SKELETAL MUSCLE INFLAMMATORY CHANGES CORRELATE WITH FUNCTIONAL CLASS AND CIRCULATING CYTOKINE LEVELS IN PATIENTS WITH CONGESTIVE HEART FAILURE

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Circulating cytokine levels are elevated in symptomatic patients with congestive heart failure (CHF). Whether peripheral abnormalities which are present in the skeletal muscles (SM) and vasculature of symptomatic patients contribute to cytokine production in CHF is unknown. Accordingly, vastus lateralis SM biopsies were obtained in 14 patients with functional class (FC) I to IV CHF (peak aerobic capacity (VO2) ranging from 6 to 23 ml/kg/min) and in 6 age-matched normal subjects who served as controls. Mean patient age and ejection fraction were 55.7 years and 22.4% respectively. The etiology of CHF was coronary artery disease (n=9) or hypertension (n=5). All patients were treated with angiotensin converting enzyme inhibitors, digoxin and loop diuretics. Parafin sections were evaluated by hematoxylin and eosin staining and immunostained using a histocyte marker (KP-1), a T cell marker (CD3) and a B cell marker (LS2). Tumor necrosis factor alpha (TNF-α) levels were measured by immunoassay (Quantikine HS R&D Systems). No B cells were detected. Reproducibility of SM biopsy findings was established in 3 patients who underwent 2 serial biopsies. In conclusion, increased numbers of perivascular and interstitial T cells in SM accompany the rise in circulating cytokine levels as the symptoms progress in patients with CHF.

Prognostic Value of Soluble Cytokine Receptor and Adhesion Molecule in Patients With Chronic Congestive Heart Failure

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To evaluate the role of immune system activation in the pathophysiology of chronic congestive heart failure (CHF), we determined the plasma soluble cytokine receptors such as soluble tumor necrosis factor receptor I (sTNF-R I) and sTNF-R II, and soluble adhesion molecules such as soluble intercellular adhesion molecule 1 (sICAM-1), and soluble vascular cellular adhesion molecule (sVCAM-1) in 83 patients with CHF (all ventricular ejection fraction (EF) <45%, mild CHF; NYHA II, n=40, severe CHF; NYHA III-IV, n=43) by means of enzyme-linked immunosorbant assay. Furthermore, they were monitored for a follow-up period of more than 1 year. The plasma levels of sTNF-R I increased with the severity of CHF (r=0.25 ± 0.07 pg/ml, p<0.0001) and the plasma level of sTNF-R II also increased with the severity of CHF (r=0.25 ± 0.07 pg/ml, p<0.0001). The plasma levels of sICAM-1 and sVCAM-1 were also increased in relation to the severity of CHF (mild CHF: 1025 ± 74 pg/ml vs. severe CHF: 1264 ± 207 pg/ml, p<0.0001). The plasma levels of sICAM-1 and sVCAM-1 were both related to the severity and mortality of patients with CHF, suggesting an important role of the immune system activation in the pathophysiology and progression of CHF.

Clinical Cardiology:

Exercise Factors by Gender, Age, and Functional Status

Tuesday Afternoon

Abstracts 2908–2916

Does the Change in Quantitatively Assessed Coronary Artery Disease After Lipid-Lowering Therapy Relate to the Change in Functional Status of the Patient?

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In general the effects of lipid-lowering therapy are evaluated by clinical events or anatomical parameters. Assessment of functional parameters is an alternative approach, that may provide relevant additional information. Therefore we assessed regional myocardial blood flow and exercise parameters and related the changes in these measurements to the results of the quantitative coronary angiography (QCA). Methods: Patients were randomized to pravastatin (prav.) 40 mg o. d. or placebo (placc.) according to the REGRESS protocol (Regression Evaluation Statin Study). Before and after 2 years of therapy the following measurements were performed: 1) Mean segment diameter (MAD) and minimal luminal diameter (MLD) assessed by QCA; 2) assessment of the regional myocardial blood flow by digital subtraction angiography after i.v. papaverine with video-densitometric calculation of the hyperemic mean transit time (HMTT). 3) Exercise time (EXT) and maximal ST-segment depression (MST), assessed during a standardized bicycle test. Results: 193 Patients as part of this study were included. Complete follow-up after 2 years was available in 25 patients in the medical management (M), 10 in the PTCA group and 14 in the CABG group, respectively. Effect analysis of prav. versus placebo was based on 36 patients (M and P) treated, PTCA patients excluded. The change in MAD was related to the change in M (r=0.39, p<0.0001, not to EXT) and MST. The change in MVD was not correlated with change in exercise parameters or change in HMTT. The change in HMTT was correlated with the change in EXT (r=0.86, p<0.002). Conclusion: Change in MOD is moderately related to maximal ST-segment depression during the exercise test. Myocardial perfusion better correlates with the functional status of the patient, presumably because HMTT also reflects changes at the microcirculatry level.

