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P8.04: DIFFERENT EFFECTS OF PLASMA MEMBRANE CALCIUM ATPASE 4 (PMCA4) ABLATION AND ACUTE INHIBITION ON CONTRACTILITY OF ISOLATED MOUSE MESENTERIC ARTERIES

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Background: The assessment of arterial stiffness and central pressures has been limited to specialised techniques and settings. New, more practical methods (ARCSolver) allow assessment using a standard brachial cuff. The objective was to assess the feasibility of central haemodynamics and surrogates of arterial stiffness from the ARCSolver in a community based setting.

Methods: Peripheral and central systolic and diastolic blood pressure (BP) and wave reflection parameters (augmentation index) were obtained from a 1,903 volunteers in an Austrian community setting. We assessed for known differences and associations according to gender and each age deciles from <30 years to ≥80 years in the whole population and a subset with a systolic BP < 140 mmHg.

Results: Age and gender associations with central haemodynamic and augmentation parameters reflected those previously established from gold-standard non-invasive techniques under specialised settings (Fig. 1). Findings were the same for patients with a systolic BP below 140 mmHg (i.e. normotensive). Differences in actual values for augmentation index are likely due to lower numbers of volunteers in these age groups and method differences.

Conclusion: One-off measures of central haemodynamics and pulse wave augmentation from the ARCSolver demonstrated known age and gender associations which were not limited to normotensive individuals. Using ARCSolver to obtain estimates of central pressure and augmentation appears robust and feasible in a community setting. Further validation is now possible in large cohort studies, particularly in primary care settings.

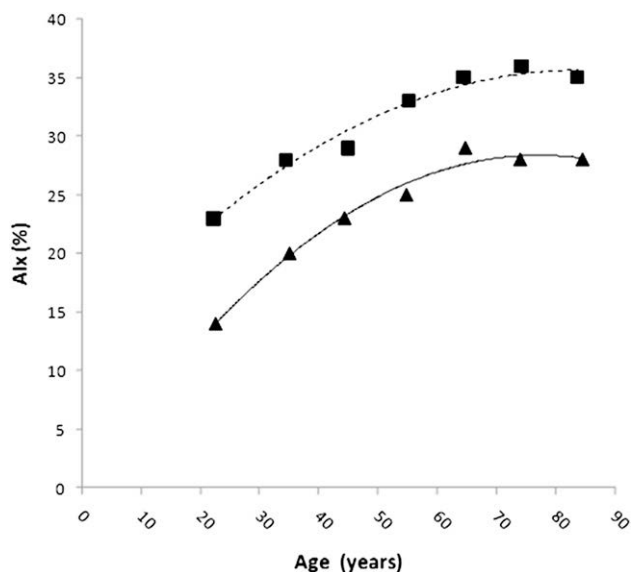


Figure 1 Regression curves for the effect of age on augmentation index in males (▲) and females (■)

P8 – Endothelium and Small Arteries 2

P8.01

ENDOTHELIAL DYSFUNCTION AND LOW-GRADE INFLAMMATION ARE ASSOCIATED WITH ARTERIAL STIFFNESS IN HEALTHY ADULTS OVER A 6-YEAR PERIOD

THE AMSTERDAM GROWTH AND HEALTH LONGITUDINAL STUDY (AGAHLS)

