

HEART FAILURE - BASIC

901-73 Association of Genetic Variants in the Angiotensin II Type 1 Receptor and Angiotensinogen With End-Stage Heart Muscle Disease

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Although local paracrine or autocrine activity of Ang II may be increased in the dysfunctional myocardium, there is heterogeneity in the effects of Ang II on cardiac function. Some of the heterogeneity may be due to genetic variance in renin-angiotensin system components. The frequency of specific point mutations in the angiotensin II type-1 receptor (AT₁R) and in angiotensinogen (AGT) is increased in several caucasian populations with essential hypertension. In addition, the same point mutations are associated with risk for myocardial infarction. As both essential hypertension and myocardial infarction are risk factors for end-stage heart muscle disease, we screened individuals with severe idiopathic dilated cardiomyopathy (IDC) or ischemic cardiomyopathy (ISC) for the AT₁RA¹¹⁶⁶ → C¹¹⁶⁶ and the AGT T⁷⁰⁴ → C⁷⁰⁴ (Met²³⁵ → Thr²³⁵) nucleotide transitions. The frequency of the AT₁RC¹¹⁶⁶ (C) allele is increased in both IDC and ISC populations compared to the disease-free control population. In contrast, the frequency of the AGT Thr²³⁵ (T) allele is increased in the ISC population only.

	IDC (n = 83)	ISC (n = 95)	control (n = 55)
C/C (AT ₁ RC ¹¹⁶⁶)	14%	15%	5%
T/T (AGT Thr ²³⁵)	11%	20%	10%

These data suggest that the C¹¹⁶⁶ mutation in the AT₁R, by altering receptor function in an as yet undetermined manner, is associated with increased susceptibility for heart-muscle disease regardless of the etiology of the disease. The AGT T allele is associated with increased risk for end-stage heart muscle disease only in ISC, and may represent residual risk for myocardial infarction in this population, not AGT-mediated functional changes in the failing myocardium.

901-74 Comparative Effects of Electrically Stimulated Contraction and Angiotensin II on Growth of Adult Feline Cardiocytes in Long-Term Primary Culture

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The purposes of this study were: 1 - determine whether angiotensin II (All) causes growth of adult cardiocytes in long-term culture, 2 - compare the growth effects of All with that resulting from electrically stimulated contraction (ESC), and 3 - determine whether the anabolic effects of ESC acts through the angiotensin 1 (AT₁) receptor. Adult feline cardiocytes were cultured on laminin coated trays in chemically defined serum-free medium for 7 days. Cardiocytes were either electrically stimulated to contract (1 Hz, 5 ms pulse duration, alternating polarity) or were non-stimulated and quiescent. Quiescent cells were studied either in the control state, during treatment with All (10⁻⁸ M), Losartan (10⁻⁶ M, an AT₁ receptor antagonist) or All & Losartan. Electrically stimulated cells were studied either in control state, during treatment with All, or Losartan. Protein content/cell (Prot/Cell, total cardiocyte fluorescence × 10⁶) using confocal microscopy of cells stained with fluorescent isothiocyanate and protein synthesis rate (Prot Syn, nmol PHE/mg protein/4 h) were measured. Measurements of protein synthesis and prot/cell were made on days 1, 4, & 7 in culture. Day 7 data are presented below.

Quiescent:	Control	All	Losartan	All & Losartan
Prot Syn	244 ± 27	272 ± 10*	243 ± 28	241 ± 29
Prot/Cell	1.06 ± 0.03	1.23 ± 0.02*	1.06 ± 0.02	1.03 ± 0.02
Stimulated:	Control	All	Losartan	
Prot Syn	303 ± 8**	308 ± 15**	309 ± 15**	
Prot/Cell	1.52 ± 0.04**	1.58 ± 0.05**	1.56 ± 0.03**	

Data = mean ± sem, *p < 0.05 vs quiescent control, **p < 0.05 vs quiescent All.

Thus, All alone had a modest anabolic effect on quiescent cells. In contracting cells, All had no effect on growth. Growth caused by ESC was more rapid and of greater magnitude than that caused by All. AT₁ blockade inhibited the anabolic effects of All but not ESC. Thus, growth caused by electrically stimulated contraction was not dependent upon activation of the AT₁ receptor.

