Core 2. Epidemiology and Prevention of CV Disease: Physiology, Pharmacology and Lifestyle

Session Title: Novel Biomarkers and CVD I

Abstract 18709: Association of Reactive Oxygen Metabolites and High-sensitivity CRP with severity of angiographic Coronary Artery Disease

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Background: Reactive oxygen species (ROS) and inflammation play the role in the pathogenesis and the development of coronary artery disease (CAD), and high-sensitivity C-reactive protein (hs-CRP), a marker for low-grade inflammation, is one of the most studied biomarkers for the evaluation of CAD risk. In contrast, there is little biomarker of ROS, which is easy to assay and is widely accepted as marker of CAD. Hence, in this study, we compared associations of hs-CRP and derivatives of reactive oxygen metabolites (d-ROM), a newly and easier-to-assay marker of ROS, with the severity of CAD.

Methods: We examined the presence of CAD by coronary angiography (coronary stenosis ≥ 50% luminal diameter narrowing) and CAD patients were divided to single-vessel disease (SVD) or multiple-vessel disease (MVD) according to the number of vessels. In consecutive CAD patients, we assessed d-ROM by simpler method for detecting hydroperoxide as a marker of ROS, and compared association between hs-CRP and severity of CAD.

Results: In preliminary study, d-ROM values were significantly increased in CAD patients compared to control patients. In consecutive 261 CAD patients, d-ROM values were significantly higher in CAD patients with MVD (n=172) than CAD patients with SVD (n=89) (d-ROM: CAD+SVD; 332.2 ± 70.9 U.CARR versus CAD+MVD; 353.2 ± 70.5 U.CARR, $p<0.05$). In receiver-operating characteristic analysis, d-ROM values was a significant determinant for the severity of CAD (area under the curve; 0.60, 95% confidence interval; 0.52-0.67, $p<0.01$). In contrast, hs-CRP of CAD patients with MVD were not changed compared to those of CAD patients with SVD (ln[hs-CRP]: CAD+SVD; -2.79 ± 1.12 mg/dL versus CAD+MVD; -2.65 ± 1.09 mg/dL, $p=0.32$). By multivariate backward logistic regression analysis among various risk factors, d-ROM values, but not hs-CRP independently associated with the severity of CAD ($p<0.05$).

Conclusion: d-ROM values reflecting ROS levels significantly increased in CAD patients and significantly correlated with the severity of CAD. d-ROM assay might be a more important biomarker than hs-CRP to evaluate the severity of CAD and screen for CAD in high-risk patients. Identifying the high-risk CAD patients by d-ROM may provide clinical benefits for risk stratification.

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Key Words: Reactive oxygen intermediates • Coronary artery disease • Biomarkers

Core 2. Epidemiology and Prevention of CV Disease: Physiology, Pharmacology and Lifestyle

Session Title: Heart Failure Management: Problems and Solutions

Abstract 15085: The Association Between Oxidative Stress, Inflammation and Cognitive Impairment in Older Heart Failure Patients

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Background: Cognitive impairment (CI) is a major problem commonly seen in older heart failure (HF) patients. CI negatively impacts on the patient's capacity to understand and follow complex medical treatments potentially leading to increased hospital readmissions and mortality rates. Previous research suggests that mechanisms underlying CI in these patients include changes in cerebral blood flow. Inflammation and oxidative stress may also contribute to CI, however their effects in the context of HF have not been investigated.

Objectives: a) to extend the range of cognitive measures which might be vulnerable to HF using a well-validated assessment instrument and b) to investigate whether inflammation and oxidative stress are associated with CI in older HF patients (aged ≥60 years).

Methods: A total of 40 patients with HF (NYHA class II, III or IV) and 40 healthy controls matched for age and gender completed the study. Cognitive function was assessed using the Cognitive Drug Research® computerised test battery and executive functioning was assessed by the Trail Making-B (TM-B) and Stroop tasks. Cerebral blood flow (CBF; Transcranial Doppler) and biomarkers were measured, including oxidative stress by determinable reactive oxygen metabolites (d-ROMs) and systemic inflammation as measured by high sensitive C-reactive protein (hsCRP).

Results: Compared to healthy controls (67±5.3 years), HF patients (68±7.0 years) performed significantly slower on the *power of attention* cognitive domain (1270±123 ms verses 1191±87 ms, $p<.01$). As expected, patients performed worse than controls on TM-B (106±42 ms verses 86±64 ms, $p<.01$). Patients' plasma d-ROM levels were significantly higher than controls (467±91 vs 352±84 Ucarr, $p<.001$). Furthermore, analyses of covariance suggest that in addition to CBF, mechanisms for impairments in *power of attention* and executive functioning include d-ROMs and hsCRP.