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Endothelial dysfunction and low-grade inflammation are associated with cardiovascular disease. Arterial stiffening plays an important role in cardiovascular disease and thus may be a mechanism through which endothelial dysfunction and/or low-grade inflammation lead to cardiovascular disease. We investigated the associations between, on the one hand, biomarkers of endothelial dysfunction (soluble endothelial selectin, thrombomodulin and both vascular- and intercellular adhesion molecules 1 and von Willebrand factor) and of low-grade inflammation (C-reactive protein, serum amyloid A, interleukin 6, interleukin 8, tumour necrosis factor α and soluble intercellular adhesion molecule 1) and, on the other hand, arterial stiffness over a 6-year period, in 293 healthy adults (155 women). Biomarkers were combined into mean Z-scores. Carotid, femoral and brachial arterial stiffness and carotid-femoral pulse wave velocity were determined by ultrasonography. Measurements were obtained when individuals were 36 and 42 years of age. Associations were analysed with generalised estimating equation and adjusted for sex, height and mean arterial pressure. The endothelial dysfunction Z-score was inversely associated with femoral distensibility [β (95%CI)-0.51(-0.95;-0.06)] and compliance coefficients [-0.041(-0.076;-0.006)], but not with carotid or brachial stiffness or carotid-femoral pulse wave velocity. The low-grade inflammation Z-score was inversely associated with femoral distensibility [-0.51(-0.95;-0.07)] and compliance coefficients [-0.050(-0.084;-0.016)], and with carotid distensibility coefficient [-0.91(-1.81;-0.008)], but not with brachial stiffness or carotid-femoral pulse wave velocity. Biomarkers of endothelial dysfunction and low-grade inflammation are associated with greater arterial stiffness. This provides evidence that arterial stiffening may be a mechanism through which endothelial dysfunction and low-grade inflammation lead to cardiovascular disease.

P8.02

CHARACTERIZATION OF THE VASORELAXANT MECHANISMS OF ENDOCANNABINOID OLEOYLETHANOLAMIDE IN THE BOVINE OPHTHALMIC ARTERY

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Background: Numerous studies show the potential therapeutic effect of different endocannabinoids and in particular the vasorelaxant effects in several vascular beds

Aim: To evaluate the vasorelaxant effect of oleoylethanolamide on isolated bovine ophthalmic arteries and to evaluate the possible mechanisms involved in relaxant responses.

Methods: Ophthalmic arteries were isolated from bovine eyes and mounted in a wire miograph for isometric tension recording. The effects time- and concentration-dependent were assayed by addition of the oleoylethanolamide to the organ bath.

Results: Oleoylethanolamide (0.1 - 10 μ M) produced a significant concentration- and time-dependent vasorelaxation in the bovine ophthalmic artery pre-contracted with 5-HT (1 μ M). The removal of endothelium provoked a slight reduction of the relaxant effects. Interestingly, a pre-treatment with antagonist PPAR α GW6471 (1 μ M) inhibited the concentration- and time-dependent oleoylethanolamide-induced vasorelaxation.

Conclusion: The present study shows that oleoylethanolamide relaxed the isolated bovine ophthalmic artery in the concentration- and time-dependent manner. The candidate responsible of the vasorelaxant response to oleoylethanolamide appear to be the PPAR α . This relaxant effect is an exciting tool to prevent ischemic injury because it improves the blood supply to the retina.

P8.04

DIFFERENT EFFECTS OF PLASMA MEMBRANE CALCIUM ATPASE 4 (PMCA4) ABLATION AND ACUTE INHIBITION ON CONTRACTILITY OF ISOLATED MOUSE MESENTERIC ARTERIES

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Plasma Membrane Calcium ATPases (PMCA's) are calcium extrusion pumps which may also modulate signal transduction. The most abundant PMCA

