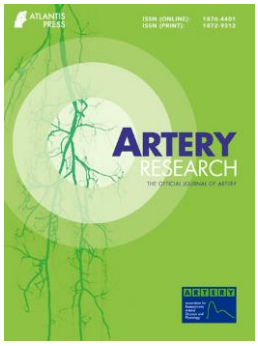

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P2.07: ENDOTHELIUM DEPENDENT AND INDEPENDENT DILATATION IN DIFFERENT VASCULAR BEDS

M. Salvetti, A. Paini, C. De Ciuceis, E. Porteri, C. Agabiti Rosei, C. Aggiusti, F. Bertacchini, D. Stassaldi, D. Rizzoni, M.L. Muiesan, E. Agabiti Rosei

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response to collagen was lower in MR-EC than in CT. To address the role of endothelial cells as cellular surfaces involved in the coagulation process, *in vitro* thrombin generation was assessed at the surface of cultured human aortic endothelial cells. Treatment of these cells with 10^{-8} M aldosterone resulted in a significant reduction of thrombin generation prevented by the MR antagonist RU28318. *In vivo*, vessel occlusion times after exposure of the carotid artery surface to ferric chloride was delayed in MR-EC compared with CT mice.
These results demonstrated that enhanced endothelial MR activation induced endothelial dysfunction. Paradoxically, MR-EC mice exhibited a decreased risk of thrombosis. Our results suggested that MR activation in the endothelium affected coagulation by enhancing the APC anticoagulant system and decreasing platelet aggregation. This finding raised interesting prospects on the potential mechanisms of action of new anti-thrombotic drugs and their interference with the mineralocorticoids.

P2.05
ARE RETINAL MICROVASCULAR PHENOTYPES ASSOCIATED WITH 1675G/A POLYMORPHISM IN ANGIOTENSIN II RECEPTOR-2 GENE?

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Background: The X-linked *AT2R G1675A* polymorphism is located in the short intron 1 of the *AT2R* gene within a sequence motif conforming to a splice branch site. AT2R is expressed in the human retina, but no previous study examined the association between retinal microvascular phenotypes and the *AT2R G1675A* polymorphism.
Methods: In 340 subjects randomly selected from a Flemish population (mean age, 51.9 years; 51.5% women), we post-processed retinal images (Canon Cr-DGi) using IVAN software to generate the retinal arteriole and venule equivalents (CRAE and CRVE) and the arteriole-to-venule-ratio (AVR). DNA fragments including the *AT2R G1675A*, *AT1R A1166C*, *ACE I/D* and *CYP11B2 C*−344T polymorphisms, were amplified by PCR. We applied a mixed model to assess phenotype-genotype associations while accounting for relatedness and covariables.
Results: CRAE, CRVE and AVR averaged 151.9 μm, 215.2 μm and 0.710, respectively. CRAE was 5.5 μm greater in women than men and decreased with age ($P<0.05$). In multivariable-adjusted analyses, CRAE was higher in hemizygous and homozygous carriers of the *AT2R A* allele than in their *G* allele counterparts in both sexes combined (+4.49 μm; $P=0.014$) and in men (+4.91 μm; $P=0.032$) with a similar trend in women (+3.41 μm; $P=0.14$). AVR was increased in the presence of the *AT2R A* allele compared with *AT2R G* hemizygotes and homozygotes (+0.024; $P=0.0082$). The associations of CRAE and CRVE with other polymorphisms was not significant.
Conclusions: Pending confirmation in experimental and epidemiological studies, our findings suggest that diameter of the retinal arterioles might be associated with the *AT2R 1675G/A* polymorphism.

P2.06
AN IMPAIRED ROLE OF EPOXYEICOSATRIENOIC ACIDS CONTRIBUTES WITH ALTERED NO AND ENDOTHELIN-1 PATHWAYS TO CONDUIT ARTERY ENDOTHELIAL DYSFUNCTION IN ESSENTIAL HYPERTENSION

