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


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Conclusions: Significant Bra-Rad-SBP_{aemp} exists during light-moderate exercise. This will result in underestimation of central SBP unless Bra-Rad-SBP_{aemp} 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. The size, shape, and orientation of the nuclei were determined using MATLAB. The SMC orientation was calculated as the angle between the long axis of each nucleus and the circumferential axis of the arterial wall. The distribution of SMC orientation was described using a probability density function.

**Results and Conclusion:** The distribution of SMC orientation was found to be non-uniform, with a peak orientation along the circumferential axis. The dispersion of SMC orientation was found to be significant, with a spread of orientations ranging from 0 to 180 degrees. The mean orientation of SMCs was found to be 45 degrees, with a standard deviation of 15 degrees.

### 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-μMGP). The risk associated with dp-μMGP in the population is unknown.

**Methods:** In a Flemish population study, we measured circulating dp-μMGP 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-μMGP and we applied a Mendelian randomization analysis based on MGP genotypes.

**Results:** Among 2318 participants, baseline dp-μMGP averaged 3.61 μg/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 was 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: 1.14±0.72 (P=0.027), but coronary events were not significantly increased (0.93 [0.88–0.99]; P=0.021). dp-μMGP 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=0.13), the Mendelian randomization analysis suggested causality. In a nested case-control study, 64 patients with coronary events had lower dp-μMGP than 107 matched controls (3.51 vs. 4.54 μg/liter; P=0.012).

### 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 (74.4) years, and 52% were men. A doubling in IAUCGLP-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;1.3), -0.8 (-1.3;0.0), and -0.4 (-1.0;0.2) mmHg, respectively. Associations with brachial blood pressure were of similar magnitude as central blood pressure. For IAUCGLP-1, only brachial diastolic blood pressure showed a statistically significant association (-1.0 (95% CI: -1.9;0.2) mmHg for an IAUCGLP-1 doubling). Besides a positive association between IAUCGLP-1 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±7 years, 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±0.3 vs. 9.1±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.