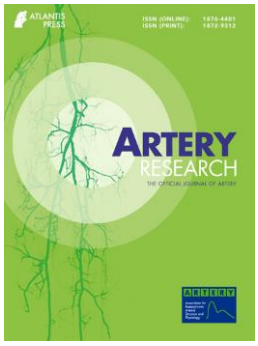

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P2.01: RELATIONSHIP BETWEEN MEDIA TO LUMEN RATIO OF SUBCUTANEOUS SMALL ARTERIES AND WALL TO LUMEN RATIO OF RETINAL ARTERIOLES EVALUATED NON INVASIVELY BY SCANNING LASER DOPPLER FLOWMETRY

D. Rizzoni, E. Porteri, C. De Ciuceis, E. La Boria, S. Duse, F. Semeraro, C. Costagliola, A. Sebastiani, P. Danzi, G.A.M. Tiberio, S.M. Giulini, C. Agabiti Rosei, A. Sarkar, D. Avanzi, E. Agabiti Rosei

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Methods: Baseline data of the B-PROOF study are used to determine associations between homocysteine level and outcomes of vascular function. A subgroup was included (n=410, 58% male, age 72.6 ± 5.5 yrs, mean homocysteine level 15.2 ± 3.1 μmol/l). We assessed carotid intima media thickness (cIMT), carotid distensibility, using ultrasonograpy, and pulse wave velocity (PWV) and augmentation index (AIx), measured with applanation tonometry. Furthermore, office blood pressure measurements (n=410) and 24-hour blood ambulatory pressure recordings (n=70) were performed. Associations were tested using linear regression analysis and adjusted for age, gender, mean arterial pressure and heart rate.

Results:

The baseline analysis of the B-PROOF trial showed that log homocysteine was associated with PWV [β 0.010 (95%CI 0.006;0.014)] and with carotid IMT [β 0.0002 (95%CI 0.0001;0.0004)]. However, the association with IMT did not remain significant after adjustment for confounders [β 0.001 (95%CI -0.001;0.003)], but this finding remained for PWV [β 0.006 (95%CI 0.002;0.011)]. No significant association with homocysteine was found for AIx, distensibility or blood pressure levels.

Conclusions:

Homocysteine is possibly associated with arterial stiffness in elderly, measured with PWV. However, a subsequent question is whether lowering of homocysteine levels, indeed improves vascular function. Currently, this trial is still in progress.

P1.13

CENTRAL BLOOD PRESSURE (BP) IS AN INDEPENDENT PREDICTOR OF WORSE OUTCOME IN YOUNG TO MIDDLE AGE SUBJECTS SCREENED FOR STAGE I HYPERTENSION

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Objective: The aim was to evaluate the association of central BP with target organ damage (TOD) and the risk of future hypertension in a cohort of subjects from the HARVEST study. Methods. We studied 305 stage I hypertensive subjects (mean age, 38±10 years). Central BP was obtained from radial artery tonometry. TOD included left ventricular hypertrophy and/or microalbuminuria.

Results: At baseline peripheral BP was 138±12/86±7 mmHg, average 24-hour BP was 130±11/80±8 mmHg, central BP was 125±13/86±8 mmHg. In a multiple logistic regression including ambulatory BP, central mean BP was associated with TOD (p=0.01). In the subjects divided according to whether their central mean BP was above or below the median (98.7 mmHg), during 9-year follow-up, sustained hypertension was developed by 38.8% of subjects with low central mean BP and by 64.5% of subjects with high central mean BP (p<0.001). Central mean BP was used because it was a better predictor of future hypertension (OR 2.5) compared to central SBP or DBP. In a multiple logistic regression central mean BP and not central pulse pressure, was an independent predictor of future hypertension (p=0.004). Also ambulatory systolic (p=0.002) and diastolic (p=0.02) BPs were independent predictors. When all pressures were included in the same model, central mean BP remained a predictor of future hypertension (p=0.004) on top of ambulatory BP.

Conclusion: In young-to-middle-age stage I hypertensive subjects central mean BP, but not pulse pressure, was associated with TOD and central BP was a significant predictor of adverse outcome on top of 24-hour BP.

