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### 5.2: SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS AND AORTIC STIFFNESS IN GENERAL POPULATION

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**Methods:** Aortic pressure and flow were measured in anesthetized, open-chest dogs ( $n = 5$ ). Wave reflections were modified with i.v. infusion of methoxamine (MTX) to increase reflections and nitroprusside (NTP) to decrease reflections. In a human sample ( $n = 226$ ), central pressure and flow were measured using carotid tonometry and phase-contrast MRI, respectively.

**Results:** Under conditions of baseline and increased reflections in both dogs and humans, peak of the forward wave (FWA) consistently occurred after time of peak flow ( $P < 0.001$ ). FWA was systematically greater than peak flow multiplied by aortic characteristic impedance ( $Q_{\max}Z_c$ ) in dogs ( $P < 0.01$ ) and humans ( $P < 0.01$ ). Only when wave reflections were abolished vasoactively (NTP) in dogs was time of FWA and peak flow the same, leading to insignificant differences in FWA and  $Q_{\max}Z_c$  ( $P = 0.59$ ).

**Conclusion:** In steady-state, wave reflections set up in previous cardiac cycles, wave re-reflections at the aortic root, and proximal reflections contribute to both the  $P_r$  and  $P_b$  waves, even during early-systole. Most importantly, peak aortic flow is also determined by aortic input impedance, which includes effects from properties distal of the proximal aorta. Under steady-state conditions, forward wave amplitude and morphology cannot be attributed solely to the LV and proximal aorta.

#### 4.5

##### A SYSTEMATIC REVIEW AND META-ANALYSIS OF CENTRAL TO BRACHIAL BLOOD PRESSURE AMPLIFICATION IN PATIENTS TYPE 2 DIABETES MELLITUS

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**Background:** Brachial blood pressure (BP) may not reflect central BP due to systolic BP (SBP) amplification. Patients with type 2 diabetes mellitus (T2DM) elicit vascular irregularities that may affect SBP amplification or other central BP indices (including pulse pressure [PP], augmentation pressure [AP] and augmentation index [AIx]). By systematic review and meta-analysis, this study aimed to determine the magnitude and variation of central-to-brachial SBP and PP amplification, AIx and AP in T2DM compared to non-diabetic controls.

**Methods:** Online databases were searched for published studies reporting invasive or non-invasive central and brachial SBP in T2DM and non-diabetic controls. Random effects meta-analyses and meta-regression were used to analyse the studies.

**Results:** We identified 17 studies with a total of 2,711 T2DM and 10,460 non-diabetic controls. There was no significant difference in SBP amplification between groups (T2DM = 10.8, non-diabetic = 10.2 mmHg; pooled estimate = 0.6 mmHg, 95%CI -0.3, 1.5,  $p = 0.21$ ), but large variation in both (T2DM range = 2.0–16.6 mmHg, non-diabetic range = 1.0–16.1 mmHg). In the meta-regression, duration of T2DM explained 16.3% of the variance in the pooled data ( $p = 0.15$ ); the difference in amplification between groups increasing by 0.3 mmHg per year of T2DM. PP amplification was not significantly different between groups ( $p = 0.16$ ). AP, AIx and AIx corrected for heart rate were significantly higher in T2DM ( $p < 0.05$  all).

**Conclusions:** Patients with T2DM have increased AP and AIx, but no difference in SBP (or PP) amplification compared to non-diabetic individuals. However, SBP amplification is highly variable and increases with duration of T2DM; altogether confirming that central systolic loading cannot be reliably estimated from brachial BP in T2DM.

#### 4.6

##### RELATIONSHIP OF CAROTID ARTERIAL FUNCTIONAL AND STRUCTURAL CHANGES TO LEFT ATRIAL VOLUME IN UNTREATED HYPERTENSION

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The contribution of arterial functional and structural changes to left ventricular (LV) diastolic dysfunction has been the area of latest research. There are

some studies on the relationship of arterial stiffness (a.s.) and left atrial (LA) remodeling as a marker of diastolic burden. Little is known on the association of arterial structural changes and LA remodeling in hypertension (H).

**The aim** of this study was to examine the relationship of carotid a.s. and intima-media thickness (IMT) to LA volume in subjects with H.

The study included 245 previously untreated hypertensives (166 women and 79 men, mean age  $53.7 \pm 11.8$  years). Each patient was subjected to echocardiography with measurement of LA volume, evaluation of left ventricular hypertrophy (LVH) and LV systolic/diastolic function indices, integrated assessment of carotid IMT and echotracking of a.s. and wave reflection parameters.

**Results:** The following parameters were identified as independent determinants of indexed LA volume on multivariate regression analysis: diastolic blood pressure ( $\beta = -0.229$ ,  $p < 0.001$ ), left ventricular mass index (LVMI;  $\beta = 0.258$ ,  $p < 0.001$ ), E/e' index (ratio of early mitral flow wave velocity - E to early diastolic mitral annular velocity-e';  $\beta = 0.266$ ,  $p = 0.001$ ), augmentation index (AI;  $\beta = 0.143$ ,  $p = 0.008$ ) and body mass index (BMI;  $\beta = 0.132$ ,  $p = 0.017$ ). No correlations between indexed LA volume and IMT were found.

