Women's Health and Cardiovascular Diseases

The pathophysiological background of heart failure with preserved ejection fraction (HFPEF)

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Aim: We aimed to characterize the myofibrillar components of diastolic heart failure (heart failure with preserved ejection fraction (HFPEF)).
Methods: Biophysical and biochemical characteristics of permeabilized cardiomyocytes isolated from left ventricular biopsies of patients with or without HFPEF, and/or with aortic stenosis (AS), or diabetes mellitus (DM) were determined under in vitro conditions.
Results: Passive force ($F_{passive}$) of cardiomyocytes isolated from HFPEF patients was significantly higher than in controls. Moreover, $F_{passive}$ correlated with left ventricular end-diastolic pressure (LVEDP) and left ventricular (LV) end-diastolic wall stress. High $F_{passive}$ of cardiomyocytes from HFPEF patients was reversible as it was normalized following the in vitro administration of protein kinase A (PKA) or protein kinase G (PKG) or antioxidants (e.g. dithiothreitol). The three-fold rise in $F_{passive}$ of HF cardiomyocytes compared to AS cardiomyocytes was partially attributed to a shift in titin isoform phosphorylation with relative hypophosphorylation of the stiff N2B titin isoform when compared to that of the more compliant N2BA isoform. $F_{passive}$ was augmented in patients with AS and DM. An additional component of increased cardiomyocyte passive stiffness was associated with myofilament protein oxidation.
Conclusions: Changes in the levels of expression, phosphorylation and oxidation of myofibrillar proteins of LV cardiomyocytes may contribute to the development of HFPEF.
Keywords: heart failure, diastolic dysfunction, cardiomyocyte, passive force, human myocardial biopsy

Gene for connexin 37 and cardiovascular risk

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Aim: The aim of this presentation is to discuss gene-environment interaction in the development of cardiovascular disease. This will be demonstrated on the example of the gene for connexin 37. Previously, we observed that the association between this gene and risk for ischemic heart disease (IHD) is modified by female gender and smoking. Recently, we further expanded the data by measuring this gene polymorphism in patients with IHD from Hungary and Croatia.

Methods: Study population comprised 704 women and 1, 884 men with IHD. As a control group we used population of 1,368 women and 1,191 women from the population based (post-MONICA) study. We compared the prevalence of connexin 37 gene variants between patients and controls after stratifying them by gender and smoking status. Differences were evaluated by chi-square test (STATA program).

Results: The frequency of genotypes in the whole group significantly differed between women smokers and non-smokers with IHD. There was significantly lower frequency of T allele in women non-smokers than in women smokers, with IHD (nonsmokers: TT, CT and CC: 9.5, 37.7 and 52.8 %, smokers: 12.4, 44.5 and 43.1 %, $p = 0.038$). Significant differences were also found between women with IHD and control population with regard to smoking status. No such differences were found in male population. Similar results were observed in the population from Romania, with borderline significance ($p = 0.09$). Data from Hungary and Croatia when stratified by gender and smoking status did not reach statistical significance because of smaller sample size.

Conclusion: Our results indicate that the T allele could be protective against manifestation of ischemic heart disease in female non-smokers while male gender and history of smoking abolishes this positive effect. In general, impact of particular gene variant could be extremely dependent on risk profile of the population under study.

Key Words: connexin 37 gene – ischemic heart disease- gender – smoking

Advanced glycation end products, insulin sensitivity and central obesity: gender-specific associations

