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### **P4.11: TYPE 2 DIABETES IS ASSOCIATED WITH GREATER CAROTID STIFFNESS AND GREATER PRESSURE-DEPENDENCY OF CAROTID STIFFNESS–THE MAASTRICHT STUDY**

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**Results:** the correlation ( $p < 0.05$ ) between FRS and CV biomarkers was the highest for WS, cPP, and PWV ( $r = 0.50, 0.49, 0.51$ ), lower for LVMI, IMT and RWT ( $r = 0.41, 0.41, 0.21$ ). Age was main independent determinant of WS, PWV and cPP; WS and PWV were also independently related to systolic BP and DM, and cPP to HBP therapy. Main determinant of IMT was DM, followed by age and HBP therapy, and independent determinants of LVMI and RWT were SBP and HBP therapy, respectively. Lipids and smoking were not independently related to any tissue biomarker.

**Conclusions:** our data indicate that arterial stiffness and local carotid PP reflect mainly the ageing process, and are more tightly related to FRS than structural carotid and LV indices. Carotid IMT or LV mass and geometry are predominantly influenced by the presence of DM or HBP, respectively. Different tissue biomarkers may contribute to a personalized estimate of CV risk.

#### P4.8

##### ARTERIAL STIFFNESS IS ASSOCIATED WITH DEPRESSIVE SYMPTOMS AND THIS ASSOCIATION IS PARTLY MEDIATED BY CEREBRAL SMALL VESSEL DISEASE: THE AGES-REYKJAVIK STUDY

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**Background:** Arterial stiffness may contribute to depression via cerebral microvascular damage, but evidence for this is scarce. We therefore investigated the association between arterial stiffness and depressive symptoms and the potential mediating role of cerebral small vessel disease therein.

**Methods:** This cross-sectional study included 2,058 participants (mean age 79.6 years; 59.0% women) of the AGES-Reykjavik study. Arterial stiffness (carotid-femoral pulse wave velocity, CFPWV), depressive symptoms (15-item geriatric depression scale, GDS-15) and cerebral small vessel disease (magnetic resonance imaging) were determined. Manifestations of cerebral small vessel disease included higher white matter hyperintensity volume, subcortical infarcts, cerebral microbleeds, Virchow-Robin spaces and lower total brain parenchyma volume.

**Results:** Higher CFPWV was associated with a higher GDS-15 score, after adjustment for age, sex, education level, smoking, digit symbol substitution test score, gait speed, mean arterial pressure, heart rate and cardiovascular risk factors. Additional adjustment for white matter hyperintensity volume or subcortical infarcts attenuated the association between CFPWV and the GDS-15 score, which became statistically not significant. Formal mediation tests showed that the mediating effects of white matter hyperintensity volume and subcortical infarcts were statistically significant. Virchow-Robin spaces, cerebral microbleeds and cerebral atrophy did not mediate the association between CFPWV and depressive symptoms.

**Conclusions:** Higher arterial stiffness is associated with more depressive symptoms; this association is partly mediated by white matter hyperintensity volume and subcortical infarcts. This study supports the hypothesis that arterial stiffness leads to depression in part via cerebral small vessel disease.

#### P4.9

##### ASSOCIATION BETWEEN ARTERIAL STIFFNESS AND SKIN MICROVASCULAR FUNCTION IN INDIVIDUALS WITHOUT AND WITH TYPE 2 DIABETES: COMBINED REPORT OF THE SUVIMAX2 STUDY AND THE MAASTRICHT STUDY

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**Background:** It has been hypothesized that arterial stiffness leads to generalized microvascular dysfunction, and that this may explain the association between arterial stiffness and different diseases, including

dementia, kidney dysfunction, neuropathy and osteoporosis. In addition, individuals with type 2 diabetes mellitus (T2DM) may be particularly prone to the detrimental effects of arterial stiffness. However, evidence for an association between arterial stiffness and direct markers of generalized microvascular dysfunction is lacking. The cutaneous microcirculation is a representative vascular bed to examine generalized microvascular phenomena. We therefore investigated the association between arterial stiffness and skin microvascular function in both individuals without and with T2DM.

