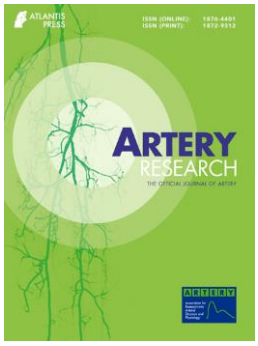

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P4.05: POLYCYSTIN DEFICIENCY RESULTS IN COMPLETE LOSS OF NO SYNTHESIS DURING SUSTAINED FLOW-MEDIATED DILATATION OF CONDUIT ARTERIES IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: POSSIBLE REVERSAL BY DOPAMINE

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P4.02
BASELINE CRP BUT NOT NSAID-USE PREDICTS FUTURE INCREASED ARTERIAL STIFFNESS IN ANKYLOSING SPONDYLITIS: RESULTS AFTER 5-YEAR FOLLOW UP

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Objective: Patients with ankylosing spondylitis (AS) have an increased risk of CVD, but previous studies have not shown a worsened risk profile regarding traditional cardiovascular risk factors. The objective was to investigate whether baseline CRP predicts future increased central arterial stiffness.
Methods: 5-year follow-up study of hospital recruited AS patients, with examinations in 2003 and 2008-2009. Information on demographics, co-morbidities and medication was assessed from questionnaires. Baseline CRP was measured in 2003. Arterial stiffness, measured as Augmentation index (AIx), was recorded in 2008-2009 (Sphygmocor apparatus, At Cor). Statistical analyses were performed using SPSS 20. Univariate associations between AIx and baseline predictors (education, smoking habits, BMI, use of NSAID and disease modifying anti-rheumatic drugs (DMARD), CRP) and factors known to have an effect on AIx (Central mean arterial pressure (CMAP), height, use of statins and antihypertensives) were adjusted for age and gender. Variables with a p-value<0.2 were included in a multivariate model. Non-significant variables were removed stepwise until only significant variables remained.
Results: 85 AS patients participated in this study. Baseline mean (SD) age was 47.3 (12.6) years. 59% were male, 25% smokers. Median (IQR) CRP (mg/l) 4 (2-13). In the multivariate linear regression models CRP was independently associated with higher future AIx (table).
Conclusion: Elevated CRP but not NSAID-use predicted higher future AIx, indicating that inflammation is a risk factor of CVD in AS.

Variables	Univariate beta (95% CI)	p-value	Multivariate beta (95% CI)	p-value
Age (years)*	0.7 (0.5-0.9)	<0.001	0.5 (0.3-0.7)	<0.001
Gender, male*	-12.0 (-17.3–-6.7)	<0.001	-10.9 (-14.4–-7.5)	<0.001
Education>12 years	-1.0 (-5.3-3.3)*	0.63		
Baseline predictors 2003				
Current smoking	3.9 (-0.5 -8.3)*	0.08		
BMI (m^2/kg)	0.8 (0.0-1.6)*	0.04		
NSAID	2.7 (-2.5-7.8)*	0.30		
DMARD	-3.2 (-8.3-1.9)*	0.22		
CRP (mg/l)	0.2 (-0.0-0.3)*	0.06	0.2 (0.0-0.3)	0.02
Current factors 2008				
Height (cm)	-0.3 (-0.5–0.0)*	0.03		
CMAP (mmHg)	0.3 (0.1-0.5)*	<0.001	0.3 (0.1-0.4)	<0.001
Statins	6.2 (0.9-11.6)*	0.02	6.3 (1.5-11.2)	0.01
Antihypertensives	0.8 (-3.9-5.5)*	0.74		

