1039 Neurohormones, Cardiac Function, and Pericardial Delivery

Monday, March 30, 1998, Noon–2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: Noon–1:00 p.m.

1039-23 Melatonin, a Pineal Hormone With Antioxidant Property, Protects Against Adriamycin Cardiomyopathy in Rats

I. Morishima, Y. Toki, K. Okumura, T. Ito. *Internal Medicine II, Nagoya University, Nagoya, Japan*

Background: The clinical use of adriamycin (ADR) is limited by its cardiotoxicity in which free radicals and lipid peroxidation may be involved. Melatonin (MEL) has gained increasing interest as a strong antioxidant. Accordingly, the protective effects of MEL against ADR cardiomyopathy was evaluated.

Method: Male Sprague-Dawley rats were divided into 4 groups as follows: ADR (ADR treated, cumulative dose 15 mg/kg bw, ip, for 2 weeks), MEL (MEL treated, cumulative dose 84 mg/kg bw, ip), MEL + ADR (MEL + ADR treated), and CONT (control). After 3 weeks of post treatment observation, their cardiac performance was assessed, and their hearts were used to study myocardial lipid peroxidation by measuring thiobarbituric acid reactive substance (TBARS) along with ultrastructure.

Results: MEL reversed the ADR induced changes in myocardial ultrastructure as well as parameters shown below.

	CONT	ADR	MEL	MEL + ADR
HW/BW ratio	2.63 ± 0.05	2.30 ± 0.05*	2.61 ± 0.06	2.71 ± 0.05
Ascites (ml)	0	31.7 ± 6.3**	0	3.2 ± 2.2
SBP (mmHg)	124.4 ± 2.6	107.4 ± 4.1*	126.3 ± 3.9	124.1 ± 3.2
FS (%)	56.8 ± 1.1	36.4 ± 2.3**	53.4 ± 1.6	50.6 ± 1.1
Mortality (%)	0	23*	0	0
TBARS (nmol/g heart)	51.3 ± 1.1	83.8 ± 2.2**	45.9 ± 1.6	51.4 ± 2.0

Data are mean ± SEM. **p < 0.01, *p < 0.05 vs all other groups. HW/BW: Heart weight/body weight. SBP: Systolic blood pressure. FS: Fractional shortening.

Conclusion: MEL may be highly effective in protecting against ADR cardiomyopathy by preventing lipid peroxidation.

1039-24 Tumor Necrosis Factor-α Induces Contractile Dysfunction in Conjunction With Nitric Oxide Production in Conscious Dogs

D.R. Murray, B. Chandrasekar, G.L. Freeman. *Medicine/Cardiology, The University of Texas Health Science Center, and ALMMVH, San Antonio, TX 78284-7874, USA*

Tumor necrosis factor (TNF)-α promotes elaboration of the inducible isoform of NO synthase (iNOS); however, the relationship between subsequent NO production and the development of contractile dysfunction in vivo is not known. Accordingly, six chronically instrumented, conscious dogs pretreated with propranolol (2 mg/kg) and atropine (2 mg) were studied before and after 1 hour infusion of TNF-α (40 μg/kg). LV contractility was determined by end-systolic elastance, E_{es} (mm Hg/ml), and plasma nitrite + nitrate levels (NO_2 + NO_3; μM) by vanadium reduction. Dogs were killed 24 hour after TNF-α or saline; hearts were frozen and assessed for iNOS protein levels (Western blotting), iNOS enzyme activity (conversion of ^{3}H-arginine to ^{3}H-citrulline in the presence of EGTA+EDTA), localization of iNOS (immunohistochemistry, IHC), and NF-κB, a transcription factor involved in the upregulation of iNOS (electrophoretic mobility shift assay). In TNF-α treated dogs, we observed a 4-fold increase in NF-κB levels, a 3-fold increase in myocardial iNOS protein, and an 18-fold increase in enzymatic activity ($P < 0.001$ for each). IHC localized iNOS predominantly to vascular endothelium and smooth muscle and less intensely to cardiomyocytes.

	Pre-TNF-α	1 h post	7 h post	24 h post
E_{es}	5.4 ± 0.4	7.9 ± 1.4*	5.2 ± 0.5	3.2 ± 0.4*
NO_2 + NO_3	17.6 ± 2.5	14.7 ± 1.4	18.6 ± 1.8	38.5 ± 6.4*

*P < 0.05 Vs corresponding pre-TNF-α

We Conclude: TNF-α administration upregulates functionally active iNOS in the heart, possibly through activation of NF-κB. Increased plasma metabolites of NO strongly correlate with in vivo cardiac depression after TNF-α.

