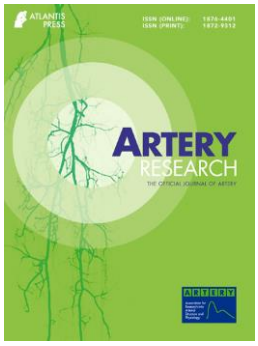

Artery Research

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

P2.2: RESISTANT HYPERTENSION AND STRUCTURAL ALTERATIONS OF SUBCUTANEOUS SMALL RESISTANCE ARTERIES

Claudia Agabiti Rosei, Carolina De Ciuceis, Claudia Rossini, Maria Lorenza Muiesan, Massimo Salvetti, Enzo Porteri, Alice Gavazzi, Anna Paini, Stefano Caletti, Maria Antonietta Coschignano, Paola Pileri, Enrico Agabiti Rosei, Damiano Rizzoni*

To cite this article: Claudia Agabiti Rosei, Carolina De Ciuceis, Claudia Rossini, Maria Lorenza Muiesan, Massimo Salvetti, Enzo Porteri, Alice Gavazzi, Anna Paini, Stefano Caletti, Maria Antonietta Coschignano, Paola Pileri, Enrico Agabiti Rosei, Damiano Rizzoni* (2015) P2.2: RESISTANT HYPERTENSION AND STRUCTURAL ALTERATIONS OF SUBCUTANEOUS SMALL RESISTANCE ARTERIES, Artery Research 12:C, 6–7, DOI: https://doi.org/10.1016/j.artres.2015.10.210

To link to this article: https://doi.org/10.1016/j.artres.2015.10.210

Published online: 7 December 2019

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P1.14
ANALYSIS OF LEFT VENTRICULAR FILLING DYNAMICS

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Diastolic filling of the left ventricle (LV) occurs in two phases, early and late filling. Early filling, manifest as the "E-wave", is thought to be substantially due to diastolic suction (DS), a phenomenon where the LV aspirates blood and fills itself, independent of atrial activity. Late filling, resulting in the mitral flow "A-wave" is a result of left atrial contraction. Adequate filling of the LV is necessary to maintain normal heart function at rest and under stress. DS is thought to be an important mechanism in the efficiency of filling.
To study DS, we have invasively measured pressure and used cardiac MRI to evaluate cavitary volume and flow in an animal model to quantify different measures of DS under varied experimental conditions.
The amount of filling due to DS (VDS), determined by the change in volume between mitral valve opening and LV pressure minimum of the pressure-volume loop (Katz 1930), is related to the measured end systolic volume (ESV). As ESV decreases the VDS increases. The smaller the ESV, the larger the recoil energy of the LV as it relaxes towards resting volume. This contributes increased energy for the suction of blood into the ventricle in early filling.
Wave intensity analysis (the separation of forward and backwards waves and wave type) and intraventricular pressure gradients will also be considered in order to determine which best describes DS and whether they can be used together to better understand changes in filling dynamics under varied loading conditions.

P1.15
CONDITIONAL INACTIVATION OF INTEGRIN AV SUBUNIT IN VASCULAR SMOOTH MUSCLE CELLS REGULATES FIBROSIS IN VESSELS

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Integrin avb3 is expressed at high density in vascular smooth muscle cells (VSMCs). It functions as a receptor for adhesion proteins in VSMCs which phenotypic modulation plays a pivotal role in arteriosclerosis and atherosclerosis.
The aim was to study the role of integrin avb3 in angiotensin II (Ang II)-induced arterial fibrosis in mice and in human samples of atherosclerotic arteries in situ. Transgenic mice conditionally inactivated for integrin av subunit in VSMCs (avSMKO) were treated with Ang II (1,5 mg/kg/day) for 4 weeks. Immunostained slices of atherosclerotic plaques at different stages of development and primary cultures of human aortic VSMCs were used.
At baseline, blood pressure was lower in avSMKO compared to control (WT) mice. Isobaric carotid distensibility was increased and remained higher in avSMKO in response to Ang II. The increase in collagen content in response to Ang II was lower in avSMKO than in WT (15 vs 36%) for similar increase in blood pressure (20 mmHg) and arterial wall hypertrophy.
The immunohistochemistry of aortic slices showed stronger staining for integrin avb3 in atherosclerotic plaques compared to healthy aortas. In VSMC cultures, the mRNA of av was decreased.
In conclusion, these results show that avb3 is strongly expressed in neointimal proliferation and in fibrous plaques. The av integrin subunit seems to regulate arterial fibrosis in response to hypertension and plaque growth. Low RNA quantities of av subunit of VSMCs contrasted with strong protein staining in plaques suggesting the participation of inflammatory cells in the synthesis of this integrin.

