P4.19: THE EFFECT OF AN 8-WEEK, MODERATE-INTENSITY, AEROBIC EXERCISE INTERVENTION ON MMP-9 AND VASCULAR HAEMODYNAMICS

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Complex elastic modulus (Ec) was calculated from the Fourier decomposition of waveforms. To examine the effect of dopamine and noradrenaline on arterial elasticity, we measured arterial pressure (AP) and pulse wave velocity (PWV) in rats before and following denervation by ganglionic blockade (intravenous hexamethonium, 20 mg/kg). Bolus intravenous administration of dopamine and noradrenaline increased AP and PWV in LPK and Lewis rats (p < 0.05). VEN increased with pressure (p < 0.001, Figure). Conclusions: Treatment with a RAAS blocker valsartan is associated with a significant decrease in aortic stiffness in a blood pressure independent manner.

**P4.18**

**ANTIHYPERTENSIVE ACTIVITY OF LONG CHAIN FATTY ACID DERIVATIVES OF FLAVONOIDS VIA INHIBITION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)**

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Hypertension is a contributing factor to pathophysiology of vascular damage and accelerated arterial stiffening. Renin-angiotensin-aldosterone system (RAAS) inhibitors are widely used for treatment of persistent hypertension. Along with conventional antihypertensive therapy, nutritional intervention has also gained attention as arterial and vascular complications are closely associated with dietary and lifestyle risk factors. Flavonoids and omega-3 polyunsaturated fatty acids (PUFA) are the key antihypertensive biomolecules emerging to prevent and manage hypertension. In the current study, twelve long chain fatty acid derivatives of flavonoids were investigated for inhibition of renin-converting enzyme (ACE), renin and aldosterone synthesis in comparison to their parent compounds in vitro. The linoleic and α-linolenic esters of PZ were the strongest (IC50 69.9-70.8 μM) while Q3G and PZ (IC50 >200 μM) were the weakest renin inhibitors in vitro (p < 0.05). Similar to renin inhibition, PZ derivatives exhibited stronger ACE inhibition compared to Q3G. The eicosapentaenoic acid (EPA) ester of PZ (IC50 16.03 μM) was the strongest, while PZ (IC50 123.96 μM) was the weakest ACE inhibitor (p < 0.05) among all tested compounds. However, all investigated compounds had no effect on aldosterone synthase inhibition (p > 0.05). Overall, the results showed that phlorizin derivatives were stronger antihypertensive agents than isoquercitrin. It is indicated from our study that these novel compounds as dual RAAS inhibitors may be used as potent bioactive ingredients to develop functional foods and nutraceuticals for prevention and treatment of high blood pressure.
**P4.20**

**SHORT-TERM EFFECT OF ANTI-VEGF DRUGS ON HEART AND VESSELS**

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**Objectives:** Drugs opposing the effect of vascular endothelial growth factor (anti-VEGF) inhibit angiogenesis slowing down and eventually stopping solid tumors growth. Nevertheless these drugs can cause hypertension (that seems to be correlated with cancer outcome) and cardiac dysfunction. We hypothesize there is a correlation between the early stiffening of cardiovascular system and the drug effectiveness. For this purpose we analyzed the short term changes in cardiovascular structure and function in patients treated with antiVEGF drugs.

**Methods:** We enrolled 20 patients suffering from metastatic cancer (17 renal, 2 thyroid and 1 GIST), age 64±11 years (mean±SD). We measured blood pressures (BPs), cardiac and vascular parameters at baseline (B) and after two weeks of treatment (T1) (transthoracic echocardiography with 2D strain evaluation, cf-PWV, Aix).

**Results:** At B our population showed normal BPs (mean±SD:121±17/69±9.5mmHg) and systolic function (EF: 59%). Global longitudinal strain (GLS) was -21±3%, cf PWV was 12.1±3.3m/sec and Aix was 0.24±0.08%. At T1 we observed a significant increase in BPs (137±16/83±10mmHg, p<0.001 vs B), impaired GLS (-19±3%, p<0.005 vs B), and increased cf-PWV (13.5±3m/sec, p=0.01 vs B) while Aix rise didn’t reach statistical significance. Adjusting for PAS only strain impairment remained significative and it was not correlated with BP and PWV modifications.

**Conclusions:** In the short term anti-VEGF drugs cause an increase of BP and of arterial stiffness, while myocardial deformation is impaired. The increase of PWV, without a significant change in Aix, may suggest that anti-VEGF drugs increase arterial stiffness, and, perhaps, have a less apparent effect on wave reflections.

**P4.21**

**MILD UREMIA INDUCES AORTIC DILATATION AND HEART REMODELLING VIA NF-KB ACTIVATION**

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**Objectives:** The aim of this study was to investigate the effects of mild uremia on aortic and heart remodelling in the rat.

**Methods:** Mild uremia was induced by reduction of renal mass after 5/6 nephrectomy (NE). Rats with proteinuria >300 mg/24h were included in further investigations. Four weeks after NE, an abdominal aortic aneurysm (AAA) was induced via continuous infusion of an isolated aortic segment with elastase. One group of NE animals was additionally treated with hydralazine (15 mg/kg). Sham operated rats served as controls (n=12). Aortic diameter and heart function were measured by ultrasound biomicroscopy.

**Results:** Uremia induced aortic dilatation (2.1±0.04mm vs 1.8±0.03mm, p<0.001). Histological analysis revealed an outward aortic remodelling, increased elastin fragmentation (p<0.05), cystic medial degeneration, calcification of tunica media and inflammatory infiltrates in the adventitia. After aneurysm induction, aortic diameter was further increased in the NE group as compared to AAA rats without NE (2.6±0.05mm vs 2.3±0.03mm, p<0.05). Hydralazine treatment significantly reduced blood pressure (115±4 vs 160±7mHg, p<0.05) but did not influence aortic diameter. Protein expression of NF-kb was strongly (3-fold) up-regulated in aortic tissues from NE rats. MMP2, MMP9, cathepsin D and TGF-beta1 were significantly (p<0.05) increased after AAA and further up-regulated in the NE/AAA group. Uremia decreased systolic heart function (p<0.05).

**Conclusion:** Mild uremia induces aortic dilatation and heart remodelling independently of blood pressure elevation. Activation of NFκB by uremic toxins may contribute to remodelling via inhibition of elastin- and collagen gene transcription.

**P4.22**

**THE ROLE OF TESTOSTERONE AND ARTERIAL STIFFNESS IN THE PREDICTION OF RISK FOR CAROTID ARTERIAL EVENTS IN HYPERTENSIVE PATIENTS**

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**Objectives:** Androgen deficiency confers an independent risk for cardiovascular events and total mortality. Hypertension, a major contributory factor to the development of cardiovascular disease (CVD), has been associated with increased prevalence of low testosterone. We investigated whether low androgen concentration predicts major adverse cardiovascular events (MACE) in hypertensive patients without clinical atherosclerosis.

**Methods:** MACE in relation to total testosterone (TT) were analyzed with proportional hazards models in 228 non-diabetic hypertensive patients without a history of known CVD.

**Results:** The mean follow-up time was 44 months, during which 19 (8.3%) subjects developed MACE. Compared to patients who did not experience MACE, subjects who developed MACE had lower TT (3.9±0.7 ng/ml vs 4.9±0.8 ng/ml, p<0.01).

**Conclusion:** Low TT was associated with a higher risk for MACE in hypertensive patients without clinical atherosclerosis.