P1.14

FORMATION OF NEW ATHEROSCLEROTIC PLAQUES IN WELL CONTROLLED RHEUMATOID ARTHRITIS DEPENDS ON CLASSICAL CARDIOVASCULAR RISK FACTORS: A PROSPECTIVE LONGITUDINAL STUDY

A. D. Protogerou [1], E. Zampeli [1], K. Stamatelopoulos [2], K. Fragiadaki [2], C. G. Katsiari [2], K. Kyrkou [2], C. M. Papamichael [2], M. Mavrikakis [2], G. D. Kitas [3], P. P. Sfikakis [1]
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Background: Rheumatoid arthritis (RA) is an independent risk factor for cardiovascular disease (CVD); RA patients demonstrate advanced pre-clinical carotid atherosclerosis compared to controls.

Objectives: To assess: the rate of progression of subclinical atherosclerotic plaque formation in RA patients and the factors leading to progression; whether the rate of progression in these patients is faster than in non-RA subjects carefully-matched for traditional CV risk factors. Methods: Carotid plaques were assessed by ultrasonography at baseline and follow-up end, separated by an average of 3.6±0.2 years, in 64 non-diabetic RA patients (53♀, aged 59.2±12 years) without concomitant CVD (RA disease duration 7.8±6.2 years). 'Healthy' controls matched 1:1 both at baseline and follow-up end for all traditional CVD risk factors with 35 RA patients were also studied.

Results: New plaques formed in 30% of patients who were significantly older, heavier tobacco user and had higher average systolic blood pressure compared to the rest RA population. Lipids, obesity, inflammatory markers and other RA related parameters were comparable between the 2 subgroups. In multivariate analysis: age and smoking predicted new plaque formation of all classical CVD factors (model 1); longer duration of corticosteroid use (low-dose) and shorter duration of biologic agent use (of all RA related parameters/drugs -model 2). In a final model: age, smoking and corticosteroid use predicted new plaque formation. Being in clinical remission on average during 62% of follow-up time, RA patients displayed similar rate of progression atherosclerotic plaque formation to the matched controls.

Conclusions: Formation of new atherosclerotic plaques in patients with well-controlled RA depends mainly on traditional cardiovascular risk factors and corticosteroid use.

P1.15

CENTRAL BLOOD PRESSURE (CBP) MEASUREMENTS IN THE PORTUGUESE POPULATION: THE GUIMARÃES STUDY (STUDY TO DETERMINE THE CARDIOVASCULAR RISK OF THE POPULATION OF GUIMARÃES/VIZELA: PREVALENCE OF ARTERIAL STIFFNESS AND EARLY VASCULAR AGING SYNDROME)

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We observed 1104 subjects of the Portuguese population coming from two northern adjacent cities: Guimarães and Vizela. They were randomly selected to be included in a cohort representative of age and gender distribution. We evaluated their blood pressure (BP) (mean three measurements), height, weight, lipidic profile, fasting glucose, HbA1c, serum creatinine, microalbuminuria (occasional sample) and CBP measurements (Sphygmocor®).

These 1104 subjects (56,4% females), had a mean global age of 47,6 years (18 − 94); 42% had hypertension, 10,7% had Diabetes, 80% had lipidic profile abnormalities, 3,1% had GFR < 60ml/min and 16,1% had microalbuminuria. The mean brachial systolic BP was 131,3 mmHg (84 to 243) and the mean brachial diastolic BP was 76,7 mmHg (44 to 128); The average BMI was 26,8 kg/m2 (16,8 to 46,2).

Mean global CBP (cSBP/cDBP) values recorded were 119/77 mmHg, with a mean Central Pulse Pressure (cPP) of 42 mmHg. Mean CBP values (cSBP/cDBP) recorded by age classes were: 18 to 30 years − 101/71 mmHg (81/50 to136/100), cPP − 30 mmHg; 31 to 40 years − 109/76 mmHg (80/57 to 162/105), cPP − 32 mmHg; 41 to 50 years − 121/82 mmHg (88/54 to 224/131), cPP − 39 mmHg; 51 to 60 years − 125/83 mmHg (90/58 to 163/113), cPP − 43mmHg; 61 to 70 years − 134/79 mmHg (96/55 to 198/112), cPP − 55 mmHg; 71 to 80 years − 137/78 mmHg (91/48 to 202/104), cPP − 59 mmHg; 81 to 90 years − 141/76 mmHg (93/57 to 194/100), cPP − 65 mmHg. These are, to our knowledge, the first CBP measurements performed on a population based cohort in Portugal.