901-75 Comparison of a Novel Calcium Channel Agonist and Dobutamine in Conscious Dogs With Heart Failure

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Dobutamine (D), a balanced adrenergic agonist, has been proposed for the treatment of heart failure (HF). However, its utility has been limited in HF, because of catecholamine desensitization. Whether or not this mechanism of desensitization in HF affects the calcium channel, which is also important in β -adrenergic signalling, is not established. We compared effects of a calcium channel agonist, BAY y 5959 ((-)-isopropyl 2-amino-5-cyano-1,4-dihydro-6-methyl-4-(3-phenyl-quinoline-5-yl)-pyridine-3-carboxylate), with D prior to HF and 4 weeks after rapid ventricular pacing (240 bpm) in 7 dogs, instrumented for measurement of left ventricular (LV) pressure, LV dP/dt and arterial pressure. HF decreased LV dP/dt from 2730 ± 82 to 1532 ± 120 mmHg/sec and increased heart rate from 96 ± 5 to 123 ± 5 bpm. Prior to HF, D (10 μ g/kg/min) increased LV dP/dt by 55 ± 9% and heart rate by 19 ± 2 bpm, whereas, BAY y 5959 (20 μ g/kg/min) increased LV dP/dt by 79 ± 7% and decreased heart rate by 33 ± 2 bpm. After ganglionic blockade, the bradycardia in response to BAY y 5959 was abolished, indicating that it was reflexly mediated. After HF, responses to D were desensitized, i.e., D increased LV dP/dt by only 27 ± 7%, and heart rate did not change, whereas in HF BAY y 5959 still increased LV dP/dt by 84 ± 7%, indicating lack of desensitization, and still decreased heart rate by 37 ± 5 bpm, indicating reflexes were intact. In contrast, reflex decreases in heart rate induced by phenylephrine (10 μ g/kg) were blunted in HF (-26 ± 4 bpm) as compared with prior to HF (-43 ± 4 bpm). Thus, BAY y 5959 exhibits several unique properties in HF, i.e., it is resistant to desensitization and restores baroreflex function. These features are potentially desirable for clinical application in HF.

HEART FAILURE - CLINICAL

901-76 Prognostic Implications of I-123 Metaliodobenzylguanidine (MIBG) in Patients With Idiopathic Dilated Cardiomyopathy (DCM) and Receiving β -Blockade Treatment

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The aim of this study is to evaluate whether MIBG myocardial imaging predicts the effect of β -blockade on functional improvement in patients with DCM. Twenty-one patients with DCM (mean age, 49.3 ± 15.1 yr, left ventricular (LV) ejection fraction < 0.35, NYHA functional class II or III) were studied. Five mg/day of metoprolol was initially given with the increment of 5 mg/week up to 40 mg/day. At 4 weeks (20 mg/day) and 3 month after the therapy, LV dimension on echocardiography, neurohormonal activities, and MIBG myocardial distributions were examined and compared with baseline values. Patients were classified into 2 groups based on the data before and 3 month after the therapy; with a good response (Gp A) and with a poor response (Gp B). (1) Before metoprolol, there were no significant difference in LV dimension, ANP, norepinephrine (NE) between groups. However, in MIBG imaging, heart to mediastinum activity ratio (H/M) of early image (2.59 ± 0.30 vs 1.85 ± 0.46, p < 0.05) and delayed image (2.19 ± 0.47 vs 1.42 ± 0.30, p < 0.05) were higher and washout rate was lower (45 ± 13.0% vs 64.8 ± 7.0%, p < 0.05) in Gp A than in Gp B, suggesting a close relation between the effects of β -blockade and the severity of sympathetic denervation. (2) Four weeks after the therapy, LV dimension, NE and ANP showed no significant changes in both groups. H/M score of delayed image (2.19 ± 0.47 to 2.3 ± 0.3 p < 0.05) increased in Gp A, but not in Gp B. (3) At 3 month after the therapy, H/M of delayed image (2.14 ± 0.51 to 2.60 ± 0.61, p < 0.01), and LV enddiastolic diameter (63 ± 9.1 to 59 ± 8.4 mm, p < 0.01) and % fractional shortening (18 ± 9.3 to 23 ± 9.4, p < 0.05) in echocardiography improved further in Gp A.

These results suggest that the MIBG imaging predicts the effects of β -blockade beforehand and also the monitoring of the MIBG accumulation after the therapy is helpful to find the timing of functional recovery in patients with DCM.

901-77 Relation Between Plasma Soluble Intercellular Adhesion Molecule-1 Level and the Severity and the Mortality of Patients With Congestive Heart Failure

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A significant role has been demonstrated for neurohumoral activation in