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### **P5.01: THE EFFECT OF PULMONARY REHABILITATION ON ARTERIAL STIFFNESS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

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#### P4.11 LOWER LIMB VASOMOTOR AND FIBRINOLYTIC EFFECTS OF KININ RECEPTOR AGONISTS IN MAN

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**Background:** Vascular B<sub>1</sub> kinin receptor expression is upregulated in human atheroma and the presence of angiotensin-converting enzyme inhibition (ACEi), but its role in man remains unclear. We examined vasomotor and fibrinolytic responses to selective kinin receptor agonism in the human femoral circulation and correlated responses with femoral arterial plaque load.

**Methods:** Femoral arterial cross sectional area, blood flow and plaque volume were determined using intravascular ultrasound and a Doppler Flow-ire during selective femoral arterial infusion of Lys-des-Arg<sup>9</sup>-Bradykinin (B<sub>1</sub> agonist; 3, 10, 30 nmol/min), bradykinin (B<sub>2</sub> agonist; 100, 300, 1000 pmol/min) and sodium nitroprusside (6, 12, 24 mcg/min) in eleven patients undergoing diagnostic coronary angiography, in the presence and absence of ACEi. Tissue plasminogen activator (t-PA) release was measured across the femoral vascular bed.

**Results:** Mean femoral arterial plaque load was 7.0 ± 0.9 mm<sup>3</sup> per mm of vessel. Bradykinin and nitroprusside caused dose-dependent increases in femoral blood flow (p < 0.05). Bradykinin alone caused a dose-dependent increase in net t-PA release (p < 0.05) that was augmented by ACEi (p < 0.05). There were no correlations between femoral plaque load and bradykinin mediated vasodilatation or t-PA release. Lys-des-Arg<sup>9</sup>-Bradykinin had no effect on blood flow or t-PA release, irrespective of femoral arterial plaque load or ACEi.

**Conclusions:** The vasomotor and fibrinolytic actions of bradykinin in the human lower limb are mediated solely by the B<sub>2</sub> kinin receptor, irrespective of the presence of atheroma or ACEi. In keeping with previous data, bradykinin-mediated t-PA release was augmented in the presence of ACEi, consistent with its putative vascular protective effect.

#### P4.12 EGRESS OF FUNCTIONALLY COMPETENT PROGENITOR CELLS OVER-EXPRESSING CXCR4 FROM THE BONE MARROW FOLLOWING CARDIAC SURGERY WITH THE USE OF CARDIOPULMONARY BYPASS

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**Background:** The mechanisms of endogenous progenitor cell trafficking in response to tissue injury in humans are poorly understood.

**Methods:** We based our study on a model of transient myocardial injury, provoked by the use of cardiopulmonary bypass during cardiac surgery in 39 patients. Bone marrow (BM) and blood samples were collected at baseline and after disconnection of bypass machine. CD34+/CD133+ cell numbers (% of 100000 lymphocytes) and stem cell trafficking molecule CXC-chemokine receptor 4 (CXCR4) expression on CD34+ cells were measured by flow cytometry. Hematopoietic colony formation units (CFU) and stromal cell-derived factor-1 alpha dependent chemotaxis were also analyzed.

**Results:** Increased numbers of circulating progenitor cells after surgery (1.64 ± 0.18% vs 1.02 ± 0.17%, p = 0.003) directly correlated with baseline BM (r = 0.7, p < 0.0001) and inversely - with post-bypass BM counts (r = -0.9, p = 0.008), indicating that circulating cells were mobilized from BM. Following surgery expression of CXCR4 on circulating progenitors increased (88 ± 43 vs 113 ± 72 mean fluorescence intensity (MFI), p = 0.031). In post-bypass BM samples CXCR4 expression on CD34+ cells decreased (58 ± 22 MFI vs 44 ± 15 MFI, p = 0.03), suggesting that over-expressing CXCR4 cells, being the most suitable for non-marrow tissues migration, were released into circulation. Positive relationship between magnitude of CXCR4 expression on mobilized progenitors and cardiopulmonary bypass time (r = 0.7, p = 0.015) were shown. Progenitors in post-bypass blood samples compared to baseline had increased chemotactic (46 ± 16% vs 59 ± 22%, p = 0.002) and clonogenic (70 ± 25 vs 110 ± 70 CFUs) potential.