P2 − Endothelium and small arteries 1

P2.01

RELATIONSHIP BETWEEN MEDIA TO LUMEN RATIO OF SUBCUTANEOUS SMALL ARTERIES AND WALL TO LUMEN RATIO OF RETINAL ARTERIOLES EVALUATED NON INVASIVELY BY SCANNING LASER DOPPLER FLOWMETRY

D. Rizzoni [1], E. Porteri [1], C. De Ciuceis [1], E. La Boria [1], S. Duse [3], F. Semeraro [3], C. Costagliola [4], A. Sebastiani [5], P. Danzi [3], G. A. M. Tiberio [2], S. M. Giulini [2], C. Agabiti Rosei [1], A. Sarkar [1], D. Avanzi [1], E. Agabiti Rosei [1]

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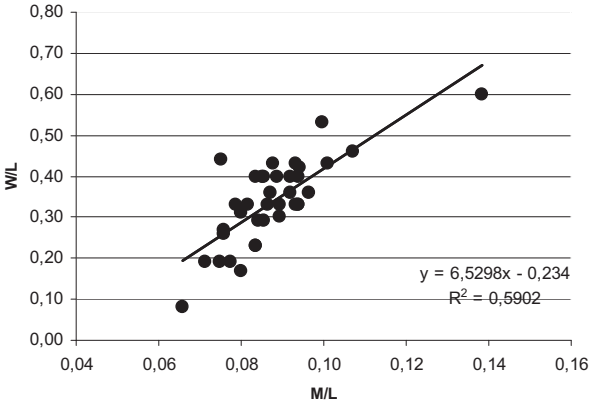
Structural alterations of subcutaneous small resistance arteries, as indicated by an increased media to lumen (M/L) ratio, are frequently present in hypertensive and/or diabetic patients, and may represent the earliest alteration observed. In addition, M/L of small arteries evaluated by micromyography has a strong prognostic significance; however its extensive evaluation is limited by the invasivity of the assessment, since a biopsy of subcutaneous fat is needed. Non-invasive measurement of wall to lumen (W/L) of retinal arterioles using scanning laser doppler flowmetry (SLDF) has been recently introduced (Harazny J et al, Hypertension 2007; 50:623-629). However, this new technique was never compared with micromyographic measurement, considered the gold standard approach.
Methods and Results: We have investigated 37 subjects and patients. Twenty-three of them were hypertensives and 14 normotensives. Blood pressure values were 139/88±17/10 mmHg and 125/71±17/12 mm Hg, respectively ($p<0.05$). All patients underwent a biopsy of subcutaneous fat during an elective surgical intervention. Subcutaneous small resistance arteries were dissected and mounted on a wire myograph, and M/L was measured. In addition, an evaluation of W/L of retinal arterioles by SLDF was performed (Heidelberg Retina Flowmeter, Heidelberg Engineering). A close correlation was observed between M/L of subcutaneous small arteries and WL of retinal arterioles: $r=0.77$, $p<0.001$ (see Figure).
Conclusion: A non invasive and easily repeatable procedure (intraobserver and interobserver variation coefficient around 10%) such as an evaluation of the arterioles in the fundus oculi by SDLF may provide similar information regarding microvascular morphology compared in respect with an invasive, accurate and prognostically relevant micromyographic measurement of M/L.