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Aim: We studied the gender-specific differences in advanced glycation end-products (AGEs) and advanced oxidation protein products (AOPPs) in young-to-early-middle-aged general population.
Methods: In 437 (183M/254F) apparently healthy volunteers aged 33±11 years plasma levels of N^{ε}-(carboxymethyl)lysine (CML, chemically defined AGE product), AGE-specific fluorescence, levels of soluble receptor for AGEs (sRAGE) and advanced oxidation protein products were determined. Waist circumference was recorded and insulin sensitivity was determined (Quantitative insulin-sensitivity check index - QUICKI). Student's T-test was used to compare 2 groups, and General linear model to assess the impact of gender, waist circumference and insulin sensitivity on above mentioned biomarker's levels.
Results: Males and females did not differ significantly by age and QUICKI. Males presented higher waist circumference (M: 93±11 cm, F: 78±11 cm, $p<0.001$), lower CML (M: 1.2±0.2 ug/ml, F: 1.3±0.3 cm, $p<0.001$), and sRAGE (M: 1.2±0.4 ng/ml, F: 1.3±0.4 ng/ml, $p<0.05$) levels, but higher AOPPs (M: 79±47 umol/l, F: 70±40 umol/l, $p<0.02$). No significant difference in AGE-specific fluorescence was revealed. General linear model revealed that waist circumference imposed the main significant impact on CML, fluorescent AGEs and sRAGE levels. It failed to reveal significant gender-specific impact, effect of waist circumference or QUICKI on AOPP levels
Conclusions: Mild but significant differences in plasma CML and sRAGE between young-to middle-aged apparently healthy males and females are mainly on the account of waist circumference.
Keywords: central obesity, insulin sensitivity, gender, advanced glycation end products, sRAGE, advanced oxidation protein products

Aknowledgement: *Study was supported by the grant from the Ministry of Health of the Slovak Republic, No.: 2005/27-SZU-05.*

Cellular mechanisms for diastolic dysfunction in the human heart

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Left ventricular diastolic dysfunction (DD) occurs in various cardiovascular diseases. DD develops during normal cardiac aging and manifests not only in heart failure with preserved and reduced ejection fraction (HFPEF and HFREF, respectively), but also in diabetic cardiomyopathy, aortic valve stenosis, hypertrophic cardiomyopathy (HCM) and Fabry disease (FD). Mechanisms leading to DD are divergent, and involve cardiomyocyte dysfunction, transcriptional and post-translational myofilamentary protein alterations, as well as abnormalities of the extracellular matrix. Moreover, the relative contribution of the distinct territories widely differs among these diseases.

Increased collagen deposition along with collagen cross-linking by advanced glycation end-products (AGEs) is proposed as the main determinant in the senescent heart. Increased production of reactive oxygen species and involvement of the renin-angiotensin system have been implicated in the background of fibrosis. In HFPEF high cardiomyocyte resting tension was shown to contribute to the myocardial stiffening. Elevated cardiomyocyte resting tension was also implicated in diabetic patients with HFNEF, whereas in diabetic patients with HFREF AGEs deposition and fibrosis were identified as major contributors to increased LV stiffness. In contrast to HFNEF, patients with aortic valve stenosis develop not only diastolic, but also systolic dysfunction, which is attributed to a complex inflammatory process involving similar mechanisms as those leading to atherosclerosis. Genetically determined diseases (HCM and FD) also exhibit diastolic dysfunction. While in HCM mutation of a sarcomeric protein leads to development of myocardial remodeling, FD is associated with an enzyme deficiency, which induces the progressive glycosphingolipid deposition in cardiomyocytes and consequent contractile dysfunction.

The divergent set of mechanisms underlying impaired diastolic function requires not only complex experimental and clinical investigations, but also individually designed therapeutic approaches, which aim to improve the function of the pathologically remodeled heart.

Keywords: cardiomyocytes, contractile dysfunction, diabetes mellitus, diastole, fibrosis, human heart.

Vitamin D status in Slovak population.

