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February 1998

1115-15 Metabolism and Tetrepyrrole as Acute Positive Inotroples in a Rat Model of Myocarditis

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Background: Cyclic guanosine monophosphate (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 iso prosotene 3 mg/kg, 2 days).

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

Results: SnP (60 µM) and ZnP (100 µM) 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 refilling 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 SnP and ZnP 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[3,4-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 observed in both age groups, i.e., percent maximal prolongation of SCL (%SCL) ranged from 12 ± 5% 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., %SCL ranged from 60 ± 28% to 183 ± 48% in the adult and from 20 ± 7% to 57 ± 15% in the old rats. In the presence of isoproterenol (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., %SCL ranged from 60 ± 28% to 183 ± 48% 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., %SCL ranged from 60 ± 28% to 183 ± 48% 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., %SCL ranged from 60 ± 28% to 183 ± 48% in the adult and from 20 ± 7% to 57 ± 15% in the old rats.

Conclusion: The anti-adrenergic action of adenosine, mediated by A1-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 Procarcinamide 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 Ca2+ 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 (50 V) through intra-arterial leads in the pulmonary: artery and left ventricular apex. Procarcinamide (Pr, 0.1 µM) 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.

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.

1116-01 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) and low HDL-cholesterol (HDL-C) reported reductions of 26 to 46% which were dose related.

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

Methods: In randomized assessments we devised a ratio of % TG reduction: % LDL-C reduction (TG/LDL-C ratio). The ratio for the Atof high TG study was 1.0 and 1.1 for 5, 20 and 80 mg respectively. The ratio for a non-high TG atorvastatin study was 0.0 and 0.4 for the 5 and 20 mg doses. We then carried out a meta-analysis using 7 previously reported studies involving Sim, 5, 10, 20, 40, 80 mg and 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: 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, reduction of 45%, 45% 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 < 150 mg/dL, Ratio 1.5 ± 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.

1116-02 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 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 1294 men (M) and 102 women (W) of similar age (61.5 and 62.4 years). Eleven risk factors (RF) were studied: T, menopause, 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%