**Conclusion:** There is a significant relationship of carotid arterial stiffness but not intima-media thickness to LA volume in patients with untreated hypertension.

#### 5.1

##### INERTIAL-VISCOELASTIC MINIMAL MODEL OF THE ARTERIAL SYSTEM RECONCILES ARTERIAL COMPLIANCE ESTIMATIONS

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**Background:** The arterial system is viscoelastic rather than purely elastic. There exist various methods to characterize the purely elastic nature of arterial compliance, each method yielding different values. The pulse pressure method ( $C_{ppm}$ ), estimating compliance by matching the pulse pressure (PP) of a two-element Windkessel to measured PP, yields consistently lower values than the pressure decay time method ( $C_{dec}$ ) and diastolic area method ( $C_{area}$ ). An alternative inertial-viscoelastic model (IVEMM) that is viscoelastic and frequency-dependent rather than purely elastic and constant has been shown in dogs to reconcile the various compliance estimation methods. We assessed the presumed merits of IVEMM compliance estimates in a clinically diverse human sample.

**Methods:** Central pressure and flow were measured using carotid tonometry and phase-contrast MRI, respectively, in 226 subjects. Arterial compliance was estimated using (1)  $C_{ppm}$ ; (2)  $C_{dec}$ ; (3)  $C_{area}$ ; (4)  $C_{IVEMM}(j\omega)$ .

**Results:**  $C_{ppm}$  was nearly perfectly correlated with  $C_{IVEMM}$  evaluated at frequency of heart rate (Pearson coefficient ( $\rho$ ) = 0.99; slope ( $B$ ) = 1.00;  $P < 0.001$ ).  $C_{area}$  ( $\rho = 0.979$ ;  $B = 0.928$ ;  $P < 0.001$ ) and  $C_{dec}$  ( $\rho = 0.974$ ;  $B = 0.954$ ;  $P < 0.001$ ) were very strongly correlated with  $C_{IVEMM}$  evaluated at 0 hertz (static compliance).

**Conclusion:**  $C_{ppm}$  is fit to PP defined in systole, when fast-acting phenomena are likely to elicit viscoelasticity of the arterial system. Its consistently lower values compared to  $C_{dec}$  and  $C_{area}$  are clarified by IVEMM to be the result of estimating viscoelastic compliance at frequency of heart rate.  $C_{dec}$  and  $C_{area}$  are estimates of static compliance. Consistent with dog studies, IVEMM appears to reconcile the three popular compliance estimation techniques.

#### 5.2

##### SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS AND AORTIC STIFFNESS IN GENERAL POPULATION

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It has been suggested that accumulation of advanced glycation end-products (AGE) is involved in several pathophysiological processes in the vessel wall. Soluble isoform of receptor for AGE (sRAGE) acts as a decoy for capturing circulating AGE, prevents them from binding to the cell-surface receptor and protects against the RAGE-AGE axis-elicited processes. We hypothesized that low sRAGE levels might be associated with increased arterial stiffness.

In a cross-sectional design, we analyzed 1077 subjects from the Czech population-based study ("Post-MONICA"). Aortic pulse wave velocity (aPWV) was measured using a Sphygmocor device. sRAGE concentrations were assessed in frozen samples by ELISA methods (R&D Systems).

Aortic PWV significantly ( $p < 0.0001$ ) increased across the sRAGE quartiles. After adjustment for all potential confounders, non-diabetic subjects in the bottom quartile of sRAGE ( $< 918$  pg/mL) had odds ratio of raised aortic PWV ( $\geq 9$  m/sec, top quartile), 1.8 (95% CI: 1.19–2.72) with  $p = 0.006$ ; the association was stronger when only hypertensive non-diabetic individuals were included: odds ratio 2.05 (95% CI: 1.26–3.32) with  $p = 0.004$ . In contrast, using similar regression models, low sRAGE was rejected as an independent predictor of raised aortic aPWV in diabetic or in normotensive subjects.

In conclusion, low circulating sRAGE was independently associated with increased arterial stiffness in a general population-based sample, but mainly in hypertensive non-diabetic patients. The lack of association in diabetics was probably due to low dispersion of sRAGE values and relatively small number of subjects (9% of the sample).

### 5.3

#### THE INFLUENCE OF SEX AND AGE ON ARTERIAL FUNCTION IN RESPONSE TO AN ACUTE INFLAMMATORY STIMULUS

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**Background:** Aging is associated with increased arterial stiffness and chronic low-grade inflammation. Acute inflammatory stimulus in the presence of low-grade chronic inflammation briefly increases the risk of cardiovascular events. The risk of cardiovascular events also increases substantially in older compared to younger women, therefore the relationship between sex and aging is important to understand.

**Purpose:** To describe the differential effects of age following induced systemic inflammation on arterial function, endothelial function, and wave reflection.

