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P1.03: ALDOSTERONE ANTAGONISTS REVERSE EFFECTS OF CARDIOTONIC STEROIDS ON VASCULAR ELASTICITY AND COLLAGEN SYNTHESIS

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Poster Presentation Abstracts

P1 – Epidemiology

P1.01

ASSOCIATION OF CAROTID STRAIN AND PRIOR RISK OF CARDIOVASCULAR DISEASE - RESULTS FROM THE SWISS AIR POLLUTION AND LUNG AND HEART DISEASE IN ADULTS COHORT STUDY (SAPALDIA3)

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Increasing carotid stiffness is associated with an ascending atherosclerotic risk and cardiovascular events. Therefore early risk detection can prevent stroke and myocardial infarction

We analyzed ultrasound clips of average strain over a standardized 1cm-segment over at least one heart cycle in 1929 participants of the SAPALDIA3 cohort study (mean 62.4(8.2) years, range 50-81 years, 41.2% men). Strain was defined as cyclic deformation of lumen diameter expressed in percent change. Furthermore we assessed the risk of cardiovascular disease with the European Systematic Coronary Risk Evaluation (SCORE) based on data from SAPALDIA2 in 2002 and divided the SCORE into three categories (G1: risk of 1% or less, G2: risk of 2 to 4%, G3: risk of more than 5%). The association between strain and this categorical risk measure was assessed using multiple linear regressions, with and without additional adjustment for sex, age and brachial pulse pressure (PP). Results are expressed as adjusted means with 95%-confidence intervals.

Mean strain was 7.22(7.13, 7.31) in G1, 6.43(6.31, 6.55) in G2 and 5.64(5.39, 5.89) in G3, these differences being statistically significant ($p < 0.001$). The difference still existed when strain was adjusted for current PP (G1: 7.27(7.17, 7.36), G2: 6.34(6.21, 6.46), G3: 5.41(5.14, 5.67)) or sex (G1: 7.24(7.14, 7.33), G2: 6.39(6.26, 6.52), G3: 5.54(5.27, 5.80)). After adjustment for age (G1: 6.97(6.88, 7.07), G2: 6.91(6.77, 7.05), G3: 6.85(6.55, 7.16)) there was no significance between the different risk groups anymore. The present data suggest that prior risk assessment can predict strain, but current age seems to be a stronger predictor.

P1.02

ACTIVE PREVENTION STUDY: ATHEROSCLEROSIS CAROTID-CORONARY INVESTIGATION BY ECHOGRAPHY

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Objective: Currently, patients are sent to coronary angiography based on clinical presentation, positive exercise testing and assessment of global cardiovascular risk with particular emphasis on early detection of organ damage. Aim of our study was to evaluate the potential of a complete vascular ultrasound examination to estimate the actual presence of plaque on coronaries.

Design and method: In 163 in-patients with a clinical indication for coronary angiography (CA), we obtained: blood pressures (BP), creatinine (Cr) and glycaemia (G) values, a complete transthoracic echocardiography with measure of Doppler velocity in proximal anterior descending coronary (vLAD), and carotid IMT and PWV (Esote gold 70). We then divided the group in G1 (N=96) (patients with at least one significant coronary stenosis), and G2 (N=67) (unaffected coronaries).

Results: G1 and G2 had similar ages (66 ± 11 vs 65 ± 10 yrs, means $\pm$ SD), BMI (26 ± 4 vs 27 ± 4 g/m²) and diastolic BP (80 ± 10 vs 78 ± 9 mmHg, $p = \text{NS}$), while G1 showed higher systolic BP (135 ± 20 vs 127 ± 17 mmHg, $p < 0.05$), blood G (119 ± 42 vs 104 ± 35 mg/dl, $p < 0.05$), Cr (1.04 ± 0.48 vs 0.85 ± 0.17 mg/dl, $p < 0.01$), carotid IMT (811 ± 163 vs 711 ± 153 μ m, $p < 0.001$), carotid PWV (10 ± 2.6 vs 8.87 ± 2.39 , $p < 0.05$), and vLAD (64 ± 38 vs 41 ± 10 cm/sec, $p < 0.0001$). The variables that showed a correlation with the number of affected vessels were: blood G ($r = 0.21$, $p < 0.01$), Cr ($r = 0.23$, $p < 0.005$), IMT ($r = 0.25$, $p < 0.01$), and vLAD ($r = 0.4$, $p < 0.0001$).

Conclusions: These preliminary results suggest that peripheral artery structure and function assessed non invasively are representative of coronary status. Moreover transthoracic Doppler flow assessed on proximal LAD is well correlated with the presence and the number of affected coronaries. A complete ultrasound and clinic evaluation help in the decision making process of the coronary patient.