**Methods:** Cross-sectional data was used of The SUVIMAX2 Study ( $n = 284$ ; 62.2y; 48.6% women; 0% T2DM (by design)) and The Maastricht Study ( $n = 737$ ; 59.7y; 45.2% women; 28.8% T2DM (by design)). Arterial stiffness was determined by carotid-femoral pulse wave velocity (cfPWV). Skin capillaroscopy was used to determine capillary density at baseline, during reactive hyperemia after arterial occlusion and during venous congestion. Laser Doppler flowmetry was used to assess acetylcholine- and local heating-induced vasoreactivity, and microvascular flowmotion.

**Results:** In both individuals without and with T2DM, cfPWV was not associated with baseline capillary density or capillary recruitment during reactive hyperemia or venous congestion. In addition, cfPWV was not associated with acetylcholine- or local heating-induced vasoreactivity, or microvascular flowmotion.

**Conclusions:** Arterial stiffness is not associated with skin microvascular function, irrespective of the presence of T2DM. This suggests that the association between arterial stiffness and different diseases cannot be explained by generalized microvascular dysfunction alone.

#### P4.10

##### PULSE WAVE VELOCITY UNDER THE CUT-OFF VALUE OF 10 M/S AND AORTIC AUGMENTATION INDEX CORRECTED TO HEART RATE MAY SIGNAL HIGHER EARLY CVD RISK IN MIDDLE-AGED MEN

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**Purpose:** Arterial stiffness may have an added value in cardiovascular (CV) risk stratification. We aimed to evaluate association of CV risk factors and arterial stiffness in middle-aged subjects.

**Methods:** 238 Caucasian subjects (men 42.4%; mean age 48 years) free of known cardiovascular disease (CVD) were enrolled in a prospective cohort study in 1977. During the last evaluation in 2012-2013, arterial stiffness (carotid-femoral pulse wave velocity [cf-PWV] and aortic augmentation index [Alx]) were measured by applanation tonometry.

**Results:** cf-PWV was significantly higher in men than in women ( $8.1 \pm 2.5$  vs  $7.5 \pm 2.1$  m/s;  $p = 0.035$ ). cf-PWV was higher in subjects with MetS ( $8.8 \pm 2.4$  vs  $7.5 \pm 2.2$  m/s;  $p = 0.0003$ ), but was not associated with individual CV risk factors. Increased cf-PWV of  $>10$  m/s was found in 10% of subjects with no significant differences between genders ( $p = 0.22$ ), and was not related to any of the individual CV risk factors. Alx ( $27.1 \pm 10.9\%$ ) was not associated with any of the CV risk factors or MetS, and did not differ between genders. However, when corrected to heart rate Alx (Alx@75) was significantly higher in men with MetS, compared to men without MetS ( $21.7$  vs  $16.7\%$ ;  $p = 0.02$ ), but not women, and was associated with hypertension ( $p = 0.003$ ) and central adiposity ( $p = 0.02$ ).

**Conclusions:** PWV was significantly higher in men than women, and in subjects with MetS. Alx@75, and not Alx, was related to worse cardiovascular risk profile. These findings suggest that higher PWV and Alx@75 values, although lower than currently established cut-off values, may signal of increased risk of early CVD in men.

#### P4.11

##### TYPE 2 DIABETES IS ASSOCIATED WITH GREATER CAROTID STIFFNESS AND GREATER PRESSURE-DEPENDENCY OF CAROTID STIFFNESS—THE MAASTRICHT STUDY

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**Purpose:** Arterial remodeling underlies the association between type 2 diabetes (T2D) and arterial stiffness. Remodeling may also affect the pressure-dependency of stiffness. Pressure-dependency can be quantified as the systolic-diastolic difference in pulse wave velocity ( $\Delta$ PWV).

In the population-based Maastricht Study, we evaluated the associations between carotid stiffness (cPWV) and  $\Delta$ PWV, and glucose metabolism status (GMS). Additionally, we investigated the interdependency of cPWV and  $\Delta$ PWV in their association with GMS as to find out whether remodeling may act differentially upon cPWV and  $\Delta$ PWV.

**Methods:** The study consisted of 594 individuals (312 normal glucose metabolism [NGM], 98 impaired glucose metabolism [IGM] and 184 T2D). cPWV and  $\Delta$ PWV were determined by ultrasonography and tonometry. Regression analyses were used to investigate the associations of cPWV and  $\Delta$ PWV with GMS (NGM as reference). Models were adjusted for age, sex, mean arterial pressure (MAP), and central pulse pressure, cPWV or  $\Delta$ PWV as appropriate, and additionally for: anti-hypertensive medication, prior cardiovascular disease, estimated glomerular filtration rate, or body mass index.

