might therefore be exploited as a novel therapeutic strategy in patients with pulmonary heart disease.

954-86 Long Term Effects of Cicletanine on Secondary Pulmonary Hypertension

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Cicletanine (C), an antihypertensive furopyridine derivative drug was shown to enhance the production of endogenous prostacyclin. The goal of the present work was to evaluate the possible effects of C on pulmonary artery hypertension (PAH) secondary to chronic obstructive lung disease (COLD). In a double blind placebo controlled study, we evaluated the long term effects of C (50 mg per os daily) on hemodynamics and blood gases of 33 patients (pts) suffering from PAH secondary to COLD. Pts receiving C (11) and those (12) who had a placebo (P) were catheterized before treatment (TO) then 3 months (T3) and 12 months later (T12).

Results (mean ± SEM):

	Cicletanine			Placebo			C/P
	T0	T3	T12	T0	T3	T12	
CI	2.8 ± 0.2	3.3 ± 0.2*	3.2 ± 0.2	2.8 ± 0.2	2.8 ± 0.1	2.7 ± 0.1	ns
MPAP	27 ± 2	23 ± 2*	22 ± 2*	30 ± 2	29 ± 3	29 ± 2	<0.05
PWP	11 ± 1	10 ± 1	9 ± 1	12 ± 1	13 ± 1	11 ± 1	ns
TPR	454 ± 28	362 ± 31*	381 ± 43*	507 ± 48	474 ± 47	489 ± 4	<0.05
PaO2	64 ± 2	58 ± 3*	59 ± 3*	60 ± 3	61 ± 3	59 ± 4	ns

CI: cardiac index (l/min/m^2), MPAP: mean pulmonary artery pressure, PWP: pulmonary wege pressure (mmHg), TPR: total pulmonary resistance (dynes.cm-5/s), PaO_2 (mmHg). *difference ($p < 0.05$) between T0 and T3 or /T12.

A significant decrease in MPAP and TPR was observed in group C and between C and P after 3 months of treatment and persisted after 12. PaO2 decreased slightly in group C but the difference with group P was not significant. These results suggest that long term treatment with low dose C can induce an effective pulmonary vasodilation in pts with PAH secondary to COLD. This vasodilation is associated with a slight venous admixture.

954-87 The Pulmonary Circulation Is an Important Site for Both Clearance and Production of Endothelin-1 in Humans

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Animal studies suggest a major role of the pulmonary circulation in the clearance of circulating endothelin-1 (ET-1). The contribution of the human pulmonary circulation to plasma ET-1 has however never been quantified. To precisely quantify and discern between ET-1 clearance and production, we studied patients during elective coronary angiography by combining the multiple indicator dilution technique with simultaneous measurement of immunoreactive ET-1 levels in companion aortic and pulmonary artery blood samples. A bolus containing trace doses of [125]-I-ET-1 and Evans blue dye was injected into the pulmonary artery and timed samples from the aorta were collected to construct a dilution curve. All patients had normal left ventricular ejection fraction (61 ± 7%; M ± SD) and baseline pulmonary and systemic hemodynamics (mean pulmonary artery pressure: 16 ± 4 mmHg). Mean cumulative tracer ET-1 extraction was 47 ± 7% during a single pulmonary transit time. The ET-1 extracted does not return to the circulation and can be characterized by a sequestration rate constant: $K_{seq} = 0.048 \pm 0.019$ s^{-1}. There was however no significant difference between immunoreactive ET-1 levels from the pulmonary artery (0.61 ± 0.29 pg/ml) and aorta (0.67 ± 0.32 pg/ml): the normal lung consequently produces an amount of ET-1 that is quantitatively similar to the quantity that has been extracted. *Conclusion:* The human lung is an important site for both clearance and production of ET-1. There is a normal physiologic "balance" of ET-1 across the pulmonary circulation explaining the absence of difference in arteriovenous ET-1 levels despite a 47 ± 7% clearance. Reduced pulmonary clearance or increased production of this peptide may contribute to the increase in circulating levels found in various cardiovascular conditions.

954-88 Digoxin Partly Restores the Abnormal Circadian Pattern of Autonomic Control During Daytime but Not During Nighttime in Patients With Congestive Heart Failure

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Recently, we demonstrated that treatment with digoxin enhances cardiac vagal tone in patients with mild to moderate congestive heart failure (CHF). To evaluate if this effect is present throughout the day, we studied the circadian pattern of heart rate variability (HRV) parameters in 22 CHF patients (age 60 ± 1 years (mean ± SEM), ejection fraction 0.30 ± 0.01) and in 18 healthy controls (age 55 ± 1 years). The CHF patients were treated with digoxin 0.25 mg once daily for 3 months. Analysis of HRV was performed using 24 Hr Holter recordings and included time and frequency domain parameters. At baseline, all HRV parameters showed a reduced circadian pattern in the CHF patients as compared to the healthy controls. After treatment with digoxin, pNN50 increased significantly from 2.9 ± 0.7% to 4.9 ± 1.2% ($p < 0.05$) during daytime hours in the CHF patients. High frequency power (0.15–0.40 Hz) also showed an increase from 117 ± 22 ms^2 to 175 ± 34 ms^2 ($p < 0.01$) during daytime hours. Low frequency power (0.04–0.15 Hz) showed a small

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