

**Objective:** Atherosclerosis is an inflammatory disease associated with an imbalance between pro- and anti-inflammatory mechanisms. While ample evidence is available in animal models, less is known about links between local vascular inflammation in human disease. T regulatory cells (Treg) have been implicated in atherosclerosis in mice but links with human vascular inflammation are poorly understood. Accordingly, we aimed to investigate the relationship between T regs in peripheral blood and locally in perivascular adipose tissue (pVAT) with endothelial function as a key mechanism in pathogenesis of vascular disease.

**Design and method:** Treg (CD3+/CD4+/CD25+/FoxP3+) infiltration was studied in pVAT of atherosclerotic coronary artery (CORO), non-atherosclerotic internal mammary artery (IMA), as well as subcutaneous AT and peripheral blood were quantified using flow cytometry from 50 CABG patients (38 M;12F;age 65y+/-1) with typical atherosclerosis risk factor profile. Vascular function was assessed in IMA segments ex vivo by isometric tension studies of vasorelaxations to acetylcholine and ROS production was measured in vascular segments with 5uM lucigenin enhanced chemiluminescence.

**Results:** Treg infiltration was observed in both IMA and CORO, but was significantly higher in IMA pVAT than in pVAT surrounding CORO ( $13,58 \pm 15,6$  vs.  $4,74 \pm 6,2$  cells/mg;  $p < 0,01$ ). Moreover, there was a significant correlation between these two AT depots suggesting systemic pVAT regulation ( $R = +0,53$ ;  $p = 0,001$ ). Indeed we observed a significant correlation between number of risk factors for atherosclerosis and Treg content ( $R_s = +0,33$   $p = 0,02$ ). Importantly, there was an inverse correlation between Treg content in peripheral blood and Ach-induced vasorelaxations ( $R = -0,31$   $p < 0,05$ ). Local T reg infiltration in pVAT was significantly correlated with indices of NO production, as measured by chemiluminescence ( $R = +0,58$   $p = 0,007$ ). However, NO produced was scavenged by ROS (measured by ratio of L-NAME enhanced/basal superoxide levels) and Treg infiltration in pVAT did not correlate with IMA endothelial function ( $R = -0,02$   $p = 0,92$ ) or total vascular ROS production ( $R = -0,12$   $p = 0,53$ ).

**Conclusions:** Atherosclerosis is accompanied by local decrease in T regulatory cell content in atherosclerotic vs. non-atherosclerotic arteries, although their amount is linked with classical risk factors for atherosclerosis. Higher peripheral blood T regs are associated with better endothelial function, although it is not achieved through locally infiltrating Tregs.

#### OP.2D.05

#### RELATIONSHIP OF OXIDATIVE STRESS WITH CARDIAC HYPERTROPHY IN HYPERTENSIVE PATIENTS

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**Objective:** Left ventricular hypertrophy is common in hypertensive patients. In these subjects increased oxidative stress has been observed. Our aim was to evaluate the association of biomarkers of both oxidative stress and inflammation with markers of cardiovascular damage in a large group of hypertensives with different stages of renal function.

**Design and method:** In 517 hypertensives we analyzed left ventricular mass indexed for body surface area, and we assayed plasma levels of 8-isoprostaglandin F2a and high sensitivity C reactive protein.

**Results:** Multivariate analysis carried out considering left ventricular mass as dependent variable, and including 8-isoprostaglandin F2a, high sensitivity C reactive protein, age, sex, body mass index, estimated glomerular filtration rate, serum glucose, (log)triglycerides, hemoglobin, pulse pressure or systolic blood pressure, mean or diastolic blood pressure, and antihypertensive treatment showed that in hypertensives plasma levels of 8-isoprostaglandin F2a were correlated with left ventricular mass ( $\beta = 0,269$ ,  $p < 0,0001$ ). The bivariate relationship of left ventricular mass with 8-isoprostaglandin F2a in hypertensives with estimated glomerular filtration rate higher and lower than  $60 \text{ ml/min/1.73m}^2$  was also calculated separately, demonstrating no significant differences in both correlations coefficients and slopes of the regression lines ( $r = 0,254$ ,  $p < 0,001$  and  $r = 0,226$ ,  $p < 0,002$ ; respectively). In the overall group, receiver operating characteristic curves showed that 8-isoprostaglandin F2a and high sensitivity C reactive protein were predictors of left ventricular hypertrophy,  $p < 0,0001$ .

**Conclusions:** To the best of our knowledge, this is the first demonstration that in hypertensives oxidative stress is correlated to left ventricular hypertrophy independently of other confounding factors. Oxidative stress might participate in the development of hypertensive cardiac hypertrophy.

#### OP.2D.06

#### DIFFERENCES IN ENDOTHELIAL GLYCOALYX IN RECENTLY DIAGNOSED AND UNTREATED MIDDLE-AGED HYPERTENSIVE PATIENTS REGARDING INCREASED CARDIOVASCULAR RISK

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**Objective:** Target organ damage (TOD) evaluation in patients with arterial hypertension is necessary in order to estimate cardiovascular risk (CVR) and plan treatment. Increased carotid intima-media thickness (IMT), an index of TOD, represents the diffuse vascular atheromatosis. The integrity of endothelial glycocalyx (EG) plays a vital role in vascular permeability, inflammation and elasticity and finally to cardiovascular disease. Sideview Darkfield imaging allows for non-invasive automated estimation of EG dimensions based on the erythrocyte column distribution. We aimed to investigate any differences in EG levels in untreated patients with essential hypertension.

