Conclusion: Plasma sFas levels were elevated in patients with DCM. One important mechanism of myocyte death in DCM may be Fas-mediated apoptosis. Plasma sFas in patients with DCM provide prognostic information independent of cardiac function.

4:15

823-2 Angiotensin Converting Enzyme Inhibitors Have a Nitric Oxide Modulated Negative Inotropic Effect in Patients With Left Ventricular Dysfunction

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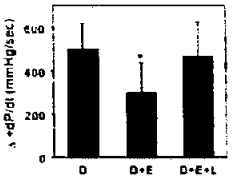
Nitric oxide (NO) has been shown to inhibit the β-adrenergic inotropic response in humans with left ventricular dysfunction. Angiotensin converting enzyme (ACE) inhibitors increase bradykinin, an agonist of NO synthase, by inhibiting kininase II. We hypothesized that ACE inhibitors would produce a NO modulated negative inotropic effect independent of angiotensin receptor-1 (AT-1). Eight patients with dilated cardiomyopathy were withdrawn from ACE inhibitors one week before study and started on the AT-1 receptor antagonist losartan (50 mg QD). Intravenous dobutamine (D) at 5–10 μg/kg/min was administered to achieve a 49 ± 8% increase in peak +dP/dt ($p < 0.001$). Enalaprilat was infused into the left main coronary artery (0.2 mg/min for 15 minutes; D + E) and continued during the infusion of the NO synthase inhibitor L-N^G-monomethyl-arginine (L-NMMA, 5 mg/min for 10 minutes: D + E + L). Left ventricular systolic (LVSP) and end diastolic (LVEDP) pressures, systolic blood pressure, and peak +dP/dt were measured during these infusions. Changes in +dP/dt relative to baseline are shown ($p < 0.05$ vs D and D + E + L). Thus, enalaprilat resulted in a reduction in the dobutamine-stimulated +dP/dt response, and this effect was reversed by L-NMMA. There was no change in LVSP, LVEDP, and systolic blood pressure, demonstrating that the effect of enalaprilat on myocardial contractility was independent of loading conditions.



These data suggest that ACE inhibitors may have a NO mediated, AT-1 receptor independent influence on myocardial contractility. This action may contribute to the therapeutic effects of ACE inhibitors in the management of heart failure by virtue of a post-receptor β-blocking effect.

4:30

823-3 Recombinant Human B-type Natriuretic Peptide Improves Symptoms and Hemodynamics in Patients With Acutely Decompensated CHF

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Recombinant human B-type natriuretic peptide (rhBNP), produced using a fusion protein in Escherichia coli, is identical to endogenous hBNP but has not been previously studied in humans. In a randomized, placebo-controlled, multicenter, double-blind study, effects of a continuous infusion of 2 doses of rhBNP on symptoms and hemodynamics were assessed in 127 patients with acutely decompensated congestive heart failure (CHF). At baseline, 80% of subjects had dyspnea at rest or with minimal exertion. Their median pulmonary capillary wedge pressure (PCWP) was 28 mm Hg and median cardiac index (CI) was 1.9 L/min/m^2. Endpoints included symptoms (based on physician assessment of a 5 point symptom scale), PCWP, CI, heart rate (HR), and blood pressure (BP).

Results: After 6 hours of infusion, dose-related improvements in symptoms, PCWP, and CI occurred with no change in HR. Mild decreases in BP (median decrease of 7% vs. baseline) were well tolerated. Symptom (Sx, % of subjects improved) and hemodynamics (median % change from baseline) results are presented below:

Endpoint	Placebo n = 42	0.015 μ/kg/min n = 43	0.03 μ/kg/min n = 43
Global Sx (% improved)	5	48*	69**
Dyspnea (% improved)	12	55**	50**
PCWP (% change)	+7.3	-20.0**	-31.6**
CI (% change)	10.9	+5.4*	+20.3**

*$p < 0.05$ and **$p < 0.005$, versus placebo.

Conclusions: A continuous infusion of rhBNP 1) safely and rapidly improves global clinical status, dyspnea, and left ventricular performance in patients with acutely decompensated CHF, without increasing heart rate, and 2) causes dose-dependent improvements in symptoms and hemodynamics. Thus recombinant hBNP is an effective agent for therapy of acutely decompensated CHF.

