



## Artery Research

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### **P7: THE URINARY PEPTIDOMIC SIGNATURE OF AORTIC STIFFNESS REVEALS MOLECULAR PATHWAYS AND DRUG TARGETS**

Zhen-Yu Zhang, Makis Izoidakis, Wen-Yi Yang, Lutgarde Thijs, Fang-Fei Wei, Qi-Fang Huang, Joost Schanstra, Jens-Uwe Voigt, Tatiana Kuznetsova, Peter Verhamme, Antonia Vlahou, Harald Mischak, Jan Staessen

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However, stress failed to affect significantly neurogenic contractions of SMA elicited by electrical stimulation of perivascular sympathetic nerves and vasoconstriction induced by exogenous noradrenaline in SMA.

**Conclusion:** In conclusion, chronic social stress can accelerate the development of hypertension in BHR, which seems to be associated with NO-independent endothelial dysfunction in small resistant arteries.

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#### ERYTHROCYTE DEFORMABILITY AND NITRIC OXIDE PRODUCTION IN ANIMAL MODEL OF PRIMARY HYPERTENSION AND THEIR AGE-DEPENDENT CHANGES

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**Objectives:** Reduced deformability of red blood cells (RBC) plays an important role in etiology of various diseases including cardiovascular. The nitric oxide (NO) was identified as one of factors responsible for maintenance of RBC deformability. Reduced bioavailability of NO might be important in the pathogenesis of hypertension. The aim of present study was to determine the effect of hypertension and aging on RBC deformability and NO production of experimental animals.

**Methods:** Spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto (WKY) rats were divided into 6 groups according to age (7, 20 and 52 weeks) and strain: SHR-7, SHR-20, SHR-52 and WKY-7, WKY-20, WKY-52. Blood was used for determination of RBC deformability using filtration method and NO production in RBCs using fluorescent NO probe DAF-2 DA.

**Results:** We found reduced deformability at WKY-52 and SHR-52 as compared to strain-matched 20-week-old animals. Strain-related differences in deformability were observed at 7 and 52 weeks of age, where the SHR-7 had reduced deformability and the SHR-52 had increased deformability as compared to age-matched WKY. We have found that at younger age, deformability and NO production in RBCs was able to increase, while in the older age there was a decrease in both parameters.

**Conclusions:** Changes in the RBC deformability under hypertensive conditions are unlikely to be related to changes in NO production. On the other hand, age-related changes in deformability of both, WKY and SHR are at least partially associated with changes in NO production. Supported by grants VEGA 1/0032/14 and Slovak Society of Cardiology.

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#### ANGIOTENSIN AT2 RECEPTOR AGONIST, COMPOUND 21, MAINTAINS VASCULAR INTEGRITY AND PREVENTS ABDOMINAL AORTIC ANEURYSM PROGRESSION IN THE RAT

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The effects of the selective angiotensin AT2 receptor agonist, compound 21 (C21), on abdominal aortic aneurysm (AAA) formation were investigated in normotensive Wistar rats.

AAA was induced by perfusion of isolated aortic segments with elastase (Anidjar/Dobrin model). Treatment with C21 (0.03 and 0.3 mg/kg daily) was started after surgery and continued for 14 days. Sham operated animals and vehicle-treated animals after aneurysm induction (AI) served as controls. Aortic diameter and wall properties (distensibility, pulse propagation velocity) were measured infrarenally via ultrasound. Hemodynamic parameters, aortic tissue protein expression and serum cytokines were analysed.

On day 14 post AI, aortic diameter of vehicle-treated animals was increased 1,6-fold compared to sham operated rats ( $p < 0.0001$ ). C21 (0.03 mg/kg) decreased aortic diameter in comparison to vehicle ( $1.9 \text{ mm} \pm 0.06$  vs.  $2.65 \text{ mm} \pm 0.06$ ;  $p < 0.0001$ ). Infrarenal blood velocity and aortic

distensibility were reduced, whereas aortic wall stiffness was increased post AI. These alterations were significantly ameliorated by treatment with C21 ( $p < 0.0001$ ;  $p < 0.0001$ ;  $p < 0.05$ ). Blood pressure and cardiac contractility were not altered. Protein expression of IL1 beta, NF kappa B, MMP9, TGF-beta1 and MLKL in the aorta was significantly ( $p < 0.05$ ) down-regulated in the C21 group compared with vehicle. In primary rat vascular smooth muscle cells, the release of MMP9, TGF-beta1 and MLKL was significantly diminished after C21 (1 μM) treatment. Serum concentration of TGF-beta1 was also decreased by C21 in comparison to vehicle ( $p < 0.01$ ).

In conclusion, AT2 receptor stimulation with C21 prevented extracellular matrix degradation, maintained vascular integrity of the aorta and prevented AAA progression.

P7

#### THE URINARY PEPTIDOMIC SIGNATURE OF AORTIC STIFFNESS REVEALS MOLECULAR PATHWAYS AND DRUG TARGETS

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**Background:** Molecular pathways leading to stiffening of the central arteries are poorly understood. We searched for differentially expressed proteins by urinary peptidomic analysis in patients with arterial stiffness and healthy controls in a case-control study.

**Methods:** To identify urinary peptides associated with aortic stiffening, we applied capillary electrophoresis coupled to mass spectrometry. We compared 18 cardiovascular disease-free patients with carotid-femoral pulse wave velocity (PWV)  $> 10 \text{ m/s}$  standardised to a heart rate of 75/minute as measured by the SphygmoCor method) with 18 controls matched for sex, age and mean arterial pressure.

**Results:** 69 urinary peptides had a different signal amplitude between cases and controls ( $P \leq 0.049$ ). Among 33 peptides with known sequence, 26 were members of the extracellular matrix family, including collagen type I  $\alpha$ -1 and  $\alpha$ -2, collagen type III  $\alpha$ -1, collagen type IV  $\alpha$ -5, collagens IX, XXI and XXVII. Collagen type I was down-regulated, whereas collagen type III was up-regulated. Epidermal growth factor receptor (EGFR), a key regulator of myoblast differentiation, and interactions of laminin with other proteins were down-regulated. Atherosclerosis signalling pathways and intrinsic prothrombin activation were the top pathways associated with increased PWV. Potential drug targets included collagen type IV  $\alpha$  3 and transforming growth factor  $\beta$  3. Angiotensin-converting enzyme inhibitors, which are widely used for vascular protection, were among the possible therapeutic agents.

**Conclusions:** We suggest that stiffening of large elastic arteries involves changes of the extracellular matrix, as reflected by collagen turnover and regulation of myoblast differentiation. Pathway analysis identified potential drug targets, possibly amenable by angiotensin-converting enzyme inhibition.

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#### PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 LEVELS AND ARTERIAL FUNCTION

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**Purpose/Background/Objectives:** Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels are modestly but significantly associated with increased risk of total cardiovascular events. Aortic stiffness and wave reflections are also important predictors of cardiovascular events. The aim