1039-25 Positive Inotropic Effect of Bradykinin: Role of Cardiac Endothelium, Nitric Oxide, Prostaglandins and Endothelin

P. Mohan, D.L. Brutsaert, S.U. Sys. *University of Antwerp, Antwerp, Belgium*

Background: Bradykinin (Brad) causes endothelium-dependent vascular smooth muscle relaxation and may explain some of the beneficial cardiac effects of angiotensin converting enzyme inhibitor therapy. Brad receptors are also present on cardiomyocytes. However, the inotropic effect of Brad on myocardium, in particular role of endocardial endothelium (EE), mediators released by EE-nitric oxide (NO), prostaglandins (PG) and endothelin, and interaction with concomitant β-adrenergic stimulation have not been investigated.

Methods: We examined myocardial effects of Brad (10^{-9} M to 10^{-5} M) in isolated cat papillary muscles (Krebs-Ringer 1.25 mM Ca^{++}, 35°C, enalaprilat: 5×10^{-5} M, atenolol: 2×10^{-5} M) before (+EE: n = 7) and after selective damage of EE (−EE: n = 7; 1s immersion in Triton-X, 0.5%). To investigate role of NO, PG and endothelin, Brad was also added in subgroups of +EE muscles incubated with L-NA (3×10^{-6} M, n = 8), indomethacin (INDO: 10^{-6} M, n = 8) or BQ123 (10^{-6} M, n = 7) respectively.

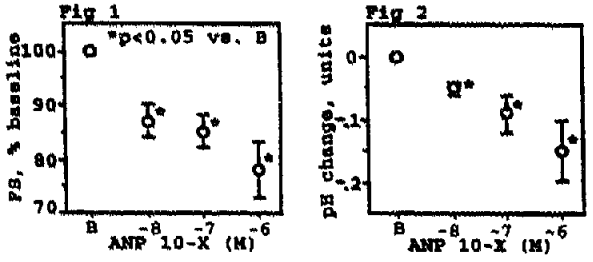
Results: (mean ± SE, Δ% baseline) In +EE, Brad induced an dose-dependent increase in peak active tension (AT; 10^{-5} M = 9.3 ± 3.1) with no change in time to half relaxation (0.7 ± 1.4). This response was blocked by the bradykinin receptor antagonist (HOE 140; 10^{-7} M, n = 3) and was absent in -EE. The inotropic response to Brad was not inhibited by LNA, INDO or BQ123 alone but was inhibited by LNA + INDO (Brad: 10^{-5} M; AT = 1.0 ± 1.6). Isoproterenol (3×10^{-7} M)-induced increase in AT (14.4 ± 2.0) was abolished by Brad (10^{-5} M) (0.2 ± 4.2), which was not modified by LNA + INDO (0.3 ± 4.3).

Conclusion: Brad induced a cardiac endothelium-dependent positive inotropic myocardial effect with no effect on relaxation, which was mediated by both NO and PG. Brad abolished the effect of concomitant β-adrenergic stimulation, independent of NO and PG.

1039-26 Atrial Natriuretic Peptide Decreases Contractility and Intracellular pH in Adult Ventricular Myocytes

M. Tajima, J. Bartunek, B.H. Lorell, B. Israel. *Deaconess Medical Center and Harvard Medical School, Boston, MA, USA*

Atrial natriuretic peptide (ANP)-cGMP signaling modifies cardiac function by natriuresis and vasodilation but inotropic effects are controversial. We studied effects of ANP on cell shortening and intracellular signaling in HEPES-buffered adult ventricular rat myocytes (n = 26) paced at 0.5 Hz. At baseline (B), fractional cell shortening (FS) was 7.0 ± 0.2% and intracellular pH (pHi, SNARF-1) was 6.92 ± 0.05. ANP caused a dose-dependent depression of contractility (Fig. 1), associated with intracellular acidification (Fig. 2). In cells loaded with Fluo-3 (n = 5), ANP caused no change in systolic $[Ca^{2+}]_i$.



Summary: ANP directly depresses contractility via intracellular acidification and decreases myofilament $[Ca^{2+}]$ sensitivity. Similar to negative inotropic action of nitric oxide, this may be related to cGMP-mediated disabling of forward Na^+-H^+ exchange.

1039-27 Pharmacokinetics of Agent Distribution From the Pericardial Space: Effects of Agent Size and Validation of a Mathematical Model for Epicardial Penetration

S.H. Baek, L.L.-F. Stoll, A. Szabo, L.K. Keefer, J. Hrabie, K.L. March. *Indiana University Medical Center, Indianapolis, IN, National Institute of Health, Bethesda and Frederick, MD, USA*

Recent data have demonstrated reduction of restenosis in the porcine model by intrapericardial delivery of diazeniumdiolated albumin (NONO-Alb). The bioactivity of intrapericardial agents will be importantly modulated by their residence time as well as penetration into epicardial tissue. We thus evaluated the dependence of residence half-life (RHL) on molecular weight (MW)

MONDAY POSTER