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

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Table 1

Predictor	$\beta$	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	$\beta$	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<sup>G</sup>-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<sup>th</sup>-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

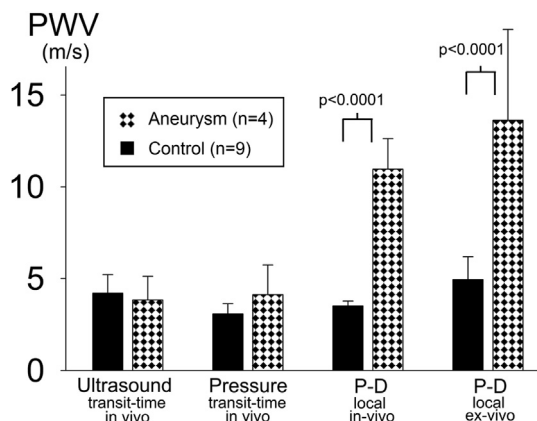
##### A COMPARISON OF DIFFERENT METHODS TO DETERMINE AORTIC PULSE WAVE VELOCITY IN ANEURYSMATIC AND CONTROL MICE

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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 (Scisense 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.



**Conclusions:** PWV measurement in mice is not straightforward and results should be interpreted carefully.

**P4.13**  
**VITAMIN D SUPPLEMENTATION IMPROVES ENDOTHELIAL FUNCTION IN TYPE 2 DIABETES – A RANDOMIZED CONTROLLED TRIAL**

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**Background:** Cardiovascular disease is prevalent in type 2 diabetes, and both endothelial dysfunction and arterial stiffness may contribute in the pathogenesis. Low levels of vitamin D are associated with both type 2 diabetes and cardiovascular disease.

**Aim:** To evaluate the effect of vitamin D supplementation on endothelial function and arterial stiffness in subjects with type 2 diabetes and hypovitaminosis D.

**Methods:** Sixty-two subjects with type 2 diabetes and serum 25-hydroxyvitamin D [25(OH)D] <50 nmol/L were included in this randomized controlled trial (NCT 00992797). Thirty-three patients received vitamin D (400 000 IU cholecalciferol) at baseline, whereas 29 patients received placebo. Endothelial function and arterial stiffness were measured at baseline and after six months. Endothelial function was assessed as the reactive hyperaemia index (RHI) using endothelial pulse amplitude testing (EndoPAT). Arterial stiffness was estimated as carotid-femoral pulse wave velocity (cfPWV) and augmentation index (Alx) with the SphygmoCor device. Serum 25(OH)D was measured using the DiaSorin-RIA.

**Results:** Mean (SD) age in the treatment and placebo group were 57.5 (9.4) and 57.8 (10.0) years, 51.5 % (n=17) and 44.8 (n=13) were females, and diabetes duration was 11.4 (6.5) and 7.5 (5.7) years. Vitamin D supplementation significantly improved RHI and increased the 25(OH)D levels, but did not change cfPWV and Alx (Table 1). In multivariable regression analysis, change in RHI was significantly associated with change in 25(OH)D levels ( $\beta$  [CI] = 0.009 [0.001-0.017], P=0.03).

**Conclusion:** Vitamin D supplementation improved endothelial function but not arterial stiffness in subjects with type 2 diabetes.

**P4.14**  
**RENAL DENERVATION IMPROVES CENTRAL HEMODYNAMICS AND PULSE PRESSURE AMPLIFICATION IN PATIENTS WITH TREATMENT RESISTANT HYPERTENSION**

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**Background:** Renal denervation (RDN) was shown to be effective in reducing peripheral BP in treatment resistant hypertension. Accumulating data suggest that central pressures may be a better predictor of cardiovascular events and outcomes than the corresponding peripheral pressure. PP amplification is among others inversely related to stiffer arteries and peripheral arterial resistance.

**Methods:** 57 patients with treatment resistant hypertension (office BP  $\geq$ 140/90 mmHg, while on at least 3 antihypertensive agents, and diagnosis confirmed by 24-h ABPM  $\geq$ 130/80 mmHg) underwent catheter-based RDN using the Symplicity Flex™ catheter (Medtronic Inc., Palo Alto, CA). In addition, in our lab pulse wave analysis was assessed with the SphygmoCor™ device (AtCor Medical, Australia) before and after 6 months of RDN. PP amplification is determined as ratio of peripheral PP to central PP.

**Results:** Patients (59±12 years) were treated with 6.0±1.3 antihypertensive drugs on average. Peripheral as well as central systolic and diastolic BP were reduced (all p<0.01) 6 months after RDN. In accordance, peripheral PP (77.5±22 versus 71.5±23 mmHg, p=0.008) and central PP (63.2±21 versus 56.7±22 mmHg, p=0.001) were reduced 6 months after RDN. Consistently, there was a significant improvement in PP amplification (1.25±0.2 versus 1.30±0.2, p=0.012). Also central augmentation pressure (20±12 versus 16±13 mmHg, p<0.001) and cAlx@75 (24±10 versus 21±11 %, p=0.005) decreased 6 months after RDN. There was no change on heart rate (63±11 versus 64±10 bpm, p=0.499).

**Conclusion:** Our data suggest that RDN might exert beneficial effects indicated by an improvement of central PP beyond peripheral PP, and hence PP amplification.

**P4.15**  
**EFFECT OF RENIN ANGIOTENSIN SYSTEM BLOCKADE ON SOLUBLE KLOTHO, ARTERIAL STIFFNESS AND ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES AND SYSTOLIC HYPERTENSION**

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**Background:** Soluble Klotho is an anti-ageing phosphaturic protein associated with cardiovascular and renal protection. In-vitro and in-vivo studies have demonstrated that rennin-angiotensin-system (RAS) blockade increases soluble Klotho levels. The effect of RAS blockers on soluble Klotho in patients with diabetic-kidney-disease (DKD) is unknown.

**Methods and measurements:** Plasma soluble Klotho was measured in a secondary analysis of a randomised controlled clinical trial performed at a single university centre. Seventy-six patients with Type-2 diabetes, and DKD (all with albuminuria and serum creatinine <1.7mg/dl) were studied at baseline and at 24-weeks (end of study), following randomisation to valsartan/hydrochlorothiazide (n=37) or amlodipine (n=39) treatment. Aortic-pulse wave velocity (Ao-PWV) by applanation tonometry and albuminuria (from 3-timed urine collections) were also measured at baseline and 24-weeks.

**Results:** Valsartan/hydrochlorothiazide treatment significantly increased soluble Klotho mean±standard deviation, from 432.7±179 to 506.4±226.8

**Table 1** Baseline values and change in endothelial function, arterial stiffness and vitamin D from baseline to 6 months. Values are given as mean (SD). P represents the significance of between-group-comparisons for baseline values and changes after 6 months respectively.

	Baseline			Change		
	Treatment (n=33)	Control (n=29)	P	Treatment (n=33)	Control (n=29)	P
RHI	1.7 (0.4)	1.7 (0.5)	0.74	0.21 (0.49)	-0.03 (0.37)	0.04
cfPWV, m/s	10.18 (1.85)	9.84 (2.33)	0.54	-0.21 (0.92)	-0.10 (0.64)	0.56
Alx, %	20.0 (8.7)	20.0 (10.1)	0.98	0.8 (5.0)	3.5 (8.4)	0.54
25(OH)D, nmol/L	38.5 (9.1)	38.1 (8.5)	0.74	15.0 (11.0)	0.7 (16.0)	<0.001