1115-15 Metalloporphyrins and Tetrapyrroles as Acute Positive Inotropes in a Rat Model of Myocarditis

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Background: Cyclic guanosine monophate (cGMP) depresses myocardial contractility. Metalloporphyrins are naturally occurring inhibitors of the activity of soluble guanylyl cyclase (SGC). In the current study, we investigated the effect of Sn- and Zn-protoporphyrin IX (SnP and ZnP) on systolic cardiac function in a rat model of myocarditis (IP isoproterenol 3 mg/kg × 2 days).

Methods: A constant flow Langendorff preparation with intact hearts was used to evaluate cardiac performance.

Results: SnP (50 μM) and ZnP (100) significantly increased maximum rate of left ventricular pressure (dP/dt) and left ventricular pressure (LVP) of myocarditic hearts ($P < 0.05$, $n = 24$). Increased contractility persisted for up to two hours, the duration of the experiments. Interestingly, SnP decreased aortic perfusion pressure, suggesting that SnP reduced coronary resistance. In control hearts, ZnP and SnP had no effect on contractility. In order to more closely link the inotropic effect of ZnP and SnP in the myocarditic hearts to inhibition of SGC, we used Protoporphyrin IX (PP), a tetrapyrrole which does not inhibit SGC, and 1H-[1,2,4]oxadiazolo [4,3,-a]quinoxalin-1-one (ODQ), a specific inhibitor of SGC. PP (100 μM) did not affect contractility while ODQ (100 nM) increased both LVP and dP/dt ($P < 0.05$, $n = 4$).

Conclusion: SGC activity contributes to systolic dysfunction in myocarditis. It is possible that soluble guanylyl cyclase is a therapeutic target and that specific metalloporphyrins are useful in the treatment of myocardial dysfunction associated with inflammation.

1115-16 Effects of Aging on the Negative Chronotropic and Anti-β Adrenergic Actions of Adenosine in the Rat Heart

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The effect of aging on the anti-adrenergic actions of adenosine was studied *in vivo* and *in vitro* using adult (6 month old) and old (24 month old) Fisher 344 rats. Adenosine (0.01–0.1 μmol/kg), given as a rapid bolus into the right atrium, exerted a negative chronotropic effect manifested as a dose dependent transient prolongation of sinus cycle length (SCL). This effect was similar in both age groups, i.e., the percent maximal prolongation of SCL (%ΔSCL) ranged from 12 ± 2% to 63 ± 14% in the adult and from 20 ± 7% to 57 ± 15% in the old rats. In the presence of isoproterenol (0.2 μg/kg/min), the negative chronotropic action of adenosine was potentiated in the adult rats much more than in the old rats, i.e., %ΔSCL ranged from 60 ± 28% to 183 ± 48% vs. 40 ± 12% to 70 ± 13%, respectively ($p < 0.05$). In addition, in the presence of isoproterenol, acute transient global myocardial hypoxia and rapid atrial pacing induced atrial fibrillation (AF) in all six old rats but in only one of the six adult rats ($p < 0.05$). Under these conditions, the blockade of A_1-adenosine receptors in the adult rats increase the frequency of induced AF to six out of the twelve. *In vitro*, adenosine's attenuation of either isoproterenol- or forskolin-induced production of cAMP was significantly less in atrial membranes isolated from old vs. adult rats.

Conclusion: The anti-adrenergic action of adenosine, mediated by A_1-adenosine receptors, is attenuated in old vs. adult rat hearts. This could suggest reduced cardioprotection by adenosine in elderly patients.

1115-17 Differential Effects of Procainamide and Verapamil on Ventricular Vulnerability in Isolated Rabbit Hearts

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Background: Mechanisms of initiation and maintenance of ventricular fibrillation (VF) are complex. We compared effects of Na^+-channel and Ca^{++}-channel blockade on ventricular vulnerability and fibrillating wavefronts in isolated rabbit hearts.

Methods: The ventricular vulnerable period (VVP) and the upper limit of vulnerability (ULV) were determined using shock energy of various strengths while scanning the electrocardiographic T-wave. Optical imaging using potential-sensitive dye (di-4-ANEPPS) was utilized, without mechanical uncoupling agents, to assess the wavefront dynamics during and after delivery of shock (S2) through internal leads in the pulmonary artery and left ventricular apex. Procainamide (Pr, 0.1 mM) and verapamil (Ve, 1 μM) were added to the perfusate in seven and four hearts, respectively.