**Design and method:** We studied 86 patients with newly diagnosed and never treated essential hypertension (mean age 53+7 years, 53 males). Increased perfusion boundary region (PBR) of the sublingual arterial microvessels (ranged from 5–25 micrometers) using Sideview Darkfield imaging (Microscan, Glycocheck) was measured as a non-invasive accurate index of reduced EG thickness. We estimated carotid intima-media thickness using carotid ultrasonography (normal levels  $\text{IMT} < 0,8 \text{ mm}$ ).

**Results:** The whole population was divided in two groups regarding IMT levels, group A ( $\text{IMT} < 0,8 \text{ mm}$ ,  $n = 30$ , mean age 52+7 years, 17 males) and group B ( $\text{IMT} > 0,8 \text{ mm}$ ,  $n = 56$ , mean age 54+7 years, 36 males). Group A and B were also matched for age and sex. No differences were found within groups regarding 24 h systolic and diastolic ABPM as well as PBR 5–25, PBR 10–19 and PBR 20–25. We found that PBR 5–9 was increased in group B ( $1,19 \pm 0,1$  vs.  $1,13 \pm 0,1$ ,  $p = 0,04$ ) compared with group A.

**Conclusions:** EG dimensions are reduced in hypertensive patients with augmented cardiovascular risk. Further studies are needed to confirm our results in a larger population and possibly establish EG measurement as a new cardiovascular risk marker.

#### OP.2D.07

#### THE EFFECTS OF ALPHA 1-ADRENOCEPTOR-BLOCKADE BY DOXAZOSIN OR ACE-INHIBITION BY RAMIPRIL ON ENDOTHELIAL FUNCTION IN PRIMARY HYPERTENSION: THE DORA STUDY

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**Objective:** To study whether reducing noradrenergic sympathetic vascular tone by doxazosin or blocking the renin-angiotensin-aldosterone system by ramipril will alter endothelial function in patients with uncomplicated hypertension.

**Design and method:** Mild-to-moderate hypertensive patients (age  $54 \pm 12$  years, 34% women, blood pressure (BP)  $148 \pm 11/88 \pm 9 \text{ mmHg}$ ) were randomized double-blind to ramipril (10 mg od,  $n = 33$ ) or doxazosin (8 mg od,  $n = 28$ ) for 12 weeks. Endothelium dependent and independent vasodilatation was studied by forearm post-ischemic flow mediated vasodilatation (FMD) and sublingual glyceryl trinitrate (GTN), respectively; by the forearm skin microcirculation responses to acetylcholine (Ach) and sodium nitroprusside (SNP) applied by iontophoresis, respectively; and by endothelium dependent vasodilatation following beta 2-adrenoceptor-agonist stimulation (sc terbutaline) assessed by the reflection index from pulse wave analysis.

**Results:** Drug treatment reduced aortic and brachial BP, and reduced indices of aortic stiffness. The effects (mean  $\pm$  SD or medians and interquartiles; and mean  $\pm$  SEM; for delta week 0–12), by ramipril and doxazosin on FMD ( $5,3 \pm 4,2$  to  $4,5 \pm 4,3\%$ , delta  $-1,1 \pm 1,0$ , and  $6,3 \pm 4,4$  to  $5,5 \pm 3,1\%$ , delta  $-0,3 \pm 1,0$ ); GTN ( $14,4 \pm 7,0$  to  $14,4 \pm 6,9\%$ , delta  $0,3 \pm 1,3$ , and  $15,5 \pm 6,8$  to  $14,4 \pm 7,0$ , delta  $-0,5 \pm 1,3$ ); endothelial function index (ie FMD/GTN,  $0,49 \pm 0,56$  to  $0,44 \pm 0,64$ , delta  $0,07 \pm 0,12$ , and  $0,47 \pm 0,38$  to  $0,51 \pm 0,41$ , delta  $0,07 \pm 0,12$ ); and reflection index ( $-6,8 \pm 3,2$  to  $-7,7 \pm 3,8$ , delta  $-0,8 \pm 1,0$ , and  $-7,3 \pm 2,8$  to  $-6,6 \pm 3,1$ , delta  $0,3 \pm 0,9$ ) were small. Also the effects by ramipril and doxazosin on skin microcirculation (peak flux, arbitrary units) were small: 33 [18–62] to 28 [19–53], delta  $-2 \pm 5$ , and 36 [21–62] to 41 [20–67], delta  $1 \pm 9$  by Ach; and 46 [34–84] to 43 [26–87], delta  $-9 \pm 8$ , and 58 [33–78] to 60 [44–82], delta  $-0,3 \pm 10$  by SNP; and  $0,5 [0,4-1,0]$  to  $0,8 [0,4-1,3]$ , delta  $0,2 \pm 0,2$ , and  $0,6 [0,4-1,0]$  to  $0,8 [0,3-1,4]$ , delta  $0,3 \pm 10$  by the peak flux ratio (Ach/SNP), respectively. Also skin microcirculatory responses to heat induced hyperemia remained unchanged.

**Conclusions:** ACE-inhibition and alpha 1-adrenoceptor-blockade for 12 weeks reduce BP and improve indices of aortic stiffness but appear to have no effects on endothelial function assessed in multiple ways in mild-to-moderate uncomplicated hypertension. Evidence of endothelial dysfunction and the potential benefit of treatment might require more advanced stages of hypertensive disease.