P1.17
THE VENTRICLE'S PROMINENT ROLE IN PRESSURE AMPLIFICATION; AN INCREMENTAL EXPERIMENTAL STUDY

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Despite central pressure's predictive power of cardiovascular risk, brachial pressure is the clinical standard. However, amplified brachial systolic pressure varies significantly with age, and during therapy. Our aim was to modulate individual arterial and ventricular parameters in an experimental model of the cardiovascular system, to quantify each parameter's contribution to arterial pressure and its amplification.
A piston driven ventricle provided computer-controlled flow waveforms into various silicone arterial trees. Silicone tubes diameters (20, 15, 10mm), wall thicknesses (0.5, 0.7, 1.0, 1.5mm), lengths (30-400cm), taper (20mm inlet to 20, 15, 10 and 5mm outlets), were each applied with various ventricular stroke profiles (sawtooth to sinewave). Intravascular pressure-tip wires and ultrasonic flow probes measured pressure and flow. MAP, flow and HR were maintained between tests for comparison.
Ventricular stroke profile independently augmented pressure amplification from 16% to 82% between sinewave and sawtooth ejections profiles. As expected for any arterial model, the transfer function from central to distal pressure measurement sites remained constant. Decreasing taper, wall thickness, and length, and increasing diameter each increased amplification by shifting the peak of the amplifying transfer function towards the more prominent lower frequencies, (1-3Hz). However, the amplification variation between all vascular parameters was $<30\%$.
Despite the arterial tree dictating how the ventricular pulse will propagate, the ventricle provides the wave packet of frequencies with which to be amplified. These findings correlate well with observations of decreasing amplification with age as the native inotropy decreases, and increasing amplification associated with decreased LV mass during hypertensive drug therapy.

P2.1
AGING AND STRUCTURAL ALTERATIONS OF SUBCUTANEOUS SMALL RESISTANCE ARTERIES IN HYPERTENSIVE PATIENTS

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Background: It was proposed that early vascular ageing may be an important mechanism of vascular damage in large conductance arteries. However it is not known whether aging may also affect small resistance artery morphology.
Patients and methods: For this reason, we investigated 100 patients with essential hypertension. Secondary forms of hypertension were excluded according to standard clinical evaluations and biochemical or instrumental assessments. In all patients, an evaluation of small resistance arteries morphology was performed by wire micromyography. A small amount of subcutaneous tissue was obtained by local biopsy or during election surgery and subcutaneous small resistance arteries were dissected and mounted on a myograph; the media to lumen ratio (M/L) was then measured.
Results: The age range of our population was 22-81 years, with a mean value of 57 ± 12 years; 14% of them were current smokers, 32% had alterations in lipid patterns, none of them had diabetes mellitus, 58 were males and average blood pressure values were $156/95\pm19/12$ mmHg.
We found a significant correlation between M/L and age ($r=0.30$, $p=0.002$): the statistical significance of the correlation persisted after correction for confounding variables (gender, serum cholesterol, smoking status, serum glucose, systolic or diastolic blood pressure values). A statistically significant inverse correlation was also observed between internal diameter and age ($r=-0.20$, $p=0.046$).
Conclusion: Our data suggest that age may affect microvascular structure in hypertensive patients. It is also possible that hypertension may anticipate the effects of physiological aging, and this should be explored in a relatively large population of normotensive subjects.

