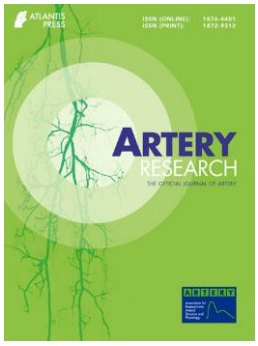

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P2.08: ENDOTHELIAL FUNCTION AND RENAL VASODILATION, BUT NOT ARTERIAL STIFFNESS, ARE IMPAIRED IN LEAN, NORMOTENSIVE PATIENTS WITH OBSTRUCTIVE SLEEP-APNEA

R.M. Bruno, L. Ghiadoni, M. Fabbrini, L. Rossi, A. Lena, M. Maestri, E. Bonanni, S. Taddei

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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?

Y. Liu [1], T. Kuznetsova [1], L. Thijs [1], Y. Jin [1], B. Schmitz [2], S. M. Brand [2], E. Brand [3], P. Manunta [4], G. Bianchi [4], H. Struijker-Boudier [5], J. A. Staessen [1,6]
[1]*Studies Coordinating Centre,Labotary of Hypertesion,University of Leuven, Leuven, Belgium*
[2]*Medical Faculty of Münster, Department of Molecular Genetics of Cardiovascular Disease, University of Münster, Münster, Germany*
[3]*Internal Medicine D, Department of Nephrology, Hypertension and Rheumatology, University Hospital Münster, Münster, Germany*
[4]*Division of Nephrology and Dialysis, San Raffaele Scientific Institute, Università Vita-Salute, San Raffaele Hospital, Milan, Italy*
[5]*Department of Pharmacology, Maastricht University, Maastricht, Netherlands*
[6]*Department of Epidemiology, Maastricht University, Maastricht, Netherlands*

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

J. Bellien [1,3], M. Iacob [1,3], D. Lucas [2], C. Monteil [3], I. Jouet [3], C. Thuillez [1,3], R. Joannides [1,3]
[1]*Rouen University Hospital, Rouen, France*
[2]*Inserm U613, Brest, France*
[3]*Inserm U644, Rouen, France*

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
Internal Medicine, University of Brescia, Brescia, Italy

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

R. M. Bruno, L. Ghiadoni, M. Fabbrini, L. Rossi, A. Lena, M. Maestri, E. Bonanni, S. Taddei
University of Pisa, Pisa, Italy

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

endothelial function, arterial stiffness, and renal vasodilating response to glyceryl trinitrate (GTN), a new parameter of renal vascular damage, in lean, normotensive patients with OSA.
Methods: 17 lean normotensive patients with moderate-severe OSA (AHI 31±19), and 21 matched healthy controls were recruited. Renal resistive index (RI) was obtained by Duplex ultrasound at baseline and after sublingual GTN (25 μg), evaluating renal vasodilation as percent RI change. Endothelium-dependent (flow-mediated-dilation, FMD) and -independent (response to GTN) vasodilation in the brachial artery was assessed by computerized edge detection system. Arterial stiffness was assessed as carotid-femoral pulse wave velocity (PWV).
Results: OSAS patients and controls presented similar RI (0.61 vs 0.59, p=ns), but impaired renal vasodilation to GTN (-5.7±6.2% vs -10.3±4.6%, p<0.05). FMD was reduced (4.1±2.5% vs 6.2±3.1%, p<0.05), while endothelial-independent brachial artery vasodilation was preserved. PWV was not different between OSAS and controls (7.9±1.5 vs 7.7±1.4 m/s, p=ns).
Conclusions: Even in the absence of hypertension and obesity, OSAS is characterized by endothelial dysfunction and impaired renal vasodilating capacity. Thus, OSAS could predispose per se to vascular and renal damage.

P2.09
DAMAGE ACCRUAL IS ASSOCIATED WITH ENDOTHELIAL FUNCTION DETRIMENT: A PROSPECTIVE COHORT STUDY

R. M. Bruno, C. Tani, A. D.Ascanio, Y. Plantinga, R. Neri, A. Tavoni, L. Carli, S. Taddei, S. Bombardieri, L. Ghiadoni
University, Pisa, Italy

Introduction: Our aim was to study endothelial function in a cohort of systemic lupus erythematosus (SLE) patients prospectively followed at our unit and to investigate its relation with disease activity and damage over time.
Materials and Methods: 38 female SLE patients without overt cardiovascular involvement were enrolled (age 35.8±8ys), followed-up for a mean of 4.45±1.5 years. Clinical history, traditional cardiovascular risk factors, and laboratory parameters were recorded. Active disease was defined as ECLAM global score >2; SLICC/ACR-DI was used for scoring disease damage.FMD was assessed in the brachial artery by high-resolution ultrasound and computerized edge detection system (Quipu s.r.l., Pisa, Italy). FMD assessment was performed at study entry and was repeated in a subgroup of 21 patients at the end of follow-up.
Results: At enrollment, 18 patients presented active disease; mean FMD was 7.9±3.1% with no differences between active (8.7±1) and inactive group (7.9±0.8; p=0.53), even after correction for age and disease duration. Baseline FMD tended to correlate with disease duration (p=0.06), and was similar in the patients with final poor outcome - death (n=3) or damage accrual (n=12) — compared to the others. In the follow-up, FMD showed a significant decline over time (from 8.0±3.2 to 5.9±3.3, P=0.04)while endothelial-independent dilation did not (from 9.2 ±3.5 to 8.6±4.9; p= 0.63). The decline was not different between active and inactive group; however, patients with poor outcome (n=7) showed a greater worsening in FMD over time (-4.1% vs -2.0%).
Conclusions: This study shows that, in SLE patients, disease duration rather than disease activity appears to influence endothelial function. Furthermore, damage accrual is associated with progressive detriment in endothelial function, with preserved response to glyceryl trinitrate.