isoform in vascular smooth muscle is PMCA4 however its effect on arterial constriction is unclear. Here, PMCA4 ablated mice (KO^{-/-}) and a novel specific PMCA4 inhibitor, AP2 were used to study effects of PMCA4 on arterial contractility. Vascular constrictor responses to 100mM potassium & noradrenaline (1x10⁻⁹M-3x10⁻⁵M) of isolated, pressurised mesenteric arteries from male PMCA4 KO^{-/-} and wild type, (WT^{+/+}) mice were determined by myography. Effects of acute PMCA4 inhibition with AP2, nitric oxide synthase (NOS) inhibition with N_ω-Nitro-L-arginine (LNNA) & neuronal NOS inhibition (nNOS) with Vinyl-L-Nio were also investigated. PMCA4 ablation had no effect on the magnitude of constrictions to 00mM K⁺ (KO^{-/-} 53.2% ± 3.5 n=11; WT^{+/+} 56.3% ± 3.6 n=14) or noradrenaline (KO^{-/-} 59.5% ± 4.7 n=11; WT^{+/+} 58.2% ± 2.5 n=14). PMCA4 inhibition with AP2, significantly attenuated constriction to noradrenaline in arteries from WT^{+/+} mice (70.6% ± 3.4 n=8 and 63.8% ± 2.6 n=10 in the absence and presence of AP2 respectively) but had no effect on KO^{-/-} mice arteries. Inhibitory effects of AP2 were reversed in arteries by NOS inhibition with LNNA (AP2 treated 61.8% ± 4 n=8; AP2+LNNA treated 69.2% ± 1.7 n=10) and also by nNOS inhibition with Vinyl-L-Nio (AP2 61.8% ± 4 n=8; AP2+Vinyl-L-Nio 75.2% ± 1.3 n=5). Therefore, PMCA4 inhibition with AP2 reduces vascular constriction by a nNOS-dependent mechanism. Ablation and acute inhibition of PMCA4 have different effects on mouse mesenteric arterial contractility.

P8.05 REACTIVE HYPEREMIA INDEX AND DETECTION OF ENDOTHELIAL DYSFUNCTION IN PAEDIATRIC HEMATO/ONCOLOGY PATIENTS

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Objective: The aim of our study was to evaluate endothelial dysfunction (ED) in children following treatment for acute lymphoblastic leukemia (ALL) in comparison with healthy controls (HC) and to correlate Reactive Hyperemia Index (RHI) with anthropometric and biochemical parameters.

Research design and methods: As part of new non-invasive plethysmographic technique, an EndoPAT 2000[®] recorder was used for the determination of RHI by measuring postocclusive endothelium-dependent changes in vascular tone (PAT) in subjects fingertips. There were also assessed plasma levels of selectin, ADMA, hsCRP, sVCAM as biochemical markers of ED in ALL children and reference controls. Meeting the including criteria 40 eligible study participants were enrolled in the study. A group of 28 ALL patients were matched with control group of 12 healthy children (HC).

Results: Significantly lower RHI were revealed in ALL patients in comparison with HC (1.57±0.50, 1.96±0.63; p<0.05) respectively, implying impaired endothelial-dependent dilation. Furthermore, significantly elevated plasma levels of selectin and hsCRP were found in ALL patients when compared to HC supporting the theory of premature endothelial dysfunction in high risk group of children. There were discovered no correlations between RHI and biochemical parameters of ED.

Conclusion: Our study demonstrated that ALL patients might have impaired endothelial dysfunction, which is associated with high risk of premature atherosclerosis manifestation. RHI is a promising non-invasive method for the assessment of ED in children with high risk of premature atherosclerosis. This work was supported by the Charles University Student Research Project SVV-2010- 260805.

P8.07 ASSESSMENT OF ENDOTHELIAL FUNCTION AND ARTERIAL STIFFNESS IN PATIENTS WITH GENETICALLY CONFIRMED FAMILIAL HYPERCHOLESTEROLEMIA WITHOUT PREVIOUS CARDIOVASCULAR EVENTS

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Purpose: The purpose of this study was assessment of endothelial function and arterial stiffness parameters in subjects with familial and non-familial hypercholesterolemia.

Methods: We studied endothelial function and arterial stiffness in 60 subjects (mean age 41.9±7.7 years): 20 patients with elevated LDL and genetically confirmed familial hypercholesterolemia; 20 patients with elevated LDL without mutations causing FH; 20 healthy controls with normal LDL. All study subjects were without previous cardiovascular events and had no symptoms of cardiovascular diseases. High-resolution ultrasound was

used to determine flow-mediated dilation in the brachial artery. Echo-tracking and photoplethysmography technique were used for assessment of the arterial stiffness parameters.

