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### **P5.02: PROTEIN ENGINEERING OF SYNTHETIC LIGANDS FOR VASCULAR PROTECTION**

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## Pathophysiology 3

## P5.01

## INCREMENTAL PREDICTIVE VALUE OF POOR PENILE ARTERIAL FLOW AS AN ADJUNCT TO INCREASED AORTIC STIFFNESS FOR DETECTING MYOCARDIAL ISCHEMIA DURING STRESS ECHOCARDIOGRAPHY IN ERECTILE DYSFUNCTION PATIENTS

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**Introduction:** Erectile dysfunction (ED) may be considered a clinical manifestation of a generalized vascular disease affecting also the penile arteries. The aim of this prospective study was to investigate arterial function determinants of wall motion abnormalities during stress testing in men with ED. **Methods:** 188 consecutive asymptomatic men (40-60 y/o), with non-psychogenic and non-hormonal ED underwent: (1) dobutamine stress echocardiography (DSE) (2) evaluation of aortic stiffness with carotid-femoral pulse wave velocity (PWV) and (3) penile vascular assessment using color duplex sonography. Criteria of positivity were regional dysfunction >2 segments demonstrated by DSE. A mean peak systolic velocity (PSV) below 25 cm/sec was considered to indicate severe arterial insufficiency.

**Results:** 49 ED patients (26 %) exhibited regional wall motion abnormalities. Men with abnormal DSE compared to men without stress evidence for myocardial ischemia had higher prevalence of multiple cardiovascular risk factor status (> 2 risk factors) (36 vs 22 %,  $P < 0.001$ ), higher PWV ( $8.8 \pm 1.2$  vs  $8.1 \pm 1.3$  m/s,  $P < 0.01$ ) and lower penile Doppler velocities ( $28.2 \pm 8$  vs  $33.9 \pm 9$  cm/s,  $P < 0.001$ ). Receiver operating characteristic curve analysis for the prediction of DSE positivity showed that PWV value > 8.2 m/s combined with PSV < 26.5 cm/s was the best predictor of DSE positivity (61 % sensitivity, 82% specificity, and 83% positive predictive value).

**Conclusion:** In asymptomatic men with ED increased PWV and decreased PSV values correlate significantly with an increased likelihood of exhibiting regional wall motion abnormalities during DSE and the greatest gain is found in men with severe penile arterial insufficiency and a stiffer aorta.

## P5.02

## PROTEIN ENGINEERING OF SYNTHETIC LIGANDS FOR VASCULAR PROTECTION

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Angiopoietin-1 (Ang1) is a relatively recently discovered vascular ligand which has been shown to have substantial potential therapeutic applications in treating a range of pathologies including: transplant atherosclerosis, stroke, diabetic retinopathies and sepsis. However, this large glycoprotein shows variable solubility and biological activity as a recombinant protein and is difficult to produce. This project aims to develop small, stable Ang1 mimetic proteins for use as potential therapeutic lead molecules.

Based on the mechanism by which the native ligand activates its receptor, a small synthetic ligand was designed and expressed in *E. coli*. The synthetic ligand was isolated and purified and its ability to bind the angiopoietin receptor analysed by *in vitro* ELISA. Cell surface binding was examined by immunofluorescence staining and the ability of the ligand to activate cellular signalling was tested by phospho-specific immunoblotting. Functionally, the influence of the ligand on endothelial cells migration was studied using Boyden chamber chemo tactic assay.

A synthetic ligand was produced of molecular mass 12kDa compared with the 70kDa native ligand. This ligand binds angiopoietin receptor *in vitro*. In cellular assays the ligand interacts with the endothelial cell surface and activates the angiopoietin receptor. In addition it stimulates downstream signalling pathways including the phosphatidylinositol 3-kinase/Akt and Erk1/2 pathways. The ligand activates endothelial cell migration.

The novel synthetic ligands are easy to produce, can be expressed in *E. coli*, are highly soluble and stable, activate the angiopoietin receptor. The properties of these synthetic ligands suggest they may be lead molecules for generating potential therapeutic Ang1 mimetics.