**Results:** After adjustment for age, sex and MAP, T2D was associated with greater cPWV ( $\beta$  (95% CI; 0.284 (0.012-0.556)) and  $\Delta$ PWV (0.299 (-0.005-0.603)). Further adjustments did not change these associations. After additional adjustment for cPWV or  $\Delta$ PWV the associations with  $\Delta$ PWV and cPWV attenuated (0.209 (-0.083-0.502) and 0.208 (-0.053-0.470), respectively). IGM was not associated with either cPWV or  $\Delta$ PWV.

**Conclusions:** In T2D both cPWV and  $\Delta$ PWV are increased. The associations were only partially interdependent, which suggests that remodeling impacts on both stiffness and its pressure-dependency.

#### P4.12

##### AGE, WAIST CIRCUMFERENCE AND BLOOD PRESSURE ARE ASSOCIATED WITH SKIN MICROVASCULAR FLOWMOTION: THE MAASTRICHT STUDY

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**Introduction:** Skin microvascular flowmotion (SMF) plays an important role in optimal delivery of nutrients/oxygen to tissue and in maintaining normal peripheral resistance. It is unclear however, which determinants influence SMF. Therefore, we investigated which cardiovascular risk factors are associated with SMF.

**Methods:** We measured SMF in 506 participants without a prior cardiovascular event. SMF was investigated using Fourier transform analysis of skin laser Doppler flowmetry. The associations of the cardiovascular determinants age, sex, waist circumference, 24-h systolic blood pressure (SBP), total-to-HDL cholesterol, fasting plasma glucose (FPG), and cigarette smoking with SMF were analyzed by use of multiple linear regression analysis.

**Results:** The mean age of the study population ( $n=506$ ) was  $58.8 \pm 8.5$  years, 260 (51.4%) were men, mean waist circumference was  $95.7 \pm 13.0$  cm, mean 24-h SBP was  $119 \pm 12$  mmHg, and 73 (14.4%) were smokers. After adjustment for cardiovascular risk factors and medication, per 1SD higher age SMF was 0.17 SD (95%CI: 0.08; 0.26;  $P < 0.001$ ) higher; per 1SD higher waist circumference SMF was -0.12 SD (-0.23; -0.01;  $P = 0.03$ ) lower; per 1SD higher 24-h SBP SMF was 0.17 SD (0.07; 0.27;  $P < 0.001$ ) higher. No other associations with SMF were found.

**Conclusions:** Age and blood pressure were directly, while waist circumference was inversely associated with SMF. The exact mechanisms underlying these findings remain elusive. The present data support the hypothesis that microvascular dysfunction, specifically, impaired SMF, plays a role in the development of obesity-related insulin resistance and hypertension.

#### P4.13

##### TYPE 2 DIABETES IS ASSOCIATED WITH ALTERED CAROTID ARTERY MECHANICS INDEPENDENTLY OF AGEING AND MEAN ARTERIAL PRESSURE—THE MAASTRICHT STUDY

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**Introduction:** Type 2 diabetes (T2D) is characterised by accelerated vascular ageing, which changes arterial wall structure and hence artery mechanics (e.g., pressure-area (P-A)). Pulse wave velocity (PWV) is affected by both blood pressure and changes in wall mechanics. To better capture underlying changes in wall mechanics in T2D, we aimed to disentangle the vascular ageing phenomena (characterised by PWV) from pressure effects.

**Methods:** We studied young (<55y) and older (>70y) individuals without and with T2D matched at the group level for age, sex and MAP ( $n=29$  each) from the Maastricht Study. Non-linear P-A curves were derived from carotid

tonometry and echo-tracking, using Langewouters-model fits. Isobaric PWV (Bramwell-Hill) was determined at MAP.