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Aim: The key role of vitamin D (VD) in the control of bone metabolism, Ca and P homeostasis is well-known. VD acts through vitamin D receptor and directly or indirectly affects the transcription of more than 200 target genes. Except skeletal effects, there are also a wide variety of non-skeletal effects of VD on the regulation of the cell differentiation and proliferation, hormones secretion and on the modulation of immune system. There is a lack of data on VD deficit in Slovakia. Thus, the aim of our study was to determine VD status in healthy adults in Slovakia.
Methods: The study sample comprised 1213 apparently healthy subjects (851F/ 362M) drawn from existing prospective cohorts of adults living in Bratislava and west Slovakia. The study was carried out during winter and spring. No supplementation of VD was allowed. Body mass index (BMI) was calculated and serum concentrations of 25-hydroxyvitamin D (25(OH) D) and intact parathormone (PTH) were analysed.
Results: The genders were similar in age range (F: 15-80; M: 15-83), but men had significantly higher BMI ($p<0.0001$) and 25(OH) D ($p<0.0001$) and lower PTH ($p<0.041$). Strong relationship between 25(OH)D and BMI ($p<0.0004$) was found in all group and in both geneders separately. A similar pattern emerged for the association between 25(OH)D and age ($p<0.0002$). VD insufficiency (20-30 ng/ml) was found in 26% of men and in 30% of women ($p<0.001$) and VD deficit (<20 ng/ml) was found in 29% of men and in 36% of women ($p<0.001$).
Conclusion: VD deficiency and insufficiency are common in Slovak healthy adults. Low VD levels correlates with age, BMI and sex. Due to the possible links between low VD status and disease risk we recommend to improve vitamin D intake through supplements.

Supported by: Research and development program financed from the European Regional Development Fund, project ITMS No.24240120033.

Key words: vitamin D status, population

Simultaneous quantification of soluble fibrin, DD and Fg in clinics

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Aim: To show the diagnostic importance of simultaneous quantification of soluble fibrin (Sf), D-dimer (DD) and fibrinogen (Fg) at various diseases.
Methods: Quantification of Sf, DD and Fg was performed by ELISA using three test-systems designed in our department.
Results: Quantification of Sf and DD in donor blood plasma showed that Sf concentration is on average 3-3.5 μg/ml and DD concentration – 120 ng/ml. Such measurements give integral information about the state of coagulation system and fibrinolysis at TELA, DVT, DIC syndrome, caesarean operation, arteriovenous form of angiodisplasy, and abdominal aortic aneurysm. Simultaneous measurements of Sf, DD and Fg are useful to diagnose and monitor antithrombotic and thrombolytic therapy including post-operation period. It has been shown the increased concentrations of these molecular markers positively correlate with the seriousness of blood vessel complications in patients, suffering from diabetes mellitus.
Conclusions: Simultaneous quantification of Sf, DD and Fg gives very useful diagnostic information about the state of haemostasis system.