*Adjusted age and gender

P4.03
APOPTOSIS IN THE MEDIA OF THE AORTIC WALL AND ITS RELATIONSHIP WITH AORTIC VALVE MORPHOLOGY IN AORTIC DILATATION

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Background: The aortic valve is normally tricuspid but may vary in that it can be made up of 1, 2 or 4 leaflets with each of these often associated with aortopathy, most commonly aortic dilatation. In patients with a bicuspid valve this association has been explained in part by molecular changes taking place in the smooth muscle cells of the aortic media resulting in their apoptosis.
Objectives: To investigate changes in apoptosis and their genetic regulators that occur in the aortic media of patients with aortic dilatation and whether this differs with different aortic valve configurations.
Methods: Aortic wall samples were collected from patients with unicuspid, bicuspid, tricuspid and quadricuspid aortic valve morphology. Samples underwent homogenisation and were then analysed for a number of apoptotic markers and their genetic regulators using western blot and rt-PCR.
Results: Cleaved caspase 3 expression is increased in the aortic media of both the unicuspid (1.1 μm^2) and bicuspid (0.42 μm^2) aortic valve samples as compared to the tricuspid (0.060 μm^2) sample. Relative gene expression of P53:BCL-X_L >1 in the aortic media of unicuspid and bicuspid aortic valves whilst p53:BCL-X_L<1 in the media of the tricuspid sample.
Conclusion: Cleaved caspase 3 assay demonstrates that smooth muscle cell apoptosis is increased in the dilated aortic media of unicuspid and bicuspid aortic valves as compared to that of the tricuspid aortic valve. This increase in apoptosis is mediated by an increase in the ratio of proapoptotic p53 to antiapoptotic BCL-X_L and may explain the association between abnormal valve morphology and aortic dilatation.

P4.04
BARORECEPTOR SENSITIVITY IS REVERSED IN DIABETES AND IS UNAFFECTED BY ANTI-HYPERTENSIVE TREATMENT: A RODENT STUDY

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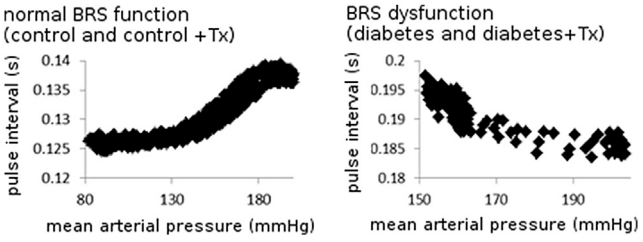
Objectives: Diabetes is a complex disease associated with cardiovascular complications. This study compared baroreceptor sensitivity (BRS) in diabetic rats with and without anti-hypertensive treatment.
Methods: Diabetes (induced by intraperitoneal injection of streptozotocin at 6 weeks of age) and control (saline injection) rats were divided into untreated (diabetic n=9, control n=5) and treated (diabetes+Tx n=9, control+Tx n=6) groups. Treatment groups received angiotensin II receptor antagonist, telmisartan (10 mg/kg/day, gavage). At 17 weeks of age, systolic pressure was measured by tail-cuff technique. The following week, rats were anaesthetised (urethane, 1.3 g/kg) and aortic pressure and heart rate measured during intravenous phenylephrine infusion (30 μg/kg/min). BRS was calculated by the slope of heart rate against mean pressure rise. Normal BRS was defined as a positive slope, and BRS dysfunction as a negative slope (Figure).
Results: Both control (142±16 mmHg) and diabetic (132±22 mmHg) animals were hypertensive. Anti-hypertensive treatment successfully lowered systolic blood pressure (control+Tx 105±11 mmHg; diabetes+Tx 119±14 mmHg). BRS was typically positive in control (100%) and control+Tx (83%) rats. Conversely, BRS was impaired in both diabetic (33% positive) and diabetes+Tx (29% positive) rats. BRS impairment was significantly different between diabetic and control rats (p=0.007) and diabetes+Tx and control+Tx rats (p=0.002). However, there was no difference with anti-hypertensive treatment (diabetes, diabetes+Tx: p=0.42; control, contol+Tx: p=0.32).
Conclusion: Baroreceptor sensitivity is impaired in diabetic rats and this is independent of the hypertensive state.



