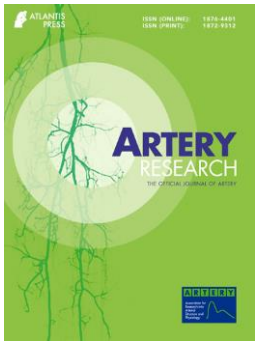

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P4.19: THE EFFECT OF AN 8-WEEK, MODERATE-INTENSITY, AEROBIC EXERCISE INTERVENTION ON MMP-9 AND VASCULAR HAEMODYNAMICS

J.E.S. Thompson, R. Webb, P. Hewlett, D. Llewellyn, B.J. McDonnell

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pg/ml, p=0.01 and reduced serum phosphate 3.25±1.18 to 2.60±0.96 mg/dl, p=0.04 compared to amlodipine (430.1±145.8 to 411.9±157.6 pg/ml and 2.94±0.56 to 2.69±1.52 mg/dl]. There was a significant between treatment group difference, mean (95% confidence interval), in soluble Klotho, 91.9 (19.9 to 162) pg/ml and serum phosphate levels -0.68 (-0.15 to -1.33) mg/dl with valsartan/hydrochlorothiazide treatment, p=0.04 for both. Attained blood pressure was similar in the two groups and levels of soluble Klotho were not associated with Ao-PWV and albuminuria, variables which fell significantly only with valsartan/hydrochlorothiazide.
Conclusions: Treatment with a RAS blocker valsartan is associated with an increase in soluble Klotho which may contribute to the blood pressure independent cardio-renal benefits of these drugs in DKD.

P4.16
EFFECT OF DENERVATION ON VISCOELASTIC PROPERTIES OF LARGE ARTERIES IN POLYCYSTIC KIDNEY DISEASE RATS

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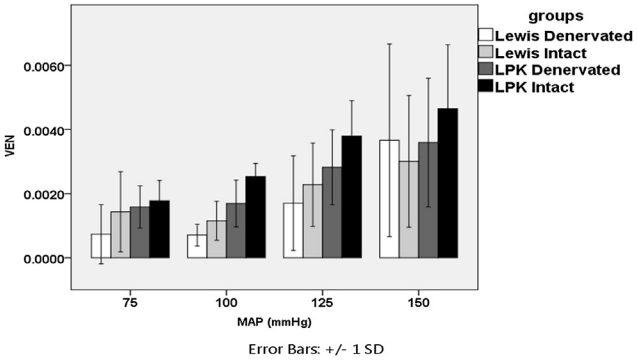
Objectives: Arterial elasticity is determined by passive mechanical properties of wall components modulated by neurogenic effects on smooth muscle. We assessed denervation effects on viscoelastic properties of the aorta of Lewis Polycystic Kidney (LPK) disease rats, compared to controls (Lewis).
Methods: Abdominal aortic pressure (intravascular, Scisence) and diameter (ultrasound, Artlab) was measured in anesthetised (urethane, 1.3 g/kg) Lewis (n=11) and LPK (n=5) rats before and following denervation by ganglionic blockade (intravenous hexamethonium, 20 mg/kg). Bolus intravenous doses of vasoactive agents (6 μg phenylephrine or sodium nitroprusside) were used to study the rats at mean pressures of 75, 100, 125 and 150 mmHg. Complex elastic modulus (E_c) was calculated from the Fourier decomposition of pressure and diameter. Viscoelasticity ($V_E = Im(E_c)$) was compared between LPK and Lewis rats in the intact and denervated state across the first three harmonics. Pressure dependency of viscoelasticity was studied using a frequency (thus heart rate) normalised viscoelastic term ($V_{EN} = V_E$/frequency).
Results: V_E increased with frequency in all but Lewis rats at 150 mmHg. LPK rats had higher V_E than Lewis ($p<0.05$), other than denervated rats at 150 mmHg and intact rats at 75 mmHg. Denervation reduced V_E in both LPK and Lewis groups ($p<0.05$). V_{EN} increased with pressure ($p<0.001$, Figure).
Conclusions: Aortic viscoelasticty was generally greater in LPK rats and was reduced with denervation. This study shows possible relationships between aortic compliance in polycystic kidney disease and sympathetic dysregulation.