P2.2
RESISTANT HYPERTENSION AND STRUCTURAL ALTERATIONS OF SUBCUTANEOUS SMALL RESISTANCE ARTERIES

Claudia Agabiti Rosei, Carolina De Ciuceis, Claudia Rossini, Maria Lorenza Muiesan, Massimo Salvetti, Enzo Porteri, Alice Gavazzi, Anna Paini, Stefano Caletti, Maria Antonietta Coschignano, Paola Pileri, Enrico Agabiti Rosei, Damiano Rizzoni [*]

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Background: It is was suggested that, in resistant hypertension, the presence of particularly pronounced microvascular alterations may contribute to explain the relative lack of response to treatment. Similarly, in diabetic patients, the persistence of an altered microvascular structure, despite the administration of multiple drug combination treatment, might partly explain the difficulty to reach target blood pressure values, especially for systolic blood pressure.
Patients and methods: For this reason, we investigated a population of 94 treated essential hypertensive patients. Secondary forms of hypertension were excluded according to standard clinical evaluations and biochemical or instrumental assessment, and in all patients a 24-hour blood pressure monitoring was performed in order to exclude a white coat effect. In all patients, we evaluated small resistance arteries morphology by a wire micromyographic approach (Mulvany's technique). A small amount of subcutaneous tissue was obtained by local biopsy or during election surgery and subcutaneous small resistance arteries were dissected and mounted on a myograph; the media to lumen ratio (M/L) was then measured.
Sixteen patients had true resistant hypertension, and were compared with the remaining 78 patients with non-resistant hypertension.
Results: The two groups were different in terms of mean age, pulse pressure/stroke volume, media to lumen ratio and internal diameter of small resistance arteries.
Conclusion: Our data suggest that hypertensive patients with true resistant hypertension have greater microvascular structural alterations compared with non-resistant hypertensive patients. This could explain, at least in part, the resistance to pharmacological treatment and the high cardiovascular risk observed in these patients.

P2.4
THE INFLUENCE OF ANTIHYPERTENSIVE TREATMENT ON ARTERIAL STIFFNESS, SHEAR STRESS AND ACTIVITY OF CHOSEN MATRIX METALLOPROTEINASES

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Objective: Comparison of therapeuthic effects of chosen antihypertensive drugs on arterial stiffness, shear stress in carotid arteries and metalloproteinases activity, moreover analysis of relationship of these variables in the course of treatment.
Design and method: 95 never treated patients with HT stage 1 or 2 were randomized to 6 months monotherapy with: quinapril, amlodipine, hydrochlorothiazide, losartan or bisoprolol. Each therapeuthic group consisted of 19 patients (N=19). Before and then after 1, 3 and 6 months of treatment carotid-femoral pulse wave velocity (PWV) by using a Complior device, ultrasound of carotid arteries were performed. Blood samples for the measurement of whole blood viscosity were taken during each visit. Shear stress (SS) was calculated on the basis of Irace formula. Serum concentration of metalloproteinase 3 (MMP-3) and plasma concentration of tissue inhibitor of metalloproteinase 1 (TIMP-1) were measured at the initial visit and after 6 months of treatment.
Results: ANOVA for repeated measurements revealed for all groups significant decrease of PWV and MMP-3 concentration and increase of shear stress in carotid artery and TIMP-1 concentration ($p<0.05$). No between groups differences appeared in above effects ($p>0.05$).
Conclusion: Irrespectively of chosen drug we observed similar effect for PWV drop. Reduction of arterial stiffness as a result of antihypertensive therapy is strongly connected with shear stress increase that is secondary to blood flow velocity growth and changes in connective tissue metabolism.