**Results:** In individuals without T2D, the average P-A curve in older, as compared to younger individuals, was shifted rightward (diastolic area ( $A_d$ ), mean $\pm$ SD:  $48.8 \pm 10.3$  vs.  $42.5 \pm 8.3$  mm<sup>2</sup>,  $p=0.003$ ), which led to higher PWV ( $9.9 \pm 2.0$  vs.  $7.4 \pm 1.6$  m/s,  $p < 0.001$ ). Next, in younger individuals with T2D, as compared to those without, a similar pattern was found ( $A_d$ :  $45.7 \pm 9.6$  vs.  $42.5 \pm 8.3$  mm<sup>2</sup>,  $p=0.068$  and PWV:  $8.2 \pm 1.6$  vs.  $7.4 \pm 1.6$  m/s,  $p=0.072$ ). Finally, in older individuals with T2D, as compared to those without, the P-A curve was again shifted rightward ( $A_d$ :  $53.1 \pm 10.4$  vs.  $48.8 \pm 10.3$  mm<sup>2</sup>,  $p=0.034$ ), but PWV was not significantly different ( $10.1 \pm 1.7$  vs.  $9.9 \pm 2.0$  m/s,  $p=0.29$ ).

**Conclusion:** Independently of blood pressure, both ageing and T2D have a dilatary effect on carotid arteries, with ageing also clearly demonstrating stiffening. Although T2D is associated with additional stiffening in individuals younger than 55y, this was not observed in individuals older than 70y.

#### P4.14

##### THE EFFECT OF GENDER AND BODY SIZE ON ARTERIAL HAEMODYNAMICS AT REST AND DURING EXERCISE

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**Aim:** The positive association between body size and blood pressure (BP) is well recognised. However, not all overweight individuals are hypertensive. This study aimed to examine the influence of body size and gender on the haemodynamic mechanisms driving systolic BP (SBP) at rest and during exercise, in young adults.

**Method:** Detailed anthropometric, biochemical and haemodynamic measurements including BP, cardiac index (CI) and peripheral vascular resistance (PVR) were obtained in 2497 untreated individuals ( $23 \pm 6$  years) at rest. Subjects were classified as normal-weight (NW; BMI <25) or overweight (OW; BMI >25). A sub-set of 86 individuals ( $29 \pm 6$  years) undertook steady-state, sub-maximal cycling exercise, with detailed haemodynamic measurements re-assessed.

**Results:** At rest, a positive association was found between SBP and cardiac index (CI) in NW but not OW males and females ( $p < 0.001$  for both). In contrast, a positive association was found between SBP and PVR in OW but not NW males ( $P < 0.001$  for both). Although BMI did not correlate with BP during exercise, body fat (BF) % was inversely associated with exercise-induced changes in PP, even after adjustment for gender. A higher BF% was also associated with a poorer maximum dilatatory response to ischaemia. **Conclusion:** The primary haemodynamic mechanisms driving SBP differ depending on body size in young adults. BF% may be a more useful tool than BMI to further examine the impact of body size on BP in young adults. Structural differences in resistance vessels may underlie the association between body size and BP responses to exercise.

#### P5.1

##### PROTEOMIC ANALYSIS ON HUMAN ARTERIAL TISSUE: RELATIONS TO ARTERIAL STIFFNESS

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We hypothesized that arterial stiffness is associated with changes in the arterial protein profile, particularly in relation to extracellular matrix (ECM) components, and aimed at determining differentially expressed proteins in human arterial tissue by quantitative proteome analysis in patients with different degrees of arterial stiffness. Arterial stiffness, assessed by carotid-femoral pulse wave velocity (PWV), central blood pressure and augmentation index by pulse wave analysis, as well as carotid intima-media thickness were measured the day prior to surgery in a group of patients undergoing coronary artery bypass grafting. Protein extracts of well-defined, homogenous, non-atherosclerotic individual samples of the left mammary artery from 10 of these patients with high PWV and 9 with low PWV, were compared by quantitative proteome analysis, using iTRAQ-labeling and nano-LC-MS/MS. Of 504 quantified proteins, 28 were differentially expressed between groups with high and low PWV ( $p < 0.05$ ). Six out of eight members of the extracellular matrix family of small leucine-rich repeat proteoglycans displayed significant or borderline significant differences between the two groups ( $p < 0.001$ , Fisher's Exact Test). Only one other of 43 identified ECM proteins were differentially regulated (collagen alpha-1(VIII)). Several proteins related to smooth muscle cell function and structure were found in different amounts between the two groups.