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3.2: INACTIVE MATRIX GLA PROTEIN IS CAUSALLY RELATED TO HEALTH OUTCOMES: A MENDELIAN RANDOMIZATION STUDY IN A FLEMISH POPULATION

Y.-P. Liu, Y.-M. Gu, L. Thijs, M. Knapen, E. Salvi, L. Citterio, T. Petit, S. Carpini, Z.-Y. Zhang, L. Jacobs, Y. Jin, C. Barlassina, P. Manunta, T. Kuznetsova, P. Verhamme, H. Struijker-Boudier, D. Cusi, C. Vermeer, J. Staessen

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Conclusions: Significant Bra-Rad-SBP_{Amp} exists during light-moderate exercise. This will result in underestimation of central SBP unless Bra-Rad-SBP_{Amp} is considered and is influenced by variation in peak blood flow velocity magnitude between the brachial and radial arteries.

3.1

QUANTIFICATION OF THREE-DIMENSIONAL VASCULAR SMOOTH MUSCLE ORIENTATION AND ITS DISPERSION IN MURINE CAROTID ARTERIES

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Introduction: Vascular smooth muscle cells (SMCs) play a pivotal role in regulating vascular tone in arteries, and are therefore an essential part of constitutive models of the arterial wall. Since an SMC exerts its contractile force mainly along its longitudinal axis, SMC orientation is a major determinant of arterial biomechanical behaviour. To our knowledge, all current constitutive models assume SMC orientation to be perfectly circumferential. Moreover, the mechanical effect of any dispersion in SMC orientation is neglected. In this study, we developed a method to quantify in 3D the orientation of SMCs in the intact arterial wall.

Methods: SMC nuclei of six excised and mounted murine carotid arteries were imaged using two-photon laser scanning microscopy. 3D image processing was used to identify individual nuclei and their orientations. Subsequently, SMC locations and orientations were converted to cylindrical and spherical coordinate systems, respectively. We found SMCs to be arranged in distinct inner and outer layers. For each layer, SMC orientations were described by a Bingham distribution, a statistical distribution to describe axis orientations in 3D.

Results and Conclusion: Distributions show a statistically significant ($p < 0.05$) helical angular component in both layers (inner: $\Theta_h = 2.7 \pm 2.7^\circ$, outer: $\Theta_h = 5.1 \pm 2.7^\circ$, mean \pm SD), and considerable dispersion. We conclude that vascular SMC orientation 1) can be quantified in 3D, 2) has a distinct helical component, and 3) shows considerable dispersion. The acquired distribution data are essential to improve constitutive modelling of the arterial wall, by quantitatively describing physiological SMC orientation and dispersion.

3.2

INACTIVE MATRIX GLA PROTEIN IS CAUSALLY RELATED TO HEALTH OUTCOMES: A MENDELIAN RANDOMIZATION STUDY IN A FLEMISH POPULATION

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Background: Matrix Gla-protein is a vitamin K-dependent protein that strongly inhibits arterial calcification. Vitamin K deficiency leads to production of inactive nonphosphorylated and uncarboxylated MGP (dp- μ cMGP). The risk associated with dp- μ cMGP in the population is unknown.

Methods: In a Flemish population study, we measured circulating dp- μ cMGP at baseline (1996–2011), genotyped MGP and recorded adverse health outcomes until December 31, 2012. We assessed the multivariable-adjusted association of adverse health outcomes with dp- μ cMGP and we applied a Mendelian randomization analysis based on MGP genotypes.

Results: Among 2318 participants, baseline dp- μ cMGP averaged 3.61 μ g/liter. Over 14.1 years (median), 197 deaths occurred, 58 from cancer and 70 from cardiovascular disease, and 85 participants experienced coronary events. The risk of death and non-cancer mortality curvilinearly increased ($P < 0.008$) by 15.0% (95% confidence interval, 6.9–25.3) and by 21.5% (11.1–32.9) for a doubling of the nadir: 1.43 and 0.97 μ g/liter, respectively. With higher dp- μ cMGP, cardiovascular mortality log-linearly increased (hazard ratio for dp- μ cMGP doubling, 1.14 [1.01–1.28]; $P = 0.027$), but coronary events log-linearly decreased (0.93 [0.88–0.99]; $P = 0.021$). dp- μ cMGP levels were associated ($P < 0.001$) with MGP variants *rs2098435*, *rs4236* and *rs2430692*. For non-cancer mortality and coronary events ($P < 0.022$), but not for total and cardiovascular mortality ($P \geq 0.13$), the Mendelian

randomization analysis suggested causality. In a nested case-control study, 64 patients with coronary events had lower dp- μ cMGP than 107 matched controls (3.51 vs. 4.54 μ g/liter; $P = 0.012$).