P4.05
POLYCYSTIN DEFICIENCY RESULTS IN COMPLETE LOSS OF NO SYNTHESIS DURING SUSTAINED FLOW-MEDIATED DILATATION OF CONDUIT ARTERIES IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: POSSIBLE REVERSAL BY DOPAMINE

A. Lorthioir [1], R. Joannidès [2,3], I. Rémy-Jouet [3], C. Fréguin-Bouilland [1], M. Iacob [2], C. Monteil [4], D. Lucas [5], M. P. Audrezet [5], D. Guerrot [1,3], V. Richard [2,3], C. Thuillez [2,3], M. Godin [1,3], J. Bellien [2,3]
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Objectives: Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in genes PKD1 and PKD2 encoding polycystin-1 and -2, which transduce flow variations into cellular signals in the renal epithelium but also in vascular endothelium. However, the impact of polycystin deficiency on the release of endothelium-derived factors during flow variations is unknown.
Methods: In 21 normotensive ADPKD patients with normal kidney function and 21 control subjects, radial artery diameter and blood flow were measured during hand skin heating and post-ischemic hyperaemia. Local blood samples were drawn during heating to quantify plasma nitrite, indicator of nitric oxide (NO) availability, epoxyeicosatrienoic acids (EETs) and endothelin-1.
Results: Basal inflammatory and oxidative stress markers were similar between groups. Flow-mediated dilatation was lower in ADPKD patients than in controls during heating (16.1±1.1 *vs.* 23.2±1.0%), as confirmed by their downward shift of the diameter-shear stress relationship, but not during post-ischemic hypaeremia, and without difference in endothelium-independent dilatation to glyceryl trinitrate. Nitrite increased during heating in controls but not in patients (30±10 *vs.* -16±8 nmol/L). Plasma EETs tended to increase in controls but not in patients, without difference in endothelin-1 reduction. Intra-brachial infusion of dopamine (0.25-0.5 mg/kg/min) during heating induced a dose-dependent upward shift of the diameter-shear stress relationship in ADPKD patients and restoration of NO release.
Conclusions: ADPKD patients display a loss of NO release and subsequent reduction in endothelium-dependent dilatation during sustained flow increase. The prevention of this alteration by dopamine may help to reduce the high prevalence of cardiovascular diseases in ADPKD.

P4.06
ARTERIAL STIFFNESS CORRELATES WITH VITAMIN D DEFICIENCY IN HYPERTENSIVE PATIENTS WITH STAGE 3 CHRONIC KIDNEY DISEASE INDEPENDENTLY OF BLOOD PRESSURE

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Objectives: To assess the prevalence of vitamin D deficiency and hyperparathyroidism as well as their relationship to blood pressure and arterial stiffness in hypertensive patients with stage 3 chronic kidney disease (CKD).
Methods: Cross-sectional study that included 134 treated hypertensives (76 women, 56,7%) with stage 3 CKD (eGFR 49,2 ml/min, SD±8) without previous vitamin D supplementation treatment. Standard clinical care was performed including ECG, microalbuminuria and usual laboratory parameters. Arterial stiffness was measured by brachial oscillometry with the validated Mobil-O-Graph® device. Normal values for vitamin D and PTH were set as 30 ng/ml and 65 pg/ml, respectively.
Results: The mean age was 73,0 years (SD±10) with office BP of 131/75 mmHg (SD±17/11). The prevalence of vitamin D deficiency was 89% (mean: 19 ng/ml (SD±10)), secondary hyperparathytoidism was observed in 49% of patients (mean: 70,5 pg/ml (SD±10)), 84 (62,7%) patients had a pulse wave velocity (PWV) over 10 m/sec (mean 10,7 m/sec, (SD±1,8). In bivariate analysis PWV correlated best with age ($r=930; p<0.0001$), followed by SBP ($r=345; p<0.0001$), vitamin D ($r=310; p<0.0001$), PTH, calcium, fosforous and ventricular mass (CORNELL). In multiple lineal regression analysis, only age, SBP and vitamin D remained significantly associated with arterial stiffness. In logistic regression with presence /absence of PWV $\geq$ 10 m/sec as dependent variable, male gender, age, elevated SBP and vitamin D categorized in tertiles were significantly related to increased PWV.
Conclusions: In hypertensive patients with stage 3 CKD vitamin D deficiency is associated to increased PWV independently of blood pressure, gender and age.