P1.03

ALDOSTERONE ANTAGONISTS REVERSE EFFECTS OF CARDIOTONIC STEROIDS ON VASCULAR ELASTICITY AND COLLAGEN SYNTHESIS

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Endogenous cardiotonic steroids (CS), including marinobufagenin (MBG) stimulate vascular synthesis of collagen. Because aldosterone antagonists competitively antagonize effect of CS on the Na/K-ATPase (NKA) (Hypertension 2010;56:914-9), we hypothesized that aldosterone antagonists would reverse the pro-fibrotic effects of MBG.

Explants of thoracic aortae from Wistar rats were cultured for 24 hours in the presence of vehicle or MBG (100 nmol/L) with or without 1 μ mol/L canrenone, an active metabolite of spironolactone. In 8 male patients (56 $\pm$ 1 yrs) with resistant hypertension (RH) on a combined (lisinopril/amlodipine/hydrochlorothiazide) therapy we measured arterial stiffness

using Sphygmocor Px device, calculated pulse wave velocity (PWV) and determined erythrocyte NKA activity before and after addition of spironolactone (50 mg/day) to the therapy.

In rat aortic explants, treatment with MBG resulted in a two-fold rise in the levels of collagen-1 and a marked reduction in the sensitivity to the vasorelaxant effect of sodium nitroprusside following endothelin-1-induced constriction ($EC_{50} = 0.05 \text{ } \mu\text{mol/L}$ vs. $1.98 \text{ } \mu\text{mol/L}$ in vehicle-treated rings; $P < 0.01$). Canrenone blocked effects of MBG on collagen synthesis and restored sensitivity of vascular rings to sodium nitroprusside ($EC_{50} = 1.7 \text{ } \mu\text{mol/L}$).

Patients with RH exhibited elevated plasma MBG concentration (0.18 ± 0.02 vs. $0.37 \pm 0.05 \text{ nmol/L}$; $P = 0.01$) and reduced NKA activity (1.9 ± 0.15 vs. $2.8 \pm 0.1 \text{ } \mu\text{mol Pi/ml/hr}$; $P < 0.01$) vs. 16 healthy controls. Six-month administration of spironolactone was associated with a decrease in PWV ($P < 0.01$) and systolic/diastolic BP ($12 \pm 3/7 \pm 2 \text{ mmHg}$; $P < 0.01$), and restoration of NKA activity (1.9 ± 0.15 to $2.3 \pm 0.11 \text{ } \mu\text{mol Pi/ml/hr}$; $P < 0.01$). These results demonstrate that CS-induced vascular fibrosis is a likely target for aldosterone antagonists.

P1.04

PREDICTORS OF VASCULAR AGE IN A POPULATION WITH CARDIOVASCULAR RISK FACTORS

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Background: We aimed at evaluating determinants of the vascular age.

Material and Methods: 187 subjects [86 M and 101 W] with CV risk factors were classified into three categories of the Framingham CV Risk (FR). Their mean carotid intima media thickness (CIMT) and arterial stiffness (a.s.) parameters were assessed. The VA was calculated from the CIMT according to the nomograms from the ARIC Study. The subjects were divided into two groups: 1- VA exceeds the chronological age (CA) for at least 5 years and 2 – others.

Results: The VA > the CA in M and W (M: 68.5 y vs 52.4 y , $p < 0.001$; W: 67.1 vs 55.00 , $p < 0.001$). No relationship between the FR category and classification to group 1 or 2 was observed. In both sexes diabetes mellitus (DM) (M: OR 3.10, 95% CI 1.28 ÷ 7.50, $p < 0.05$; W: OR 4.40, 95%CI 1.85 ÷ 10.47, $p = 0.001$) and additionally in W BMI >25 kg/m² (OR 5.87, 95%CI 2.15 ÷ 15.99, $p = 0.009$) differentiated group 1 from group 2. Increased β (9.36 vs 7.77 , $p = 0.005$) and Ep (131.9 vs 110.1 , $p < 0.05$) in M and Ep (132.3 vs 106.5 , $p < 0.05$) in W distinguished group 1 from group 2. In the multivariate analysis, DM and elevated BMI in W and DM and increased β in M were proved to be independent predictors of VA > CA.

Conclusions: FR categories did not allow for prediction if the VA > CA. DM appeared as the strongest predictor of the VA > CA.

P1.05

SEDENTARY LIFESTYLE IS ASSOCIATED WITH INDICES OF ARTERIAL STIFFNESS, DIASTOLIC DYSFUNCTION AND OBESITY

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The aim of the present study was to examine the relationship between weekly physical activity patterns, obesity and early sub-clinical cardiovascular dysfunction.

