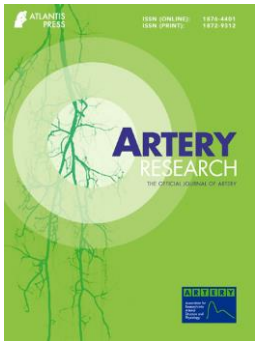

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P4.08: INSULIN RESISTANCE IS THE MAIN TARGET IN PREVENTING ACCELERATING ARTERIAL AGING

I.S. Strazhesko, O.N. Tkacheva, D.U. Akasheva, A.S. Kruglikova, E.V. Plokhova, O.U. Isaykina, M.S. Poktovskaya, V.A. Vygodin, V.S. Pykhtina, S.A. Boytsov

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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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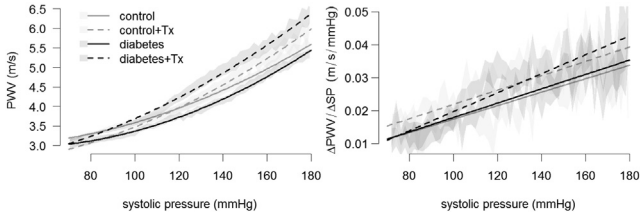
Objectives: Diabetes is associated with cardiovascular risk and increased arterial stiffness. Whether large artery stiffness is associated with diabetes *per se* or concomitant hypertension is currently unknown.
Methods: Male, Wistar rats (6 weeks) were divided into control (n=8), control with anti-hypertensive 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

I. S. Strazhesko, O. N. Tkacheva, D. U. Akasheva, A. S. Kruglikova, E. V. Plokhova, O. U. Isaykina, M. S. Poktovskaya, V. A. Vygodin, V. S. Pykhtina, S. A. Boytsov
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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).

Table 1

Predictor	β	Standard Error	p
Age	0,099	0,028	0,001
Telomere length	-0,658	0,309	0,037
Fasting glucose	0,388	0,160	0,017
Hb1Ac	0,801	0,362	0,031

Table 2

Predictor	β	Standard Error	p
Age	-0,026	0,010	0,015
HOMA-IR	-0,176	0,056	0,027
Hb1Ac	-0,213	0,148	0,155

In conclusion: TL along with indicators of glucose metabolism mainly determine arterial stiffness. There is a considerable impact of glucose regulation on telomere dynamics. IR may be the main target in preventing accelerating arterial aging.

P4.09
DIFFERENT EFFECTS OF 7-NITROINDAZOLE AND L-NAME ADMINISTERED INDIVIDUALLY AND/OR TOGETHER ON CARDIOVASCULAR SYSTEM OF ADULT WISTAR RATS

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Objectives: We evaluate the effect of N^G-nitro-L-arginine methylester (L-NAME) and 7-nitroindazole (7NI) administered individually and/or together on cardiovascular system of adult Wistar rats.
Methods: L-NAME (50 mg/kg/day in tap water) and 7NI (10 mg/kg/day in pellets) was administered to Wistar rats from 10^{th}-16th week of age. Blood pressure (BP) was measured by the plethysmographic method weekly. For morphological study the animals (n=10 in each group) were perfused with a fixative (120 mmHg) and carotid and coronary arteries were processed for electron microscopy. For functional investigation aortal rings (n=10 in each group) in organ bath were used.
Results: L-NAME administration to Wistar rats evoked increase of BP, hypertrophy of the heart and arterial wall, increase of cross sectional areas (CSA) of endothelial and muscle cells, increase of extracellular matrix, decrease of endothelial dependent relaxation (EDR) to acetylcholine, and increase of noradrenaline contraction. 7NI administration resulted in BP independent hypotrophy of the heart and arterial wall, decrease CSA of endothelial and muscle cells without affecting CSA of extracellular matrix, mild decrease of acetylcholine induced EDR, and noradrenaline contraction. Common administration of 7NI and L-NAME evoked (i) lower effect on BP, and trophicity of both arteries and heart compared to L-NAME, and (ii), similar decrease of EDR as in L-NAME group, and (iii) decreased contractile effect.
Conclusions: The results indicate that two different NO-synthase inhibitors L-NAME and 7NI via decreased synthesis of the same NO molecule evoked different and in many causes the opposite effects on cardiovascular system of normotensive Wistar rats.