Conclusions: 1. D-ROM is a useful measure of oxidative stress in HF; 2. Systemic inflammation and oxidative stress may represent additional mechanisms for impaired cognitive function in HF and 3. Anti-inflammatories and antioxidants merit investigation as novel interventions to ameliorate cognitive decline in HF.

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Key Words: Heart failure • Behavioral aspects • Biomarkers • Inflammation • Oxidative stress

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Abstract 4026: Immunoadsorption Therapy Reduces Oxidative Stress in Patients With Dilated Cardiomyopathy

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Introduction: Although the mechanisms responsible for the development and progression of left ventricular failure in DCM have not yet been fully elucidated, a variety of experimental studies suggest that alterations of the immune system are involved. Indeed, several literatures reported that the elimination of anti-β1-adrenoreceptor (AR) autoantibodies with immunoadsorption (IA) therapy induced in short- and long-term improvements of LVEF, cardiac output, and NYHA functional class in patients with DCM. We assessed the hypothesis that the reduction of reactive oxygen species (ROS) is also related to the mechanism of left ventricular functional benefit from IA.

Methods: Seven patients (NYHA functional class III/IV, LVEF <30%, cardiac index <2.2 l/min/m^2) with DCM were enrolled in this study. Removal of β1-AR autoantibodies with IA was achieved by passing a patient's plasma over columns; a plasma filter (Plasmaflo OP®) for plasmapheresis and a tryptophan column (Immusorba TR®) for immunoglobulin extraction. The level of anti-β1-AR autoantibodies was measured by ELISA. As a marker for oxidative stress, we determined the level of diacron-reactive oxygen metabolite (d-ROM).

Results: During IA, the values of IgG3 and β1-AR autoantibodies of all patients decreased significantly from 63.5±15.0 to 14.6±2.9 mg/dl and from 27.8±5.0 to 18.7±5.5 U/ml ($p<0.01$), respectively. Simultaneously, the IA induced hemodynamic improvement: cardiac index increased from 1.71±0.40 to 1.97±0.41 l/min/m^2 and LVEF increased from 22.8±6.1 to 29.1±9.1% ($p<0.05$). The level of d-ROM was decreased significantly from 392.7±17.03 to 314.1±22.03 U.CARR ($p<0.05$), and the reduction rate of d-ROM was associated with the reduction rate of β1-AR antibodies ($p<0.01$). In cardiac parameters, best correlations were found for d-ROM to PCWP ($r=0.668$, $p<0.05$), and inversely for d-ROM to LVEF ($r=–0.601$, $p<0.05$).

Conclusions: The reduction of oxidative stress could be one of the mechanisms of beneficial effect of IA therapy in patients with DCM.

Resuscitation Science Symposium

Session Title: Session VIII: Best Original Resuscitation Science

Abstract 283: Oxidant and Antioxidant Levels During Brain Hypothermia Therapy After Cardiopulmonary Resuscitation

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Oxidative stress has important roles in global brain ischemia. The control of free radical production is one of the targets in the treatment for prevention from brain damage. Therapeutic brain hypothermia therapy (BHT) has neuroprotective effect and is thought to have the effect on the control of free radical production. On the other hand, the kinetic of free radical during BHT remains unclear. The aim of this study is to investigate of the kinetic of oxidative stress and endogenous bio-antioxidant potential during BHT in the patients with post cardiopulmonary resuscitation (post CPR). Twenty one post CPR patients are enrolled. Patients were treated at 33°C. The generation of free radicals was evaluated in each plasma sample by the colorimetric determination of reactive oxygen metabolites (d-ROM test) using the free radical analytical system (FRAS; Health&Diagnostic Limited Co., Italy). The serum antioxidant abilities were measured by the BAP (bioantioxidant potency) test performed with FRAS (Health&Diagnostics Limited Co., Italy) ROM level during hypothermic phase (33°C) was suppressed significantly in comparison to pre-induction phase (333.6±79.0 CarrU vs 266.7±57.6 Carr U, P>0.05). BAP level was also suppressed during hypothermic phase (2523.0±550.5 IU vs. 2021.4±272.2 IU, P>0.05). ROM levels were increased along the rewarming (33–36°C). BAP levels also recovered along the rewarming. Especially, BAP levels were rapidly recovered during 35–36°C. In conclusion, we demonstrated that BHT suppressed free radical production in clinical settings. On the other hand, BHT also led to suppression of bio-antioxidant potential. Our data also indicated that the imbalance of oxidant and antioxidant balance exists in rewarming phase (33–35°C). Supporting therapies of antioxidant potential in rewarming phase in BHT may settle some troubles during rewarming phase in BHT.

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Key Words: Hypothermia • Oxidative stress • Resuscitation