**Conclusion:** Increased expression of CXCR4 on mobilised functionally competent progenitors suggests about their ability to migrate towards non-marrow tissues, such as ischemic myocardium.

#### P4.13 REDUCTION OF ARTERIAL STIFFNESS AND CENTRAL BP IN PATIENTS WITH ARTERIAL HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA ON CPAP- THERAPY

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Arterial stiffness (AS) and central BP (CBP) are new «target-objects» for Antihypertensive Therapy (AT), but the possibility to correction these parameters on nonmedicament treatment is discussed.

**Aim:** To research the possibilities of correction of AS and CBP by AT and Continuous Positive Airway Pressure (CPAP) in patients (pts) with severe arterial hypertension (AH) and obstructive sleep apnea (OSA) in prospective, randomized, double-blind, placebo- controlled cross- sectional study.

**Methods:** Included 44 pts (34men) 55,8 ± 9,4 years with AH II-III gr. and OSA index >30, treated with combination of amlodipine 5-10 mg, valsartane 160 mg and HCT 25 mg. After 3-9 week AT pts were randomized into 2 groups: additional effective CPAP (eCPAP) and CPAP-placebo (P = 4 mmH<sub>2</sub>O). After 3 weeks on CPAP-therapy we carried out the crossover of these groups. At each step of intervention we produced ABPM and CBP measuring (SphygmoCor). AS was estimated by Ambulatory AS Index (AASI) and by carotid-to-femoral pulse wave velocity (PWV).

M ± STD	Initial	AT	AT+ eCPAP
PWVcf (m/s)	14,3 ± 2,7	12,1 ± 3,2*	11,8 ± 2,2*#
AASI	0,55 ± 0,17	0,48 ± 0,19 ns	0,41 ± 0,18*ns
24hBPmmHg	157/96 ± 21/11	139/86 ± 10/10*	137/81 ± 14/8*#
CBPmmHg	154/99 ± 14/14	129/87 ± 11/9*	122/81 ± 8/7*#

\*- p < 0,05#vs initial, #- p < 0,05 vs medication.

**Results:** PWV demonstrated reduction of AS during AT and additional positive effect of eCPAP. Significant reduction of AASI was demonstrated only in cases of combination of AT and CPAP. We estimate additive decreasing of 24 h-BP and CBP on eCPAP in comparison CPAP- placebo.

**Conclusion:** Effective CPAP induced only mild reduction in 24-hBP, but significant decreasing in AS and CBP.

## Therapeutic Aspects 2

#### P5.01 THE EFFECT OF PULMONARY REHABILITATION ON ARTERIAL STIFFNESS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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**Background:** We have previously shown increased arterial stiffness using aortic pulse wave velocity (PWV) in patients with COPD. Pulmonary rehabilitation (PR) (exercise, education and nutritional advice) has respiratory and functional benefits, though effects on cardiovascular (CV) risk have not been explored. We hypothesised PWV would improve with PR.

**Methods:** 22 (8 male) clinically stable patients, free from overt CV disease had BP, PWV, spirometry (FEV<sub>1</sub>), shuttle walk (ISWT) and fasting glucose and lipids performed pre and post PR. 20 age and gender matched controls were studied for baseline comparison.

**Results:** Median (range) age for patients was 62.5 (54-79) years, mean (SD) FEV<sub>1</sub> was 44.9 (15.6)% predicted. Aortic PWV, cholesterol and BP reduced with PR. 3 of 11 patients no longer met the criteria for hypertension. The fall in aortic PWV was attributable to the fall in BP.

**Conclusions:** PR improves the haemodynamic profile of subjects with COPD. Longer term CV effects of PR should now be investigated.

Mean (SD)	Control	COPD - Pre PR	COPD - Post PR
Aortic PWV (m/sec)	8.5 (1.4)	9.82 (3.0)†	9.26 (2.7)*
Systolic BP (mmHg)§	130.0 (15.9)	137.6 (20.0)	127.9 (23.6)**
Diastolic BP (mmHg)§	78.7 (8.4)	82.8 (9.5)	78.4 (11.8)**
MAP (mmHg)§	96.0 (10.0)	100.9 (11.9)	94.9 (14.1)**
Heart Rate (bpm)	67.8 (11.0)	76.1 (12.1)††	75.9 (14.1)
Cholesterol (mmol/L)	5.2 (1.2)	5.6 (1.2)	5.4 (1.2)*
Glucose (mmol/L)	5.2 (0.5)	5.0 (0.7)	4.8 (0.8)
ISWT (m)	-	190.4 (69.8)	273.6 (75.5)**

§ Peripheral pressures; †p < 0.05; ††p < 0.001 difference from controls. \*p < 0.05; \*\*p < 0.001 difference with PR.