P4.17
ACUTE DIETARY SODIUM CHANGES IS A PHYSIOLOGICAL DETERMINANT OF AORTIC STIFFNESS

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Objective: Aortic stiffness evaluation is recommended in standard care as hypertension target organ damage. The main determinants of aortic stiffness are age and blood pressure. We aimed to evaluate the impact of short-term extracellular volume changes induced by dietetic and pharmacological interventions on aortic stiffness.
Methods: 74 healthy male subjects, age (median [IQR]) 23,9 [5,7] years, non-smokers, were assigned to a low sodium/high potassium diet during seven days, followed by a high sodium/low potassium diet for 14 days, the last seven with concomitant administration of amiloride. Carotid-femoral pulse wave velocity (PWV) (SphygmoCor®) was measured at baseline, 7th, 15th and 21st days.
Results: PWV was stable during the low sodium/high potassium diet, significantly decreased during the high sodium/low potassium diet (-0,4 m/s, CI 95% -0,7 to -0.2, $p<0.001$) (day 7 to 15), and came back to baseline after the concomitant administration of amiloride (day 15 to day 21). In a mixed model analysis, mean daytime blood pressure (MBP), age and visit day 15 were independent determinants of changes in PWV. For each increase of 10 mmHg on MBP, PWV increased by 0,3 m/s (CI 95% 0,1 to 0,5, p=0,006), for each increase of 10 years of age, PWV increased by 0,4 m/s (CI 95% 0,1 to 0,7, p=0,01), and at visit 15 (high salt diet), PWV decreased by 0.3 m/s (CI 95 %, -0,52 to -0,12, p=0,002).
Conclusions: Short-time increase in extracellular volume is associated with a signification 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 isoquercitrin (Q3G) and phloridzin (PZ) were investigated for inhibition of angiotensin-converting enzyme (ACE), renin and aldosterone synthase 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 phloridzin 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.

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

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Objective: The Matrix Metalloproteinase-9 (MMP-9) enzyme is involved in degrading extracellular matrix (ECM) proteins, including collagen and elastin. Increased MMP-9 levels are associated with increased vascular remodelling and arterial stiffness. Exercise improves age-related vascular stiffening. It is therefore hypothesised that participation in an aerobic, moderate-intensity exercise programme will down-regulate mRNA expression of MMP-9.
Methods: Thirty-six healthy, sedentary individuals (43±14 yrs) joining an aerobic, moderate-intensity exercise programme, were recruited. Exercise (measured using IPAQ MET-minutes), supine blood pressure, augmentation

index (AIx), aortic-pulse wave velocity (aPWV) and blood samples were obtained at baseline and 8-weeks into the programme. MMP-9 mRNA expression was analysed using real-time PCR, circulating MMP-9 levels assessed via ELISA, and AIx and aPWV were measured via applanation tonometry (SphygmoCor). Participants were split into those who adhered and did not adhere to the exercise programme.
Results: MET-minutes significantly increased; whilst MMP-9 expression, MAP and AIx significantly decreased in the exercise-adherent group compared to the non-adherent group, between baseline and 8-weeks. aPWV did not change significantly between the groups (Table-1). Significant correlations were observed between ΔIPAQ MET-minutes and ΔMMP-9 expression.
Conclusion: Adherence to the exercise programme reduced wave reflection and MAP. These pilot data demonstrate that MMP-9 expression is down-regulated in healthy, sedentary adults after 8-weeks of aerobic, moderate-intensity exercise. Thus suggesting that exercise-induced down-regulation of MMP-9 may result in a reduction in ECM degradation and therefore reduce vascular remodelling. These data provide a biomolecular rationale for how aerobic exercise is effective at delaying age-related increases in aPWV.

Table 1

Parameter	Adherent n=17 (Mean±SE)	Non-Adherent n=19 (Mean±SE)	P Value
Δ IPAQ (MET-minutes)	+2848 ±547	-404 ±267	<0.001
Δ MMP-9 (Ct)	-0.56 ±0.09	+0.42 ±0.44	0.034
Δ Supine MAP (mmHg)	-2.64 ±1.59	+1.45 ±1.16	0.044
Δ Supine AIx@75 (%)	-4.1 ±1.75	+1.9 ±2.23	0.045
Δ CF-PWV (m/s)	+0.3 ±0.2	+0.2 ±0.2	0.854

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 hypnotize 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 causes 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. Aortic tissues, renal functional parameters and serum pro-inflammatory cytokines were investigated.
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 degradation, 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±7mmHg, 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 dilation and heart remodelling independently of blood pressure elevation. Activation of NFkB 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 CARDIOVASCULAR 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