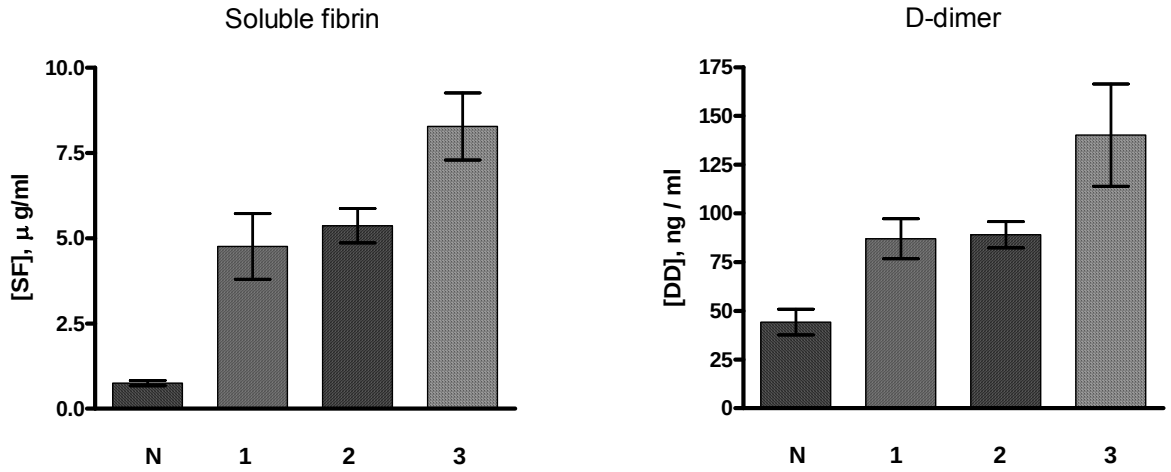

Fig. Soluble fibrin and D-dimer contents in blood plasma of health individuals (N) and patients suffering from diabetes mellitus with initial (1), medium (2) and severe (3) blood vessel complications.

Keywords: soluble fibrin; DD; fibrinogen; simultaneous quantification in clinics

Cellular cardiomyoplasty: new possibilities

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Aim: Nowadays conception of cellular cardiomyoplasty consist in preventing the progression and consequence of cardiac disease (CD), and also enhancing regeneration of damaged tissues. Cell-based myocardial regeneration is currently being explored for a wide range of CD, including acute and chronic ischemic myocardial damage and cardiomyopathy. The goal of cell therapy for heart failure is improving cardiac function, accordingly with inhibition of remodeling process. Ideally, transplanted stem cells (SCs) would replace and mimic the lost cardiomyocytes morphologically and functionally showing the ability to contract and to establish electrical connectivity with the native cells.
Methods: Different SC types have been tested and the methods of their introduction and delivery to damaged myocardium have been developed by using experimental models.
Results: At least two types of bone marrow-derived SCs, skeletal myoblasts, cardiac stem and progenitor cells, embryonic SCs, endothelial progenitor and precursor cells have been investigated in experimental models, and they revealed different potential for differentiation to cardiomyocytes and stimulation of myocardial regeneration. Two fundamental mechanisms by which SCs may repair damaged myocardium have been established: 1) direct or indirect improvement of neovascularization; 2) differentiation into cardiomyocytes and formation of heart tissue. Functional improvement may also be mediated through paracrine secretion of growth factors and cytokines which indirectly promote survival of cardiomyocytes by inhibition of apoptosis, and may also lead to mobilization of endogenous progenitor cells. Address delivery of SCs to damaged myocardium zones is being developed by using nanoparticles in experimental models. During last years a few clinical protocols have been approbated in clinics of USA, Europe and Russia.
Conclusions: According the results of selected clinical trials the methods of cellular cardiomyoplasty are safe for health of patients and their application in the scheme of treatment lead to improvement of cardiac function. But there is a big difference in individual response on the introduction of exogenous cells or cellular products.
Keywords: cell cardiomyoplasty, stem cells, myocardial regeneration

Transcardiac gradients of IL6, TNFa and adiponectin in CAD patients

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Aim: Adiponectin (ADIPOQ), protein produced by adipose cells, has antiatherogenic effect while interleukin 6 (IL6) and tumor necrosis factor (TNFa) have proatherogenic effect. Aim of this study was to determine concentrations of ADIPOQ, IL6 and TNFa in aortic root (AR) and coronary sinus (CS) along with transcardiac gradients in CAD patients.
Methods: Of 36 patients who underwent coronarography 16 of them had CAD. Blood samples were taken from AR and CS. Concentrations of IL6, TNFa and ADIPOQ were obtained by commercially available kits.
Results: IL6 showed a decrease in concentration from AR to CS, CAD patients had significantly higher concentrations ($p=0.012$) (5.81 Me=5.10; 4.35 Me=4.50 pg/ml) in CS. TNFa did not show significant difference throughout heart and in between groups. CAD patients had significantly lower ($p<0.001$) concentrations of ADIPOQ in AR (2.67 ± 1.27; 5.68± 3.10 µg/ml) and significantly lower ($p=0.002$) concentrations in CS (3.89 ± 2.23; 6.86 ± 3.57 µg/ml). Transcardiac gradient, concentration ratio of coronary sinus to aortic root, with average value for IL6 less than 1, did not show significant difference between groups, same as TNFa, where ratio was barely above 1.There was no significant difference between groups. Transcardiac gradient for ADIPOQ was significantly higher ($p=0.018$) in CAD group (1.47 ± 0.31; 1.23 ± 0.25).
Conclusions: CAD patients have decreased levels of adiponectin, higher transcaridac gradient and increased levels of IL6 in CS.
Keywords: adiponectin, CAD, adipose tissue