P2.10
MECHANISTIC INSIGHTS INTO THE RELATIONSHIP BETWEEN WAVE REFLECTION AND RETINAL ARTERY FLOW PULSATILITY

B. J. McDonnell [1], J. Coulson [4], M. Zagura [2], M. Munnery [4], E. Stohr [1], R. Shave [1], C. M. McEniery [3], I. B. Wilkinson [3], J. R. Cockcroft [4]
[1]*University of Wales Institute, Cardiff, United Kingdom*
[2]*University of Tartu, Tartu, Estonia*
[3]*University of Cambridge, Cambridge, United Kingdom*
[4]*Cardiff University, Cardiff, United Kingdom*

Background: Increased arterial stiffness is associated with a reduced buffering capacity of the large arteries, therefore predisposing the microcirculation to increased flow and pressure pulsatility. Previous data from our group have illustrated a positive relationship between aortic pulse wave velocity and an inverse relationship between wave reflection and retinal artery flow pulsatility.Therefore, the aim of this study was to investigate the macrovascular haemodynamic mechanisms involved in retinal artery flow pulsatility, by manipulation of wave reflection by Glycerol Trinitrate Nitrate administration.
Methods: Nine individuals, aged 63±6 years and free from CV acting medication participated in this study. Augmentation index (AIx) was recorded using the SphygmoCor system (Atcor) as a measure of wave reflection. Pulsatility index (PI), a measure of retinal artery flow pulsatility was recorded using doppler ultrasound (GE) and both peripheral and central blood pressure were measured using the Mobilograph system (IEM). All vascular haemodynamic measurements were recored simultaneously at basline and then again at 1,3,5,10 and 15 minutes post GTN administration.
Results: The relationship between AIx and PI change from baseline were significantly different at 3 and 5 minutes (P=0.02 and P=0.03, respectively). See figure 1.
Conclusion: This study illustrates a direct inverse relationship between AIx and retinal artery flow pulsatility, suggesting a direct link between large artery haemodynamics and pulsatile flow in the microvasculature.

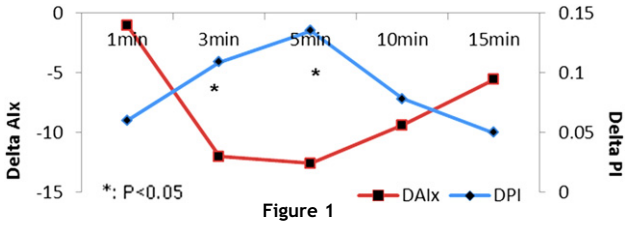
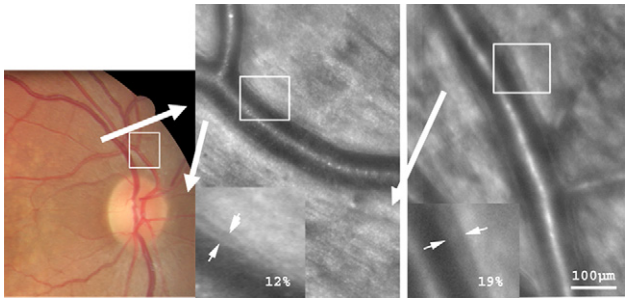


Figure 1

P2.11
IMAGING OF RETINAL ARTERIOLAR WALL IN VIVO IN HUMANS

M. Paques [1], K. Gocho-Nakashima [1], O. Genevois [3], E. Plaisier [2], J. A. Sahel [3]
[1]*Clinical Investigation Center 503, Quinze-Vingts Hospital, Paris, France*
[2]*Nephrology Department, Tenon Hospital, Paris, France*
[3]*Ophthalmology Department, Rouen, France*

Purpose: Adaptive optics (AO) is an opto-electronic technique improving lateral resolution of fundus images. Here we report a novel application of AO imaging, namely the visualization of the arteriolar wall in the human retina.
Methods: This study was done in compliance with French ethical regulations. AO fundus imaging was performed using a prototypic camera (RTX1, ImagineEye, Orsay, France) in a cohort of healthy subjects and in patients affected by arterial hypertension. The camera uses infrared light, and the total acquisition time is less than 1 minute. The wall-to-lumen ratio (WLR) was measured in an arteriolar segment approximately 500 microns from the disc.
Results: 12 healthy subjects, 2 hypertensive patients and 1 patient affected by branch retinal vein occlusion were examined. The wall-to-lumen ratio varied from 11 to 15% in healthy eyes, and was 18% and 19% in the two hypertensive subjects. In the subject that had branch retinal vein occlusion, irregular thickening of the vessel wall was found.



Conclusions: We provide here the first in vivo images of the arteriolar wall in humans. This technique may be useful for the quantitative assessment of microvascular damage in aged and/or hypertensive patients.
Funded by the Agence Nationale de la Recherche (TecSan 09-009)

P2.12
THE INTERPLAY OF ENDOTHELIAL FUNCTION, INFLAMMATORY AND OXIDATIVE STATUS IN HIV INFECTION. DOES ANTIRETROVIRAL THERAPY PLAY A ROLE?

P. Xaplanteris [1], C. Vlachopoulos [1], E. Mariolis [2], E. Sambatakou [2], D. Terentes-Printzios [1], N. Ioakeimidis [1], D. Kardara [1], A. Synodinos [1], C. Stefanadis [1]