Conclusions: Higher dp- μ cMGP predicts total, non-cancer and cardiovascular mortality, but lower coronary risk. For non-cancer mortality and coronary events, these associations are likely causal.

3.3

ASSOCIATIONS BETWEEN PLASMA INCRETIN HORMONE RELEASE AND AORTIC STIFFNESS AND BLOOD PRESSURE IN INDIVIDUALS WITHOUT KNOWN DIABETES: THE ADDITION-PRO STUDY

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The role of incretin hormone release on vascular structure and function remains unclear. Hence, in 836 Danish individuals without known diabetes and without antihypertensive treatment, we examined the associations of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) release during a 3-point 75 g oral glucose tolerance test (0, 30, 120 minutes) with carotid-femoral pulse wave velocity (PWV), and brachial and central blood pressure. For GLP-1 and GIP, total area under the curve (AUC) reflecting circulating incretin levels, and incremental AUC (iAUC) reflecting the incretin response were calculated and transformed by the base 2 logarithm. Associations were analysed by linear regression adjusting for age and sex, and for heart rate and mean blood pressure in the PWV analyses. Mean age was 55.1 (SD: 7.4) years, and 52% were men. A doubling in iAUC_{GLP-1} was associated with a PWV (95% CI) of -0.04 (-0.12; 0.04) m/s, and a central systolic and diastolic blood pressure and pulse pressure (95% CI) of -1.2 (-2.1; -0.3), -0.8 (-1.3; -0.2), and -0.4 (-1.0; 0.2) mmHg, respectively. Associations with brachial blood pressure were of similar magnitude as central blood pressure. For AUC_{GLP-1}, only brachial diastolic blood pressure showed a statistically significant association (-1.0 (95% CI: -1.9; -0.2) mmHg for an AUC_{GLP-1} doubling). Besides a positive association between iAUC_{GIP} and brachial pulse pressure, GIP was not associated with PWV or blood pressure. Although cross-sectional, these results indicate that a high GLP-1 response has a beneficial impact on the vascular function but not on vascular structure, whereas GIP does not affect the vasculature.

3.4

EFFECT OF VITAMIN D SUPPLEMENTATION ON AORTIC STIFFNESS AND CENTRAL HAEMODYNAMICS IN OLDER INDIVIDUALS WITH VITAMIN D DEFICIENCY: PROMISING OBSERVATIONAL DATA IS NOT SUPPORTED WHEN TESTED BY DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMISED TRIAL DESIGN

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Background: Observational studies report a relationship between increased aortic stiffness and low vitamin D levels. This suggests that aortic stiffness may be improved with vitamin D supplementation, but there is limited intervention data to support this hypothesis. This study aimed to determine the effect of vitamin D supplementation on aortic stiffness and associated central haemodynamic indices.

Methods: In a double-blind, placebo-controlled trial, 265 individuals (63 \pm 7, female 50%) with vitamin D deficiency were randomized to 12-months intervention (vitamin D 50,000 IU/month; n = 132) or matching placebo (n = 133). Aortic stiffness (carotid-femoral pulse wave velocity; aPWV), central haemodynamic indices (augmentation index, augmented pressure, central pulse pressure) and brachial blood pressure were measured at baseline, six and 12 months.

Results: At baseline there were no significant differences between the groups in aPWV (9.0 \pm 0.3 vs 9.1 \pm 0.2 m/s; $P = 0.6$), nor any other central haemodynamic indices or brachial blood pressure (all $P > 0.05$). Intervention failed to make any clinical or statistically significant changes to aPWV