## P5.03

## ENDOTHELIAL PROGENITOR CELLS AND ARTERIAL STIFFNESS IN MALE HYPERTENSIVE PATIENTS

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**Background and aim:** Several recent studies showed conflicting results on the association between colony-forming capacity of circulating endothelial progenitor cells (EPC) and arterial hypertension, but none of it assessed arterial stiffness parameters. Therefore we aimed to investigate the relationship of EPC with blood pressure (BP) and arterial stiffness.

**Methods:** Sixty-four male patients (aged  $49.33 \pm 5.65$  years) with different stages of essential hypertension referred to the primary prevention unit for assessment of cardiovascular (CV) risk were included into the study. Detailed assessment of CV risk profile and measurements of local, regional and systemic arterial stiffness (AS) was performed. Peripheral blood samples were collected and EPC colony-forming capacity was measured *in vitro* using a colony-forming unit (CFU) assay.

**Results:** We found that EPC CFU number was inversely correlated with heart-rate adjusted aortic augmentation index (Alx@75) ( $R = -0.311$ ,  $p = 0.015$ ). Multiple regression analysis revealed that this association remained significant after adjustment for age, mean blood pressure, smoking, blood lipids, waist circumference and fasting glucose ( $p < 0.01$ ). Mean blood pressure (beta = 0.294,  $p = 0.023$ ) and number of CFU (beta = -0.315,  $p = 0.0076$ ) explained 19% of overall variability of Alx@75. Neither other AS parameters (aortic or radial pulse wave velocity and carotid stiffness) nor peripheral or central arterial BP were significantly associated with EPC CFU number.

**Conclusion:** The present study shows that in male hypertensive subjects number of EPC CFU is associated with aortic augmentation index but not the level of arterial blood pressure or other stiffness parameters.

## P5.04

## THE ASSESSMENT OF METABOLIC PROFILE AND COMMON CAROTID ARTERY INTIMA-MEDIA THICKNESS IN YOUNG ADULTS WITH ESSENTIAL HYPERTENSION

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**Objectives:** In the population of young hypertensive adults the presence of coexisting cardiovascular risk factors and early symptoms of atherosclerosis, including common carotid artery intima-media thickness (cIMT) should be estimated.

**Methods:** In the study group there were 37 patients, age  $21.2 \pm 2.7$  years, with not already treated essential hypertension (EH). Secondary hypertension was excluded. We evaluated anthropometrical data, systolic and diastolic blood pressure (SBP, DBP), fasting serum lipids and glucose. The measurement of cIMT was done using B-mode ultrasonography. The control group consisted of 35 healthy individuals, age  $22.3 \pm 2.2$  years.

**Results:** In young hypertensive adults we observed significantly higher values of body mass index ( $27.27 \pm 8.39$  kg/m<sup>2</sup> vs  $21.47 \pm 1.80$  kg/m<sup>2</sup>), total cholesterol ( $4.61 \pm 1.04$  vs  $4.30 \pm 0.67$  mmol/l, LDL-cholesterol ( $2.87 \pm 0.89$  vs  $2.45 \pm 0.63$  mmol/l), triglycerides ( $1.29 \pm 0.98$  vs  $0.80 \pm 0.40$  mmol/l), fasting glucose ( $4.94 \pm 0.42$  vs  $4.62 \pm 0.43$  mmol/l), lower HDL-cholesterol ( $1.28 \pm 0.28$  vs  $1.57 \pm 0.33$  mmol/l). In this study we noticed higher values of cIMT in patients with EH: they equal  $0.05 \pm 0.01$  cm in the right and left common carotid arteries (CCA), whereas in healthy subjects the value of cIMT in both CCA was  $0.04 \pm 0.01$  cm.

**Conclusions:** 1. Higher values of cIMT and some classical cardiovascular risk factors are present in the population of young hypertensive adults. 2. The progression of atherosclerosis in vessels of young patients with EH should be estimated using high-resolution B-mode ultrasound and describing the parameter of cIMT.

## P5.05

## REACTIVE HYPEREMIA INDEX AND DETECTION OF ENDOTHELIAL DYSFUNCTION IN CHILDREN

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**Objective:** To evaluate Reactive Hyperemic Index (RHI) as an indicator of endothelial function (EF) in children with type 1 diabetes mellitus (T1DM)