P4.10 Withdrawn by author

P4.11
SERUM UREA IS A NEW BIOMARKER OF CELLULAR AND VASCULAR AGING

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Objective: Large arteries stiffness is a feature of arterial aging and a predictor of cardiovascular diseases. The length of telomere (TL) in leukocytes is widely considered as a biomarker for cellular aging, cardiovascular aging and cardiovascular diseases. High concentrations of urea is known to increase oxidative stress. The aim of our study was to determine whether the indicators of renal function are associated with TL and arterial stiffness, evaluated by measuring aortic pulse wave velocity (PWV).
Methods: The study group included 150 subjects free of known cardiovascular diseases, kidney diseases, anti-diabetes, antihypertensive and lipid lowering medications. PWV was measured with the help of SphygmoCor (AtCor Medical). Telomere length has been determined by quantitative polymerase chain reaction. Renal function was assessed by creatinine clearance calculated with the MDRD formula . Microalbuminuria (MAU) and urea levels were determined using routine laboratory methods.
Results: Pearson's correlations are demonstrated in the table 1 and table 2.

Table 1

	TL
Age	r= -0,2860 p= 0,0003
Creatinine clearance (ml/min)	r= -0,4267 p= 0,0167
MAU (mg/l)	r= -0,2718 p= 0,0175
Urea (mmol/l)	r= -0,2521 p= 0,0098

Table 2

	PWV
Age	r= 0,5223 p= 0,0001
TL	r= -0,2657 p= 0,0096
Creatinine clearance (ml/min)	r= 0,1964 p= 0,2814
MAU (mg/l)	r= 0,0186 p= 0,8544
Urea (mmol/l)	r= 0,1784 p= 0,0384

In conclusion, even physiological concentrations of plasma urea contribute to cellular and vascular aging. TL may play a role in kidney function. The relationship between TL and kidney repair and regeneration needs increasing studies.

P4.12
A COMPARISON OF DIFFERENT METHODS TO DETERMINE AORTIC PULSE WAVE VELOCITY IN ANEURYSMATIC AND CONTROL MICE

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Introduction: Accurate determination of aortic pulse wave velocity (PWV) in mice is not straightforward, due to the high resolution needed in both time and space. We compared different techniques in control and aneurysmatic mice.
Methods: N=30 male, 18 weeks-old C57Bl/6 mice were included. N=20 animals got implanted an osmotic pump delivering Angiotensin II, and were injected anti-TGF-beta antibodies to provoke aneurysm formation. PWV was determined using 4 different methods: (i) global foot-to-foot transit time based on ultrasound pulsed Doppler velocities (VisualSonics Vevo 2100) at the ascending aorta and 4 cm distal to it (tape-measured); (ii) abdominal foot-to-foot transit time based on 2 invasive pressure sensors placed exactly 2 cm apart (Sciscense catheter), considered the gold standard; (iii) abdominal, in vivo, invasive pressure-diameter (P-D) waveforms obtained via RF wall tracking; (iv) abdominal, ex-vivo P-D curves measured at in vivo stretch using an in-house myograph. The latter were restricted to the in vivo measured pressure range. P-D data were converted to PWV using the Bramwell-Hill equation and groups were statistically compared via a paired student-test.
Results: 13 complete datasets were available for analysis. In the control animals all in vivo methods yielded significantly different PWVs compared to the gold standard ($p<0.05$), and none of the investigated methods were found to correlate to each other. Moreover aneurysm presence was not picked up by transit-time methods, while it resulted in a significant increase in PWV ($p<0.0001$) in both P-D methods.