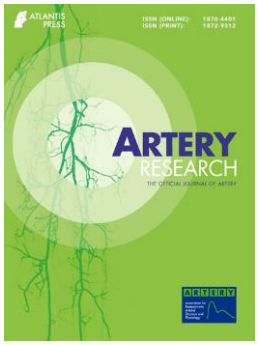

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

P4: SOCIAL STRESS-INDUCED BLOOD PRESSURE INCREASE IN BORDERLINE HYPERTENSIVE RATS IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION IN THE RESISTANT ARTERIES

Angelika Puzserova, Ruzena Sotnikova, Jozef Torok, Anna Zemancikova, Iveta Bernatova

To cite this article: Angelika Puzserova, Ruzena Sotnikova, Jozef Torok, Anna Zemancikova, Iveta Bernatova (2017) P4: SOCIAL STRESS-INDUCED BLOOD PRESSURE INCREASE IN BORDERLINE HYPERTENSIVE RATS IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION IN THE RESISTANT ARTERIES, Artery Research 20:C, 62–63, DOI: https://doi.org/10.1016/j.artres.2017.10.057

To link to this article: https://doi.org/10.1016/j.artres.2017.10.057

Published online: 7 December 2019

Artery Research (2017) 20, 62—110

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

ARTERY 17 Poster Presentation abstracts

Poster Session 1 — Basic

P2

LOCAL ABDOMINAL VERSUS THORACIC AORTA STIFFENING IN HYPERTENSIVE RATS UNDER EITHER NO RESTRICTION OR SALTED DIET

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Background: Hypertensive humans exhibit reduced nitric oxide bioavailability and increased salt sensitivity, both of which are related to central artery stiffening. We studied the effect of 5 week NO restriction via L-NAME treatment in spontaneously hypertensive rats (SHR) and 5% salted diet in salt-sensitive SHR (SHRSP), on the thoracic (TA) and abdominal (AA) aorta.
Methods: Ultrasonic recording of the pulsatile aortic diameter together with blood pressure allowed the measurement of diameter distension and ß-stiffness index. SHRLN and SHRSP salt were compared to their respective control normotensive rats WKY and two measurements were performed in each rat for TA and AA: at operating basal pressure and at reduced WKY matched pressure, n = 6—8. Aortic structure was then characterized by immunohistochemical analysis.
Results: At basal blood pressure, stiffness was greatly increased (range 263—330%) and distension decreased at both TA and AA in both models. At WKY-matched blood pressure and pulse pressure, AA parameters remained significantly altered whereas TA recovered to values not significantly different from WKY values.
Immunohistochemistry evaluation showed similar increases of markers of fibrosis and remodeling for AA and TA in the two models (fibronectin and its integrin alpha5-beta1 receptor, Focal Adhesion Kinase).
Conclusions: This study confirms the potency of ultrasonic derived stiffness measurements and that aortic remodeling is non-uniform along the aortic trunk. The thoracic aorta, which has an important role in dampening cardiac output appears less sensitive to salt loading and NO reduction induced stiffening. Surprisingly, fibrosis does not appear to account for these dynamic differences.

P3

THE EXTENT OF ENDOTHELIAL DYSFUNCTION IN THE FEMORAL ARTERY IS SIMILAR IN THE JUVENILE MALE AND FEMALE SPONTANEOUSLY HYPERTENSIVE RATS

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Objectives: Endothelial dysfunction (ED) plays an important role in the pathogenesis of hypertension. In this work, we studied sex differences in the endothelium-dependent relaxation (EDR) of the femoral artery (FA) and its nitric oxide (NO)-dependent and NO-independent components in peri-pubertal (7-week-old) spontaneously hypertensive male and female rats (SHR). Age-matched Wistar-Kyoto (WKY) rats served as the control groups.
Method: Systolic blood pressure (sBP) was measured non-invasively by tail-cuff. Vascular studies were conducted using the wire myograph at isometric conditions. EDR was determined using acetylcholine test. Biochemical parameters (lipid profile, uric acid) were determined in plasma.
Results: We found a significant increase in sBP of SHR vs. WKY, however, there were no sex-dependent differences in sBP. Significantly reduced EDR was found in both male and female SHR and the extent of ED was similar in males and females. ED in SHR of both sexes was associated with a reduced NO-independent component, while NO- dependent component was reduced only in females. Concentrations of high-density lipoproteins were significantly increased in females vs. males in both WKY and SHR. Uric acid concentration was decreased only in male SHR vs. male WKY.
Conclusion: In conclusion, we did not find differences in sBP and overall endothelial function between juvenile SHR males and females. ED in both young SHR males and females was NO-independent. In addition, results suggested the association between low serum uric acid concentrations and ED in male SHRs. Supported by the grants VEGA No. 2/0190/17, APVV-16-0263 and Slovak Society of Cardiology.

P4

SOCIAL STRESS-INDUCED BLOOD PRESSURE INCREASE IN BORDERLINE HYPERTENSIVE RATS IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION IN THE RESISTANT ARTERIES

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Objectives: Several studies have observed that altered endothelial function is involved in the development of stress-induced hypertension. The aim of this study was to investigate the effects of chronic social stress (crowding) on endothelium-dependent relaxation (EDR) of the superior mesenteric artery (SMA) and of small resistant mesenteric arteries (MA) as well as on neurogenic contractions of SMA in adult borderline hypertensive rats (BHR).
Methods: Twelve-week-old BHR (offspring of spontaneously hypertensive dams and Wistar-Kyoto sires) males were exposed to crowding (living space: 200 cm^2/rat) for eight weeks. Control BHR were kept in the groups of four rats per cage (living space: 480 cm^2/rat). Systolic blood pressure (sBP) was determined by the tail-cuff method.
Vascular function was investigated in the isolated arteries at isometric conditions.
EDR was assessed using acetylcholine test.
Results: Crowding significantly increased sBP of BHR to the hypertensive values. Results showed that stress did not affect total acetylcholine-induced relaxation and its nitric oxide (NO)-dependent and NO-independent components in the SMA. In the resistant MA, stress reduced total acetylcholine-induced relaxation by reducing NO-independent component, without the alterations of its NO-dependent component.

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.
Supported by the grants VEGA No. 2/0190/17 and APVV-16-0263.

P5
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.

P6
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 mm $\pm$ 0.06 vs. 2.65 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

Zhen-Yu Zhang [1], Makis Izoidakis [2], Wen-Yi Yang [1], Lutgarde Thijs [1], Fang-Fei Wei [1], Qi-Fang Huang [1], Joost Schanstra [3], Jens-Uwe Voigt [1], Tatiana Kuznetsova [1], Peter Verhamme [1], Antonia Vlahou [2], Harald Mischak [4], Jan Staessen [1]
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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 cardiovarscular disease-free patients with carotid-femoral pulse wave velocity (PWV $>$ 10 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 α-1 and α-2, collagen type III α-1, collagen type IV α-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 α 3 and transforming growth factor β 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.

P8
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