P2.5
SEX-DEPENDENT DIFFERENCES IN OBESITY INDICES AND INFLAMMATORY MARKERS IN NON-DIABETIC OBESE PATIENTS

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Background: The aim of the study was to asses sex-dependent differences of obesity indices and inflammatory markers in non-diabetic hypertensive obese patients.
Material and methods: 40 females and 25 males aged 59.8 ±10.1 and 54.6±11.9 years, respectively, were enrolled into the study. Serum TNF-α, IL-6 and high-sensitivity C-reactive protein (hs-CRP) levels were estimated. Waist circumference (WC), waist-to-hip ratio (WHR), body mass index (BMI), waist-to-height ratio (WHtR), visceral adiposity index (VAI) and body adiposity index (BAI) were measured or calculated.
Results: In males WC and WHR were higher than in females (117.0 ±10.8 cm vs 108.5 ±10.4 cm; $p < 0.01$ and 1.01±0.06 vs 0.91±0.06; $p < 0.0001$, respectively). In females BAI and hs-CRP were higher than in the males (41.7 ±6.9 vs 33.5 ±5.0; $p < 0.0001$ and 3.2 ±2.2 mg/l vs 2.1 ±1.5 mg/l; $p < 0.05$, respectively).
In females hs-CRP positively correlated with WHtR ($r = 0.321$; $p< 0.05$), BMI and BAI ($r = 0.305$; $p = 0.05$, and $r = 0.309$; $p = 0.05$, respectively). In males hs-CRP positively correlated with WHtR, BAI and VAI ($r= 0.458$; $p < 0.05$; $r = 0.440$; $p < 0.05$ and $r = 0.443$; $p < 0.05$, respectively), IL-6 positively correlated with VAI ($r = 0.472$; $p < 0.05$) and TNF-α negatively correlated with WHR ($r = -0.408$; $p < 0.05$).
Conclusions: Obesity related chronic inflammation is more evident in females than in males. Differences in WC, WHR and BAI are sex dependent.

P2.6
PWV IS AN INDEPENDENT DETERMINANT OF COGNITIVE DYSFUNCTION IN CKD PATIENTS

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Objectives: In the general population aortic stiffening assessed by carotid femoral pulse wave velocity (cf-PWV) is associated with cognitive dysfunction (CO/DY). Data in chronic kidney disease (CKD) are limited. Our study tests the hypothesis that large artery stiffness and microvascular damage in CKD patients are related to brain microcirculation changes reflected by impaired cognitive function.
Methods: Among 244 patients, finally 44 with CKD stage 1; 47 stage 2; 25 stage 3; 35 stage 4, with mean age 58.4 years (64.5% males), were enrolled in a cross-sectional study. Cognitive impairment measured by Mini Mental State Examination (MMSE), Clock — drawing test (Clock-test), and Instrumental Activity of Daily Living (IADL) was considered as primary outcome. We directly measured brachial, aortic, systolic blood pressure, pulse pressure, mean blood pressure and cf-PWV.
Results: Our patients revealed a significant linear deterioration in all the domains of cognitive function according to CKD stages, assessed by MMSE, Clock-test and IADL. The risk of cognitive dysfunction increased significantly from CKD stage 3 to 4 ($p<0.01$). High levels of cf-PWV ($p=0.029$) and aortic pulse pressure (aPP) ($p<0.026$), were independent predictors of cognitive decline according to MMSE.
Conclusions: The present trial supports the interaction between the kidney and the brain injury microcirculation. In clinical practice cf-PWV and aPP measurements may help to predict cognitive decline. Whether, the reduction in aortic stiffness following an aggressive treatment translates into improved cognitive outcomes remains to be determined.

P2.7
AMELIORATION OF COGNITIVE FUNCTION IN HEMODIALYSIS PATIENTS IN ABSENT OF HYPOTENSIVES EPISODES

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Objective: Patients in hemodialysis frequently have cognitive dysfunction (CO/DY). Hemodialysis session often results in acute intravascular volume loss, fluid shifts, hypotensives episodes, decrease of cerebral perfusion and cerebral ischemia, all of which may cause transient deterioration of cognitive function. On the contrary, improvement in "uremic milieu" after a dialysis session can result in improved cognition. The aim of this study is to evaluate the effect of a single, random hemodialysis session on cognitive function, in absent of hypotensive episodes.
Method: Global cognitive function was assessed, pre-and post-dialysis by using the Mini Mental State Examination.