4:45

823-4 Endothelin ET_B Receptors are Functionally Important in Mediating Vasoconstriction in the Systemic Circulation in Patients With Left Ventricular Dysfunction

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The functional significance of ET_A and ET_B receptors in chronic heart failure is not clear. Endothelin (ET)-3, a selective ET_B receptor agonist, is a less potent vasoconstrictor of normal forearm resistance vessels than ET-1, non-selective ET_A and ET_B receptor agonist. We infused ET-1 (5 and 15 pmol/min) into 8 patients with left ventricular dysfunction (LVD) and ET-3 (5 and 15 pmol/min) into a further 8 patients with LVD with similar baseline hemodynamic indices. Hemodynamics were measured by thermodilution catheter and arterial line. Results are expressed as mean ± standard deviation. ET-1 and ET-3 values are given for the 15 pmol/min dose.

	Baseline	ET-1	Baseline	ET-3
HR	73 ± 18	73 ± 16	67 ± 14	68 ± 16
MAP	100 ± 8	105 ± 8*	99 ± 17	105 ± 17*
RAP	6 ± 1	5 ± 2	6 ± 2	5 ± 2
MPAP	21 ± 6	22 ± 6	19 ± 4	21 ± 5
PCWP	13 ± 6	15 ± 7	12 ± 4	13 ± 5
CI	2.44 ± 0.58	2.22 ± 0.56*	2.66 ± 0.79	2.42 ± 0.67**
SVR	1727 ± 403	2054 ± 465**	1639 ± 593	1918 ± 692**
PVR	152 ± 44	149 ± 41	122 ± 37	132 ± 39

*$p < 0.05$, **$p < 0.01$

Exogenous ET-1 and ET-3 caused systemic but not pulmonary vasoconstriction in patients with LVD. The hemodynamic changes were of a similar magnitude at the same molar concentration. This suggests that ETB receptors are functionally important in mediating vasoconstriction in the systemic circulation in patients with LVD.

5:00

823-5 Left Ventricular Remodelling 6 Months After Infarction is Predicted by Myocardial β-Adrenoceptor Density at 1 Month

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Background: Following acute myocardial infarction (AMI) there is evidence of sustained sympathetic overactivity which has been shown to contribute to left ventricular (LV) remodelling in animal models. Increased tissue levels of norepinephrine lead to a reduction of β-adrenoceptor (βAR) density which can be measured noninvasively with positron emission tomography (PET). We aimed to assess: 1- if there is a reduction of myocardial βAR density 1 month after AMI and 2- if this correlates with changes in LV volumes at 6 months.

Methods: We studied 42 patients aged 53 ± 12 years with AMI and no previous angina, diabetes, hypertension or renal disease. All had single vessel disease. LV end-systolic (ESV) and end-diastolic (EDV) volumes were assessed 1 week and 6 months after AMI by echocardiography. Changes (Δ) in ESV and EDV were calculated by dividing the 6 month by the 1 week result. Myocardial βAR density and coronary vasodilator reserve (CVR, dipyridamole) were measured 1 month after AMI with PET using ^{11}CGP-12177 and $H_2{}^{15}O$ respectively. PET data in patients were compared with those in a group of 18 age-matched controls.

Results: ESV was 61 ± 20 ml at 1 week and 64 ± 28 ml at 6 months (p = ns) and EDV was 111 ± 31 and 121 ± 40 ml respectively (p = ns). The patients had lower βAR density (5.95 ± 0.99 vs 8.35 ± 2.00 pmol/g, $p = 0.0001$) and CVR (1.81 ± 0.75 vs 3.22 ± 1.19, $p = 0.0001$) than controls. In patients there was an inverse correlation between βAR and ΔEDV ($r = 0.42$, $p = 0.006$) and between CVR and ΔESV ($r = 0.33$, $p = 0.04$) and ΔEDV ($r = 0.38$, $p = 0.05$).

Conclusion: 1. There is a significant downregulation of myocardial βAR 1 month post AMI which predicts an increased EDV at 6 months; 2. There is an inverse correlation between CVR and deterioration in ESV and EDV.