P2.02
INVESTIGATION OF THE EFFECTS INDUCED ON ENDOTHELIAL FUNCTION BY THE HUMAN T2238C ANP GENE MOLECULAR VARIANT

S. Rubattu [1], S. Sciarretta [1], C. Calvieri [1], L. Castello [1], A. Battistoni [1], M. De Giusti [1], E. Dito [1], A. Marra [1], I. Laurino [1], B. Pagliaro [1], M. Volpe [1,2]
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Objective: The T2238C ANP gene molecular variant has been related to increased risk of cardiovascular events. *In-vitro* investigations of its pathogenetic mechanisms demonstrated that the 2238C allele variant induced detrimental effects on endothelial cells through increased ROS production. Based on these observations we hypothesized that T2238C ANP gene variant could exert a pathogenic impact on endothelial function *in-vivo*.
Design and methods: We enrolled 10 double mutant CC2238/ANP healthy subjects and 10 healthy subjects carrying the 2238TT wild type genotype. NT-proANP levels were measured in a fasting venous sample. Endothelial-dependent vasodilation was assessed through FMD procedure at brachial level and endothelial endothelial-independent vasodilation was evaluated by means of FMD after sublingual nitrate administration. All subjects underwent carotid ultrasonography.
Results: No significant differences were observed between the two groups in terms of prevalence of cardiovascular risk factors. NT-proANP plasma levels were comparable in double mutant and in wild type subjects (2200±190 vs 2353±340, respectively). Endothelial-dependent vasorelaxation was significantly lower in 2238C as compared to 2238T allele carriers (6.97±2.4 vs 9.31±1.6, $p=.02$). No significant differences were observed regarding endothelial-independent vasodilation (13.4±3.4 vs 14.5±5.6, NS). Carotid ultrasonography did not show any significant alteration of arterial wall in either group.
Conclusions: The 2238C ANP molecular variant, responsible for detrimental effects on endothelial cells *in-vitro*, leads to significant early impairment of endothelial function *in-vivo*. The functional derangement induced by T2238C ANP gene variant may contribute to the increased predisposition to cardiovascular events observed in 2238C allele carriers. Further studies are needed to fully explore this issue.

P2.03
RECOMBINANT HUMAN ERYTHROPOIETIN ALTERS SUBCUTANEOUS RESISTANCE ARTERY ENDOTHELIAL FUNCTION THROUGH A MECHANISM INVOLVING OXIDATIVE STRESS AND ENDOTHELIN-1 IN PATIENTS WITH STAGE 4 CHRONIC KIDNEY DISEASE

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Objective: Recent studies have raised concern about the safety of recombinant human erythropoietin (RhuEPO) because of evidence of an increase in the risk of cardiovascular disease in chronic kidney disease (CKD) patients. In the present study we investigated the effect of RhuEPO on the function of resistance arteries isolated from CKD patients.
Design and method: 19 patients (mean age 63 ± 14 years) with stage 4 CKD (mean eGFR 20 ± 5 mL/min/1.73m^2), none treated with RhuEPO, were included. Resistance arteries from gluteal subcutaneous tissue were assessed on a pressurized myograph. Endothelium-dependent and independent relaxations were tested with acetylcholine and sodium nitroprusside respectively, with RhuEPO (0, 1, 10 and 20 UI/mL). Tempol (10^{-3} M), a superoxide dismutase mimetic, was used to inhibit oxidative stress. ABT-627 (10^{-7} M) was used as a selective endothelin subtype A receptor antagonist.
Results: At 20 UI/mL, RhuEPO had no effect on norepinephrine-induced vasoconstriction ($n=10$) nor on sodium nitroprusside-induced relaxation ($n=10$). RhuEPO altered endothelium-dependent relaxation in a dose-dependent manner (maximal relaxation with RhuEPO at 0, 1, 10, 20 UI/mL, 77.7 ± 3.5 %, 68.5 ± 4.7%, 53.2 ± 3.8 %, 45.7 ± 4.6 %, $P<0.001$, $n=7$-14). Tempol and ABT-627 partially reversed the altered endothelial function in presence of RhuEPO 20 UI/mL ($P<0.01$, $P<0.01$, respectively).
Conclusion: RhuEPO alters endothelial function of subcutaneous resistance arteries in predialysis CKD patients via a mechanism in part involving oxidative stress and signaling through endothelin subtype A receptors, which could contribute to the deleterious effect of RhuEPO described in large interventional trials.

P2.04
PARADOXICAL INVOLVEMENT OF THE ENDOTHELIAL MINERALOCORTICOID RECEPTOR IN PLATELET ACTIVATION AND VASCULAR THROMBOSIS IN MOUSE

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Our aim was to investigate whether mineralocorticoid receptor (MR) overexpression in the vascular endothelium modifies the *in vitro* thrombin generation using thrombography and enhances the thrombotic risk *in vivo*. We used our mouse model with conditional overexpression of the MR in endothelial cells (MR-EC) (Nguyen Dinh Cat et al, FASEB J. 2010;24:2454-63).
The plasma level of von Willebrand factor was significantly increased in 3 month-old MR-EC mice compared with that in control mice (CT). In the presence of the activated protein C (APC) anticoagulant system, thrombin generation was lower in the plasma of MR-EC mice than in CT. Maximal platelet aggregation in