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Background: The mechanisms involved in the endothelial dysfunction of conduit arteries, which is an independent contributor to the high incidence of cardiovascular events during essential hypertension, remains to be fully elucidated.
Methods and results. Radial artery diameter, blood flow and mean wall shear stress were determined in 28 non-treated essential hypertensive patients and 30 normotensive control subjects, during endothelium-dependent flow-mediated dilatation (FMD) induced by hand skin heating. The role of epoxyeicosatrienoic acids (EETs) and NO was assessed during heating using the brachial infusion of inhibitors of cytochrome P450 epoxygenases (fluconazole) and NO-synthase (L-NMMA). First, as compared with controls, hypertensive patients exhibited a decreased FMD in response to post-ischemic hyperemia as well as to heating, as shown by the lesser slope of their diameter-shear stress relationship, with no modification in endothelium-independent dilatation. In controls, heating-induced FMD was reduced by fluconazole, L-NMMA and, to a larger extent, by L-NMMA+fluconazole. In patients, FMD was not affected by fluconazole and was reduced by L-NMMA and L-NMMA+fluconazole to a lesser extent than in controls. Local plasma EETs level increased during heating in controls (an effect diminished by fluconazole), but not in patients. Plasma nitrite level, an indicator of NO availability, increased during heating in controls (an effect abolished by L-NMMA), and to a lesser extent in patients. Plasma endothelin-1 level decreased during heating in controls but not in patients.
Conclusions. These results show that an impaired role of EETs contributes with alteration in NO and endothelin-1 pathways to conduit artery endothelial dysfunction in essential hypertension.

P2.07
ENDOTHELIUM DEPENDENT AND INDEPENDENT DILATATION IN DIFFERENT VASCULAR BEDS

M. Salvetti, A. Paini, C. De Ciuceis, E. Porteri, C. Agabiti Rosei, C. Aggiusti, F. Bertacchini, D. Stassaldi, D. Rizzoni, M. L. Muiesan, E. Agabiti Rosei
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Objective Several methods have been proposed for the evaluation of endothelial dysfunction in patients with cardiovascular risk factors. Whether the flow-mediated dilation (FMD) in medium size arteries is related to the vasodilating response to different agonists in small resistance arteries has not been adequately evaluated. Aim of the present study was to assess the endothelial dysfunction in subcutaneous small resistance arteries (response to acetylcholine, Ach or bradikinin, BK) and in the brachial artery (FMD) in normotensive subjects (NT), essential hypertensives (EHT), patients with primary aldosteronism (PA) and patients with type2 diabetes (DM). Methods 46 DM (20 F, age 39-77 yrs, 14 NT and 32 HT), 6 EHT (3 F, age 40-66 yrs), 6 PA (4 F, age 40- 57yrs), and 4 NT (2 F, age 16-64 yrs) underwent a biopsy of the subcutaneous fat. Small resistance arteries were mounted on a micromyograph and a concentration-response curve to Ach (from 10^{-9} to 10^{-5}) and to BK (from 10^{-10} to 10^{-6}) was performed. In all patients we measured, by a high resolution ultrasound, the brachial artery (BA) diameter at rest, during reactive hyperemia (5 mis of BA occlusion); BA flow velocity was measured by pulsed doppler
Results:

	NIDDM (NT)	NIDDM (EH)	EH	PA
Ach 10^{-5} mol/L (%)	-37 ± 20	-56 ± 22	- 63 ± 35	- 63 ± 13
BK 10^{-6} mol/L (%)	-35.2 ± 25	-44 ± 27	- 54 ± 39	- 58 ± 15
FMD %	8.56± 4.6	5.19 ± 3.0	6.12 ± 6.8	4.76 ± 2.82

There was a small, although statistically significant, correlation between FMD and the maximal response to BK ($r = 0.34$, $p < 0.05$) while no significant correlation was observed between FMD and the maximal response to Ach ($r= 0.19$, ns) in all patients. A significant correlation was observed between BA dilatation after NTG 40 mcg s.l and the maximal response to NTP ($r= 0.30$, $p = 0.05$). Conclusions These results indicate that, although endothelial dysfunction may be observed in both small resistance arteries and medium size arteries, the degree of impairment may differ according to the vascular bed observed, and to the pathophysiology of the disease.

P2.08
ENDOTHELIAL FUNCTION AND RENAL VASODILATION, BUT NOT ARTERIAL STIFFNESS, ARE IMPAIRED IN LEAN, NORMOTENSIVE PATIENTS WITH OBSTRUCTIVE SLEEP-APNEA

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Background: Patients with obstructive sleep apnea (OSA), a condition with a strong comorbidity with hypertension and obesity, exhibit an accelerated vascular aging and renal damage. The aim of the study was to evaluate