Results: Pr significantly increased the midpoint of VVP, but had no effects on ULV. It changed the direction of the principal reentrant pathways from parallel to 45° relative to fiber orientation. Further-more, Pr significantly prolonged the dominant arrhythmic cycle length (ACL). In contrast, Ve slightly shifted VVP, but greatly shortened ACL. Fibrillating wavefronts disrupted into small fragments with short conduction pathways after Ve treatment.

	mid-VVP (ms)	ULV (V)	ACL (ms)
Control	143 ± 12	212 ± 39	101.9 ± 11.3
Pr	164 ± 24*	213 ± 42**	150.9 ± 19.6*
Control	123 ± 5	133 ± 39	93.3 ± 7.4
Ve	133 ± 5*	143 ± 30**	74.8 ± 11.6*

(* $P < 0.05$, ** p = NS)

Conclusion: In isolated rabbit hearts, Pr stabilizes VF possibly by modifying preferential conduction pathways, whereas Ve may have adverse effects on VF by shortening its ACL and fragmenting the wavefronts.

1116 Clinical Trials of Lipid Lowering Drugs

Tuesday, March 31, 1998, Noon–2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: Noon–1:00 p.m.

1116-1 Insights into Statin Treatment of Hypertriglyceridemia

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Background: The focus of statins has been on LDL-cholesterol (LDL-C). A study in subjects with high triglycerides (Tg) with atorvastatin (Ator) reported reductions of 26 to 46% which were dose related.

Purpose: To determine if: (a) all statins were effective in lowering Tg; (b) the % Tg reduction was independent of baseline Tg as occurs for LDL-C; (c) the efficacy for Tg and LDL-C lowering were related.

Methods: To standardize assessments we devised a ratio of % Tg reduction ÷ % LDL-C reduction (Tg/LDL-C ratio). The ratio for the Ator high Tg study was 1.6, 1.0 and 1.1 for 5, 20 and 80 mg respectively. The ratio for a non-high Tg Ator study (Tg <300 mg) was 0.8, 0.7 and 0.4 for the 5, 20 and 80 mg doses. We then carried out a "meta-analysis" using 7 previously reported studies involving Sim, 5, 10, 20, 40, 80 and 160 mg, lovastatin (Lov) at 20, 40 80 mg and pravastatin (Pra) at 10, 20, 40 mg. The protocols were of similar design; 4 wk placebo with randomized double-blind active therapy for 4–6 weeks. A total of 2689 subjects were included and for all protocols, entry Tg were <400 mg/dL. Baseline (BL) Tg were stratified at <150 mg/dl, 150–250 mg/dL and >250 mg/dl.

Results: The data for all statins was consistent with Tg lowering highly related to BL Tg. At Tg <150 mg/dL minimal reduction occurred and was not dose related. For BL Tg >250 mg/dL Tg reductions of 45%, 44% and 35% were found for Sim 160 mg, Lov 80 mg and Pra 40 mg. Irrespective of dose or drug the Tg/LDL-C ratio was as follows: BL Tg 150, Ratio 0.0 ± 0.3; BL Tg 150–250, Ratio 0.5 ± 0.2; Bl Tg >250, Ration 1.2 ± 0.3.

The Tg/LDL-C ratio was evaluated by linear models assessing BL Tg, drug and dose. Only BL Tg was statistically significant ($p < 0.001$).

Conclusion: (a) Tg reduction by statins is highly dependent on BL Tg. At higher BL Tg, Tg reduction is dose dependent. All statins will be effective in reducing Tg in high Tg subjects but statins with greater LDL-C reducing efficacy will also be more effective in reducing Tg. (b) The Tg/LDL-C ratio is fairly constant at any BL Tg level for all statins irrespective of dose and there is a single mechanism involved in both Tg and LDL-C reduction.

1116-2 Delayed Progression of Atherosclerosis in Coronary Bypass Grafts Is Similar in Women Compared to Men Following Aggressive Cholesterol Lowering Despite More Frequent Risk Factors: Post CABG Trial

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Background: The study is based on data from the Post Coronary Artery Bypass Graft (CABG) trial designed to determine the effect on atherosclerosis in saphenous vein grafts of 4 to 5 years of aggressive LDL-cholesterol lowering to 93–97 mg/dl (AL) and moderate lowering to 132–136 mg/dl (ML).

Methods: The prevalence of associated risk factors and the treatment effect (probability of progression) were compared in 1249 men (M) and 102 women (W) of similar age (61.5 and 62.4 years). Eleven risk factors (RF) were studied: family history, diabetes mellitus, systolic and diastolic hypertension, smoking, no regular exercise, LDL cholesterol (C) ≥160 mg/dl, HDL-C <35 mg/dl, LDL-C/HDL-C >3, triglycerides ≥200 mg/dl and body mass index.

Results: The mean number of RF in W was 5.0 ± 2.0 compared to 4.5 ± 1.7 in M ($p = 0.002$). Five RF were more frequent in W: family history (80%

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