**Method:** Healthy volunteers aged 18–35 yrs ( $n = 18$ ,  $\approx 26$ yr, male = 6) or 55–75 yrs ( $n = 21$ ,  $\approx 64$ yr, male = 9) participated. Ultrasound of the common carotid and brachial artery was performed, Beta-stiffness ( $\beta$ ) and flow mediated dilation (FMD) were calculated. Aortic mean arterial (aMAP), pulse wave analysis with wave separation, pulse wave velocity (PWV) measurements were obtained in the supine position at rest using applanation tonometry. Participants received an influenza vaccine to induce acute inflammation following baseline measurements and returned for 24-hour follow-up.

**Results:** C-reactive protein and interleukin-6 increased pre-to-post similar in all groups ( $p < 0.05$ ).  $\beta$  was higher for older adults pre/post. ( $p < 0.05$ ). Older males exhibited decreased MAP and reflected wave pressure (RP), but increased PWV following vaccination ( $p < 0.05$ ). However, FMD significantly decreased only in young males.

**Conclusion:** The results suggest that differential responses occur between young and older adults and between males and females in response to acute inflammation. Although inflammation increased similarly, inflammation had limited effects on vascular function in both young and old females, suggesting there are significant sex effects for arterial function in response to acute inflammation.

### 5.4

#### MATRIX GLA PROTEIN IN RELATION TO LEFT VENTRICULAR DIASTOLIC FUNCTION

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**Introduction:** Matrix Gla Protein (MGP) is highly expressed in cardiomyocytes and is upregulated after acute and chronic pressure overload and in myocardial hypertrophy in mice and humans. However, no study addressed the relation between cardiac function and MGP in humans.

**Methods and results:** In 767 participants randomly recruited from the Flemish population (51.5% women, mean age 50.6 years), we measured circulating levels of nonphosphorylated and uncarboxylated MGP (dp-ucMGP) and recorded early and late diastolic peak velocities of mitral inflow (E and A) by conventional Doppler and the mitral annular velocities (e' and a') by tissue Doppler imaging. Using principal component analysis, we summarized 7 Doppler indexes - namely, E, A, e' and a' velocities, and their ratios (E/A, e'/a', and E/e') - into a single diastolic score. According to published definitions, 73 (9.5%) participants had impaired relaxation and 114 (14.9%) had elevated LV filling pressure. In the continuous analysis, a doubling of dp-ucMGP is associated with a 6.9% increase in the diastolic score (95% CI 2.7–10.6,  $P < 0.001$ ). No association was seen between systolic function and dp-ucMGP. Multivariable-adjusted odds ratio for a doubling of dp-ucMGP was 0.70 (95% CI 0.50–0.98;  $P = 0.038$ ) for having elevated LV filling pressure. No significant association was seen between impaired relaxation and dp-ucMGP.

**Conclusion:** Higher circulating levels of dp-ucMGP are associated with better LV diastolic function. Pending confirmation in other cohorts and further experimental studies are required to translate our epidemiological findings into underlying molecular mechanisms.

### 5.5

#### MEASUREMENT OF ARTERIAL STIFFNESS BY ULTRAFAST ECHO: COMPARISON WITH ECHOTRACKING IN NORMOTENSIVE SUBJECTS AND HYPERTENSIVE PATIENTS

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Because measurement of arterial stiffness is highly dependent on blood pressure (BP), methods independent of BP are required. Ultrafast echography (UFE, Supersonic Imagine, Aix en Provence, France) makes use of very fast sampling rate (up to 10 kHz), so transient events such as pressure wave arrival can be tracked. This method has never been tested against classical echotracking (Artlab, Esaote, Maastricht, NL) and carotid-femoral pulse wave velocity (cf-PWV, Sphygmocor, AtCor, Sydney, Australia).

We included 56 subjects, 27 normotensives (NT) and 29 essential hypertensives (HT), matched for age and sex. We optimized UFE algorithms for pressure wave detection and tracking, for both foot of the wave (FW) and dicrotic notch (DN) PWV.

Feasibility appears good (FW: 78%, DN: 96%). The relations of arterial stiffness with age and blood pressure were stronger for echotracking and cf-PWV than for UFE. DN wave fronts appeared better associated with cf-PWV ( $r = 0.32$ ,  $p < 0.001$ ) and carotid PWV ( $r = 0.47$ ,  $p < 0.001$ ). FW was not associated with cf-PWV nor with carotid PWV. The residuals between DN and carotid PWV were not associated with BP or age. Similar associations between DN and cf-PWV/carotid PWV were found in NT and HT.

**Conclusion:** After optimizing algorithms for wave front identification and tracking, UFE appears as a promising technique for assessing arterial stiffness. DN showed the best associations with echotracking, whereas FW did not provide meaningful data. As previously shown by Hermeling et al (J Hypertens 2008 and 2009), FW is not appropriate for local stiffness measurement likely because of very early wave reflections.

### 5.6

#### ASSOCIATION BETWEEN ENDOGENOUS SERUM TESTOSTERONE CONCENTRATIONS AND AORTIC PRESSURES AND PULSE WAVE AMPLIFICATION INDICES IN ERECTILE DYSFUNCTION PATIENTS

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**Purpose:** Erectile dysfunction (ED) is an independent predictor of future cardiovascular (CV) events. Aortic pressures (central) and low testosterone independently predict future CV events and mortality. The relationship