Anti-mullerian hormone and cardiovascular protection

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Aim: To study dynamics of anti-mullerian hormone (AMH) for perimenopausal women for timely correction of menopausal disorders and prevention of cardiovascular accidents.
Methods: Levels of AMH, low-density lipoprotein-cholesterol (LDL-C), numbers of antral follicles (AF) by ultrasound scan, were studied on 69 women (age 46,69±3,21 y.o.), who have initial involutive changes. 39 women (group I) have cardiovascular diseases (CVD) history (arterial blood pressure > 135/85 mmHg and/or heart attack episodes), 30 women (group II) don't have CVD history.
Results: Group I: noted positive correlation between AMH level (0,54±0,38 ng/mL) and numbers of AF (2,28±1,32) (r= +0,85); also noted negative correlation between AMH and LDL-C (132,97±8,86 mg/dL) (r= -0,54). Group II: AMH level was 2,58±0,32 ng/mL, LDL-C level was 105,04±12,3 mg/dL (r AMH-LDL-C= -0,46); numbers of AF were 4,92±1,35 (r AMH-AF = +0,76). In 27 women from I group after 3 month of Replacement Hormone Therapy (RHT) LDL-C decreasing from 134,82±9,94mg/dL to 119,27±4,45mg/dL, ($p<0,05$). These changes were accompanied by reduced numbers of CDV events and reduction of early climacteric symptoms. In 12 women from I group, who didn't use RHT, trends to increasing of LDL-C were detected (from 129,±5,17mg/dL to 136,41±2,32), numbers CDV events did not change, climacteric autonomic disorders and anxious or depressive episodes were continued.
Conclusions: AMH control for perimenopausal women with CVD history must be done every 3 month for timely correction of menopausal disorders and prevention of cardiovascular accidents. Reduction of AMH for perimenopausal women more than factor of 10 within a short time is the evidence of premature aging of the ovarian and of lowering of hormonal protection of vessels. Appointment of RHT for hormone deficiency contributes into the normalization of lipid profile, CVD prevention and the improvement of quality of life.

Key words: Anti-Mullerian Hormone, cardiovascular risks, Replacement Hormone Therapy.

Should C-reactive protein be linked with some noninvasive parameters for improving the prognosis in acute coronary syndrome patients