#### P5.02

##### EFFECT OF ACUTE INTENSE EXERCISE ON ARTERIAL STIFFNESS

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**Purpose:** Aortic stiffness and wave reflections are determinants of left ventricular performance and independent predictors of cardiovascular risk. Though it is well recognized that regular aerobic exercise can affect arterial stiffness and wave reflections, the acute effect of intense aerobic exercise has not been defined. In this study we examined the acute effect of the extreme exertion of marathon race on the arterial elastic properties in highly trained athletes.

**Methods:** We studied 20 healthy, regularly trained ( $5 \pm 2.5$  hours/week for  $12.4 \pm 7.4$  years) marathon runners (mean age:  $36 \pm 10$  yrs, 16 M/4F) before and after the race. Aortic stiffness was evaluated with pulse wave velocity (PWV) and wave reflections with augmentation index (Alx) of the aortic pressure waveform.

**Results:** Marathon race led to a significant fall in Alx corrected for the heart rate ( $6.96 \pm 13.3$  vs.  $0.04 \pm 10.9$ ,  $P = 0.01$ ) indicating reduced heart afterload. Mean pressure ( $94 \pm 14$  vs.  $85 \pm 9$ ,  $P < 0.05$ ), systolic brachial ( $127 \pm 16$  vs.  $122 \pm 11$ ,  $P < 0.05$ ), systolic aortic pressure ( $113 \pm 16$  vs.  $102 \pm 10$ ,  $P = 0.01$ ), as well as diastolic brachial ( $78 \pm 12$  vs.  $70 \pm 8$ ,  $P < 0.01$ ), diastolic aortic pressures ( $79 \pm 12$  vs.  $73 \pm 8$ ,  $P < 0.05$ ), were also decreased, whereas heart rate was significantly increased ( $62 \pm 9$  vs.  $90 \pm 9$ ,  $P < 0.01$ ). PWV did not differ before and after marathon race ( $6.65 \pm 0.9$  vs.  $6.74 \pm 1.2$   $P = NS$ ).

**Conclusions:** Our findings demonstrate that marathon race results in an acute decrease of wave reflections. This indicates reduced afterload that facilitates left ventricular performance. Since there is no effect on PWV, it is caused most likely by peripheral vasodilation. These findings elucidate the interrelations between biophysical properties of the arteries and exercise capacity.

#### P5.03

##### ACUTE VASCULAR EFFECTS OF RECOMBINANT HUMAN TSH IN YOUNG SUBJECTS FROM CHERNOBYL AREA FOLLOWED-UP FOR PREVIOUS DIFFERENTIATED THYROID CANCER

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**Objectives:** To evaluate the effect of recombinant human TSH (rhTSH) on endothelial function, aortic and carotid stiffness, and wave reflection in a population living in the Chernobyl area at the time of 1986 blast, treated with thyroidectomy for thyroid cancer.

**Methods:** 23 subjects (age  $26 \pm 3$  years, 10 men) underwent evaluations at baseline and after rhTSH administration, 0.9 mg daily on 2 consecutive days. A real time contour tracking algorithm was applied to B-mode scans for assessing brachial artery endothelium-dependent (flow-mediated dilation, FMD), and -independent dilation (glycerol trinitrate, GTN, 25 µg sublingual) and carotid stiffness (CS) by Bramwell-Hill equation. Carotid blood pressure (BP) waveform, augmentation index (Alx), and carotid-femoral PWV were assessed by applanation tonometry.