For this study, 84 healthy lifelong non-smoking, normotensive subjects (54 male & 30 female) were recruited (age 39 ± 11 years, BMI $25.2 \pm 3.3 \text{ kg.m}^2$). Weekly physical activity levels were objectively measured over a five day period using triaxial accelerometry (RT3, Stayhealthy, USA). Activity data was categorized as relative time spent being sedentary, lightly active, moderately active and vigorously active¹. Body fat composition was estimated using bioelectrical impedance (TBF410GS, Tanita, UK). Augmentation index (Alx, Sphygmocor, Skidmore Medical, UK) and pulse wave velocity (PWV, Vicorder, Skidmore Medical, UK), indices of arterial stiffness, were measured using applanation tonometry. Early/late mitral valve filling velocity (MV E/A) was used to assess cardiac diastolic function (Vivid 7 Dimension, GE, USA).

Mean Alx, PWV, MV E/A ratio, body fat composition were $13.43 \pm 14.32 \%$, $6.79 \pm 0.93 \text{ m.s}^{-1}$, 5.11 ± 13.23 and $24.54 \pm 7.70 \%$. Spearman's correlation analysis identified significant correlations between relative time spent being sedentary and Alx $r = 0.3008$ $p < 0.0054$, PWV $r = 0.2174$ $p < 0.0469$, MV E/A ratio $r = -0.3541$ $p < 0.027$ and % body fat $r = 0.3440$ $p < 0.0017$. The results of the study show that people who spend more time being sedentary have greater body fat, greater arterial stiffness and poorer diastolic function. These observations have important implications for public health.

1. Treuth MS, et al. Defining accelerometer thresholds for activity intensities in adolescent girls. *Med Sci Sports Exerc* 2004;**36**(7):1259-66.

P1.06

IS IMPAIRED FASTING GLUCOSE ASSOCIATED WITH SUBCLINICAL ARTERIAL DISEASE? THE STRONG HEART STUDY

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Background: Vascular disease is a leading cause of morbidity and mortality in diabetes mellitus (DM). It is uncertain whether pre-diabetes (impaired fasting glucose [IFG]) increases risk for subclinical vascular disease.

Methods: Cardiovascular disease (CVD) risk factors and carotid artery structure (wall thickness [IMT] and vascular mass) and presence and extent of atherosclerosis were compared in 2461 Strong Heart Study participants free of prevalent CVD: 1038 with normal fasting glucose (NFG), 254 with IFG (110-125 mg/dl), and 1169 with DM.

Results: Participants with IFG were more obese and had lower HDL cholesterol than those with NFG but were comparable in other CVD risk factors. Participants with DM were more likely to be female, hypertensive, non-smoking, and to have higher triglycerides than the other two groups. Following adjustment for differences in CVD risk factors, DM had greater carotid IMT (0.75 mm), mass (16.38 mm^2) and presence (69.1%) and extent (log transformed plaque score: 0.78) of atherosclerosis compared to NFG and IFG. NFG and IFG had comparable adjusted IMT (0.73 vs. 0.73 mm), arterial mass (15.51 vs. 15.67 mm^2), plaque (58.8 vs. 58.5 %) and plaque score (0.64 vs. 0.66).

Conclusions: Other than elevated fasting glucose, the distinguishing features of IFG are obesity and reduced HDL cholesterol (comparable to DM). Greater degrees of arterial hypertrophy and atherosclerosis are seen in DM but not IFG. These findings have implications for public health efforts to identify individuals with IFG and intervene to limit progression to the vascular disease associated with DM.

P1.07

RELATIONSHIP BETWEEN ECHOES FROM THE CAROTID MEDIA, CLINICAL VARIABLES AND ARTERIAL STIFFNESS: A CROSS-SECTIONAL ANALYSIS

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Introduction: The radiofrequency (RF) matrix conveys information on texture and composition of atherosclerotic plaques. Few studies have analyzed the "normal" carotid wall out of plaques. We tested a novel method to measure echoes from the media layer and analyzed their correlation with clinical variables and arterial stiffness in a large population sample.

Methods: We analyzed RF matrices from ultrasound scans of the common carotid in 1,827 untreated subjects recruited from the general population, aged 50 to 75, for the Etude Prospective Parisienne 3. The first strong echo from the blood-intima interface was excluded; media power (MP) was defined as the ratio of amplitude of RF echoes from the media and that from the lumen. Intima-media thickness (IMT) was also measured.

Results: IMT was correlated with carotid diameter, age, pressure, and body size. MP was inversely correlated with body size and serum lipids, but not with age or pressure. IMT was higher, and MP lower, in obesity and metabolic syndrome (MS); obese with MS had higher IMT, and lower MP, than non-obese