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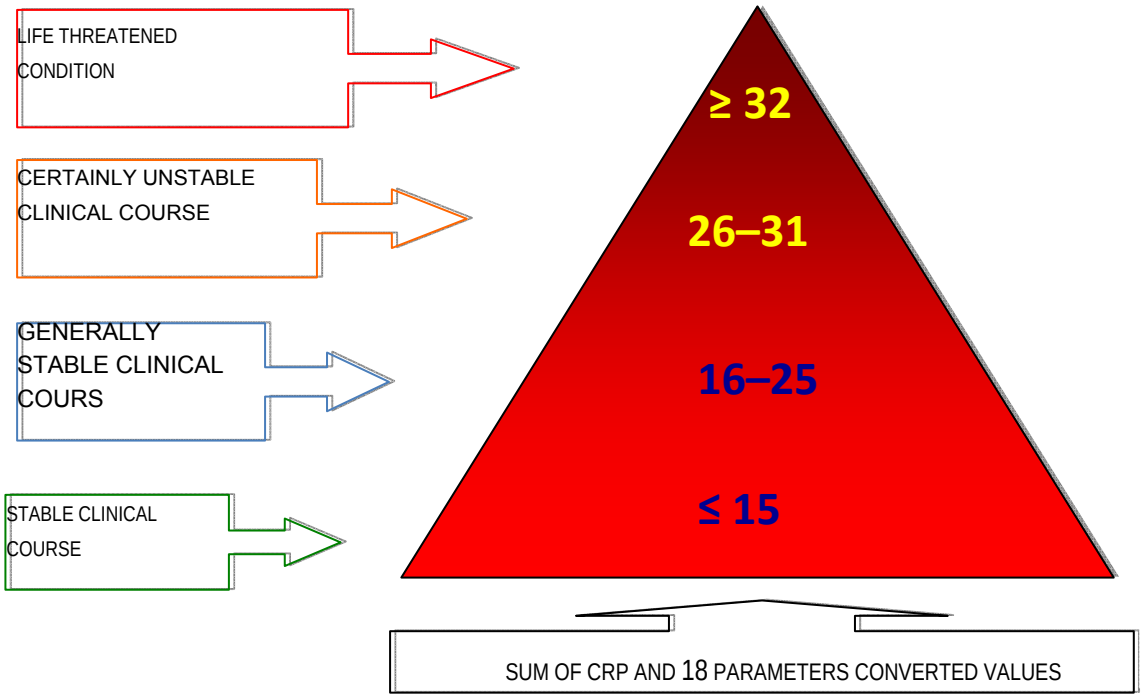
Aim: C-reactive protein (CRP), when associated with noninvasive parameters, improves prediction of outcomes in patients with acute coronary syndrome (ACS). The aim of this study was to improve the prognostic and predictive value of C-reactive protein (CRP) in acute coronary syndrome (ACS) settings by combining it with a number of other noninvasive parameters obtained at the time of presentation to the hospital, creating simple procedure affordable to majority of doctors.

Methods And Results: When CRP is linked to certain noninvasive parameters, such as risk factors number, leukocytes, hemoglobin, total cholesterol, low-density lipoprotein, total cholesterol and high-density cholesterol ratio, microalbuminuria, brain natriuretic peptide or its precursor, fibrinogen, antithrombin III, troponin, duration of QRS complex, ventricular ectopic activity by Lown' classification, NYHA functional class, standard deviation of all normal nonectopic RR intervals, silent and symptomatic myocardial ischemia observed by ambulatory electrocardio-graphic monitoring and pulse recovery after treadmill exercise testing, accurately prediction of the medium-term outcome in patients with ACS can be achieved. To obtain such prognosis, the author has created original score procedure.

In order to create conditions for comparing different indicators transformation of all these parameters was made to form a unique scoring system. Values of parameters were classified into three basic groups: normal, less adverse and more adverse. Nominal values of parameters were associated with the empirically-driven numerical values. An award system of parameters was created, and dependent relationship as well, which made possible calculation of the medium-term prognosis in ACS patients.

$$S_{bv} = (CRP \Rightarrow CRP_{bv}) \sum_{NeP=1}^{NeP=18} + (NeP \Rightarrow NeP_{bv})$$



Pyramid of outcomes is also an empirical product which, based on the summary score of CRP and the selected parameters, allows easy and reliable classification of patients with ACS the risk groups, and consequently, the individualization of further therapeutic procedures or treatment on each patient.
Based on the hypothesis testing was performed on 247 patients lasting more than two years.
Test results have confirmed the validity of the hypotheses.

Conclusion: Study has confirmed that the prognostic value of CRP in ACS patients can be improved, by linking CRP with some noninvasive parameters. New system of values was created; the prognostic relations and the *Pyramid of the outcomes* were formed.
The intension of the author is to make software program in order to simplify procedure.

Key Words: *C-reactive protein, Acute Coronary Syndrome, Unstable Angina, NSTEMI, STEMI*