**Results:** rhTSH decreased diastolic BP (from  $79 \pm 11$  to  $72 \pm 9$  mmHg,  $p < 0.01$ ), but not systolic BP, increasing pulse pressure (from  $38 \pm 7$  to  $43 \pm 10$  mmHg,

$p < 0.01$ ). FMD tended to decrease (from  $9.0 \pm 4.4$  to  $6.9 \pm 2.2\%$ ,  $p = 0.09$ ), while GTN was unchanged (from  $10.5 \pm 4.0$  to  $10.6 \pm 3.4\%$ ,  $p = ns$ ). Aortic PWV tended to decrease (from  $5.78 \pm 1.32$  to  $5.44 \pm 1.02$  m/s,  $p = 0.057$ ); carotid stiffness (from  $5.07 \pm 0.73$  to  $5.20 \pm 0.82$  m/s,  $p = ns$ ) and Alx (from  $-5.5 \pm 11.0$  to  $-8.7 \pm 16.7$ ,  $p = ns$ ) were unchanged. Augmentation pressure (AP) decreased (from  $-2.7 \pm 4.7$  to  $-5.8 \pm 9.6$  mmHg,  $p < 0.05$ ), while time to wave reflection was unaffected (from  $164 \pm 22$  to  $167 \pm 21$  ms,  $p = ns$ ).

**Conclusions:** In a population of environmental radiation-exposed thyroidectomized young patients, rhTSH influences magnitude of wave reflection, possibly through microcirculatory vasodilation, as suggested by diastolic BP and AP decrease. A reduction of aortic stiffness and an impairment of endothelial function was also observed.

#### P5.04

##### RELATIONSHIP BETWEEN ENDOTHELIAL FUNCTION, INTIMA-MEDIA COMPLEX THICKNESS AND BILIRUBIN LEVELS IN PATIENTS WITH METABOLIC SYNDROME

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Endothelial dysfunction (ED) and carotid artery intima-media complex thickening (IMT) are regarded as predictors for the progress of atherosclerosis. The anti-oxidant properties of bilirubin and its ability to prevent oxidation of lipids of low density lipoproteins, and thus, development of vascular atherosclerosis have also been described.

Our aim was to assess bilirubin levels in patients with metabolic syndrome and various levels of brachial artery flow-mediated dilatation (FMD) registered during reactive hyperaemia test and different carotid artery IMT. **Methods:** We examined 181 male subjects, age 31-52 years, with different levels of FMD and IMT, using standard protocol which included physical examination, ECG, carotid arteries ultrasound, brachial arteries ultrasound with reactive hyperaemia test, blood biochemistry tests.

**Results:** After initial examination patients were divided into two groups in regard to their FMD: 89 patients comprised the group with lower FMD (less than 5%) and 92 subjects who had normal FMD (more than 5%). Performing the ultrasound examination of the carotid arteries we found out that IMT was higher in patients with impaired FMD ( $p = 0.02$ ). On the contrary, in this group we found lower total bilirubin levels comparing to those with normal FMD ( $8.5 \pm 3.2$  vs.  $16.8 \pm 4.5$  µmol/l,  $p < 0.01$ , respectively).

**Conclusions:** Patients with metabolic syndrome and lower total bilirubin levels present higher IMT and lower FMD and more significant signs of vascular atherosclerosis (as seen in carotid arteries) comparing to those with higher bilirubin levels.

#### P5.05

##### INTERICTAL ARTERIAL WALL PARAMETERS IN WOMEN WITH MIGRAINE

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**Objective:** According to data of epidemiological and clinical studies, migraine with aura (MA) is associated with cardiovascular disorders, and migraine without aura (M0) is linked to carotid artery dissection. The aim of this cross-sectional study was to evaluate and compare arterial wall parameters – intima-media thickness, distensibility and stiffness of common carotid artery (CCA), augmentation index and pulse wave velocity – in female patients with two types of migraine: MA and M0.

**Methods:** Arterial wall structural and functional properties were measured using echo-tracking method (Art.Lab system) and applanation tonometry (SphygmoCor device) in 63 patients with M0 (age  $35.32 \pm 7.83$  years, migraine duration  $17.25 \pm 8.44$  years), 37 with MA (age  $36.57 \pm 9.10$  years, migraine duration  $19.62 \pm 9.17$  years) and 50 age-matched controls. Groups were compared using one-way ANOVA test. To explore the relationship between arterial wall parameters and type of migraine stepwise linear regression was applied.

**Results:** MA patients had highest values of augmentation index ( $16.65 \pm 13.23\%$ ), comparing with M0 patients ( $15.41 \pm 10.62\%$ ) and controls ( $12.42 \pm 13.32\%$ ). Distensibility of CCA was lowest in M0 patients ( $443.78 \pm 106.99$  µm), comparing with MA patients ( $449.99 \pm 113.50$  µm)