P4.07
EFFECTS OF ANTI-HYPERTENSIVE TREATMENT ON FUNCTIONAL AND STRUCTURAL COMPONENTS OF LARGE ARTERY STIFFNESS IN A RODENT MODEL OF TYPE I DIABETES

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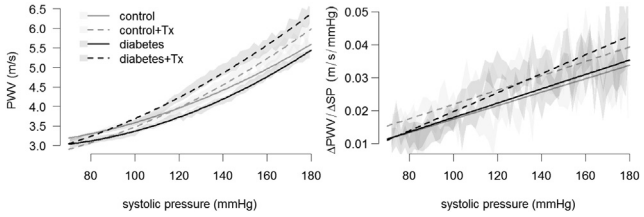
Objectives: Diabetes is associated with cardiovascular risk and increased arterial stiffness. Whether large artery stiffness is associated with diabetes *per se* or concomitant hypertension is currently unknown.
Methods: Male, Wistar rats (6 weeks) were divided into control (n=8), control with anti-hypertensive treatment (telmisartan, 10mg/kg/day, n=8), induced diabetes (intraperitoneal streptozotocin, 50 mg/kg, confirmed by blood glucose measurement, n=12) and diabetes with anti-hypertensive treatment (n=12). At 18 weeks, rats were anaesthetised (urethane, 1.3 g/kg) and aortic pulse wave velocity (aPWV, aortic stiffness) measured invasively across a full range of physiological arterial pressure (intravenous phenylephrine, sodium nitroprusside, 30 μg/kg/min). Passive (elastin, collagen) and active (endothelial, smooth muscle function) components of stiffness were quantified using tensile testing and myography.
Results: Conscious, systolic blood pressure was high in both control and diabetic animals (142±16, 132±22 mmHg) compared to control and diabetic animals on anti-hypertensive therapy (105±11, 119±14 mmHg, $p<0.01$). Diabetic animals had marginally but significantly lower aPWV across all pressures (Figure). Anti-hypertensive treatment increased aPWV in controls and diabetic animals, but increased the pressure dependency of aPWV (Figure). There was no difference in endothelial dependent or independent vasorelaxation. Sensitivity to phenylephrine (vasoconstriction) was less in diabetic animals ($p<0.05$). Anti-hypertensive therapy caused a rightward shift in the aortic stress-strain curve ($p<0.001$).
Conclusions: Diabetes appeared to have a small but positive effect on arterial stiffness when studied independent of blood pressure. However, high blood pressure decreased the artery's ability to respond to acute pressure changes, possibly due to remodelling of passive aortic wall components.



P4.08
INSULIN RESISTANCE IS THE MAIN TARGET IN PREVENTING ACCELERATING ARTERIAL AGING

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Objectives: Increased arterial stiffness (AS) is the most prominent feature of arterial aging. It has been shown an association of AS not only with age, but also with insulin resistance (IR). Leukocyte telomere length (TL) has been proposed as an independent predictor of CVD. The origin of the association between TL and CVD may be related to its effect on AS. TL attrition is accelerated by chronic inflammation and oxidative stress associated with IR. We assessed the hypothesis that TL attrition under the influence of IR leads to arterial stiffening.
Methods: The study group included 99 subjects mean age 51.3 ±12.3 years, free of known CVD, 20 subjects had T2DM. Serum fasting glucose (FG), insulin, Hb1Ac were determined using routine laboratory methods. HOMA-IR was calculated as fasting insulin (mU/ml) x FG (mmol/l)/22,5. TL was determined by PCR. AS was evaluated by measuring aortic pulse wave velocity (PWV) with the help of SphygmoCor (AtCor Medical).
Results: Through multiple linear regression analysis, PWV was found to be independently and positively associated with age, FG, Hb1Ac, independently and negatively associated with TL (see table 1). TL was found to be independently and negatively associated with age, HOMA-IR (see table 2).
In all subjects age, TL, FG, Hb1Ac predicted 43% of the variance in PWV (p-0,0001). Age, HOMA-IR predicted 24% of the variance in TL (p-0,0001).