



Artery Research

ISSN (Online): 1876-4401

ISSN (Print): 1872-9312

Journal Home Page: <https://www.atlantis-press.com/journals/artres>

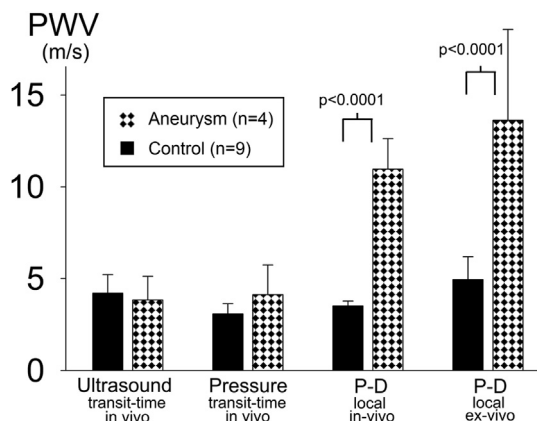
P4.15: EFFECT OF RENIN ANGIOTENSIN SYSTEM BLOCKADE ON SOLUBLE KLOTHO, ARTERIAL STIFFNESS AND ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES AND SYSTOLIC HYPERTENSION

G. Maltese, G. Viberti, L. Gnudi, J. Karalliedde

To cite this article: G. Maltese, G. Viberti, L. Gnudi, J. Karalliedde (2013) P4.15: EFFECT OF RENIN ANGIOTENSIN SYSTEM BLOCKADE ON SOLUBLE KLOTHO, ARTERIAL STIFFNESS AND ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES AND SYSTOLIC HYPERTENSION, Artery Research 7:3_4, 139–140, DOI: <https://doi.org/10.1016/j.artres.2013.10.133>

To link to this article: <https://doi.org/10.1016/j.artres.2013.10.133>

Published online: 14 December 2019



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

K. Angel¹, H. L. Gulseth¹, C. Wium¹, E. F. Eriksen^{1,2}, D. Atar^{1,2}, K. Birkeland^{1,2}

¹Oslo University Hospital, Oslo, Norway
²University of Oslo, Oslo, Norway

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-hydroxy-vitamin 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 (β [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

C. Ott¹, A. Schmid², T. Ditting¹, R. Veelken¹, M. Uder², R. E. Schmieder¹

¹Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany

²Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany

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

G. Maltese, G. Viberti, L. Gnudi, J. Karalliedde
 King's College London, London, United Kingdom

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

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

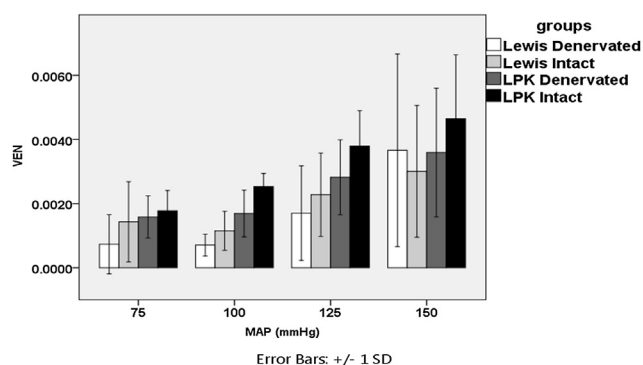
Z. Kouchaki, G. Lindsay, M. Butlin, J. K. Phillips, A. P. Avolio
Australasian School of Advanced Medicine, Macquarie University, Sydney, Australia

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, Scisense) 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 ($6\ \mu\text{g}$ 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 ($V_E = \text{Im}(E_c)$) 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 ($V_{EN} = V_E/\text{frequency}$).

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 viscoelasticity 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

H. Ribeiro¹, M. Briet¹, A. Blanchard¹, E. Curis¹, X. Jeunemaitre^{1,2}, M. Azizi¹

¹Centre d'investigation clinique 9201, Hôpital européen Georges-Pompidou, AP-HP, Université Paris-Descartes, Inserm, Paris, France

²Service de Génétique, Hôpital européen Georges-Pompidou, AP-HP, Université Paris-Descartes, Inserm, Paris, France

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 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)

Bhullar Khushwant Singh, Zia ullah, Rupasinghe Vasantha
Dalhousie University, Truro, Canada

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

J. E. S. Thompson¹, R. Webb¹, P. Hewlett¹, D. Llewellyn², B. J. McDonnell¹

¹Cardiff School of Health Sciences, Cardiff Metropolitan University, Cardiff, United Kingdom

²Groundwork Wales, Treforest, United Kingdom

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