Results: FMD was significantly lower in patients with FH and in all patients with elevated LDL compared with controls (10.5±9.6% vs 21±14.3%, p<0.05; 12.5±10 vs 21±14.3%, p<0.05). There were no differences in arterial stiffness parameters in all groups. Significant correlation between FMD and arterial stiffness parameters measured with used echo-tracking methods were noted. There were no significant correlations between echo-tracking and photoplethysmographically assessed arterial stiffness parameters.

Conclusions: Reduced FMD in FH patients may be due to endothelial dysfunction. No significant differences in arterial stiffness parameters show that atherosclerosis is not advanced in patients with hypercholesterolemia. Significant correlations between ultrasonographically assessed arterial stiffness parameters and endothelial dysfunction show that echo-tracking methods can be used for early detection of arterial remodeling in patients with hypercholesterolemia. FMD can be used for early detection of endothelial dysfunction preceding atherosclerotic process in patients with FH without significant cardiovascular disease.

P8.08 THE RELATIONSHIP BETWEEN BRACHIAL ARTERY FLOW-MEDIATED DILATION AND SHEAR RATE IN INDIVIDUALS WITH INCREASED CARDIOVASCULAR RISK

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Brachial artery flow-mediated dilation (baFMD) is a frequently-used technique to assess endothelial function. Although shear rate (SR) is currently considered as a determinant of baFMD, a previous study in healthy humans found that the relationship between baFMD and SR was not evident in older adults. Furthermore, the relationship has not been studied in individuals with increased cardiovascular (CV) risk. The purpose of this study was to examine the relationship between FMD and estimated SR stimulus in middle-aged and older adults with increased CV risk. Data from 2 groups [37 individuals with increased CV risk (history of recent stroke or transient ischemic attack, presence of hypertension and type2 diabetes, 68.9±9.1 yrs, 6F), and 17 apparently healthy individuals (64.2±4.6 yrs, 12F)] were compared. baFMD was assessed using a 5-min forearm occlusion method. Diameter and blood velocity data obtained by a Doppler ultrasound machine were used for the calculation of baFMD and SR using semi-automated edge detection software. In the increased CV risk group, baFMD was significantly correlated with baseline SR (r=0.52), peak SR (r=0.62), and SR area under the curve until time to peak dilation (r=0.62, all p<0.05), whereas no SR indices were associated with baFMD in the healthy group. Multivariate analysis revealed that age and baseline diameter were independent determinants of baFMD in the pooled data set (R²=0.322). These findings suggest that in individuals with increased CV risk baFMD is correlated well with SR stimulus. The significance of the association between SR stimulus and baFMD in this population requires further investigation.

P8.09 25-HYDROXYVITAMIN D MAY CONTRIBUTE TO DIFFERENCES IN ARTERIAL STIFFNESS AND ENDOTHELIAL FUNCTION IN HEALTHY AFRICAN AMERICANS COMPARED TO EUROPEAN AMERICANS

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Vascular function is reportedly influenced by vitamin D and is worse in African Americans (AAs) relative to European Americans (EAs). Reasons remain unclear especially if ethnic differences in 25-hydroxyvitamin D [25(OH)D] levels mediate differences in vascular function. This prospective study investigated the relationships of serum 25(OH)D with indices of vascular function among 45 healthy, 18-50 yo AA and EA adults. The main outcomes were augmentation index (Aix75), central aortic pressure, pulse wave velocity (PWV), flow-mediated dilation (FMD), and seated and supine blood pressures. Results showed that 25(OH)D was inversely associated with Aix75, supine systolic blood pressure (SBP), central aortic SBP and central aortic diastolic blood pressure (DBP), independent of age, sex, and percent body fat (P<0.05 for all). 25(OH)D was associated with Aix75, PWV and FMD (P=0.05 to 0.08) among AAs, but not EAs (P=0.44 to 0.96). AAs had greater