Platelets in Athletes are Supersensitive to Nitric Oxide

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Animal studies have revealed that regular exercise may enhance coronary vasodilatation in response to S-nitrosothiols (NOy) system. However, the effect of chronic aerobic exercise on the sensitivity of target cells to NO have not been extensively studied. We conducted in vitro studies on the responsiveness of the platelets to NO in athletes. Fifteen male athletes (Group A, aged 22-26 years), training daily for a triathlon-race, and 15 age- and gender-matched sedentary subjects (Group S) entered this study. Fasting blood samples were obtained and washed platelets were prepared for determination cyclic GMP (cGMP) accumulation in response to 1 µM to 10µM SIN-1 (NO donor). Cyclic GMP accumulation in the platelets was measured by guanine prelabelling method and was expressed as percentage of conversion from radioabeled GTP. Physical fitness of the athletes was confirmed by the blunted heart rate and blood pressure response to submaximal treadmill exercise. Cyclic GMP accumulation in the platelets of athletes was significantly enhanced at basal levels (in percentage of conversion, A: 0.19±0.012, S: 0.12±0.009, mean±SEM, P<0.01) and in response to SIN-1 in the concentration range of 1-100 nM (in fold of basal values, at 1 nM, A: 1.5±0.03, S: 1.1±0.03, mean±SEM, P<0.01, at 100 nM, A: 4.4±0.29, S: 3.0±0.25, P<0.01). However, there were no differences at 1 µM and more. In summary, cGMP levels in the platelets of athletes were significantly higher at basal levels possibly due to enhanced NO synthesis associated with chronic exercise. In addition, platelets may be supersensitive to physiologically-relevant low concentrations of NO in athletes. These similarities in platelet cGMP metabolism in athletes may partially explain the protective effects of regular exercise against thrombotic cardiovascular diseases.

Myocardial Injury in Athletes Participating in the Hawaii Ironman Triathlon

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Can prolonged aerobic exercise cause myocardial injury? CK-MB and myoglobin, biochemical markers of muscle injury, lack the specificity to detect cardiac specific muscle damage. Cardiac troponins I (cTnI) and troponin T (cTnT) are both highly sensitive and specific for detecting cardiac myocyte necrosis. To assess whether exercise can induce cardiac specific myocyte injury, blood samples were collected from 23 athletes (11 males, mean age 38.3±10.5 years, none with risk factors for CAD) 24 hours prior and immediately after the Hawaii Ironman Triathlon (2.4 mi swim, 112 mi bike, 26.2 mi run). cTnI (Enzyme, Boehringer Mannheim) and cTnT were measured by immunobiosys. The cTnT assay has <0.05% cross-reactivity with skeletal TnT. No subject had detectable cTnT or cTnT in the pre-race samples. However, following the race 2 subjects (8%) had marked increases in both cTnT (0.15-3.03 ng/ml) and cTnT (2.03 and 4.400 ng/ml) 4 subjects (17%) had mild increases in cTnT (0.04-0.05 ng/ml) but no detectable cTnT. Quantitative electrocardiographic wall motion analysis was performed on 16 myocardial segments in 11 of the subjects before and immediately after the triathlon. All pre-race echo scores were completely normal. Average increase in the mean echo score, indicating worsnent ventricular function, was 0.6 in those with a marked increase in cTnT and cTnT, 2.3 in those with a moderate increase in cTnT and cTnT, and 1.4 in those with no increase. Therefore, ultra-endurance exercise may cause myocardial damage manifested as a rise in cTnT and cTnT and wall motion abnormalities detected by echocardiography, individuals could be aware of the possibility of myocardial injury associated with prolonged periods of exercise.