



## Artery Research

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### **06.06: EVIDENCE OF AUGMENTATION OF SYSTOLIC CORONARY BLOOD FLOW BY RETROGRADE WAVE REFLECTION TRAVELLING-BACK FROM THE PROXIMAL AORTA**

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were assessed by Echo-Doppler. Early and late diastolic mitral annulus longitudinal velocities (E' and A') were assessed by tissue velocity imaging. AS was estimated by carotid-femoral pulse wave velocity (PWV).

**Results:** compared to controls, patients had higher ( $p < 0.05$ - $0.001$ ) PWV ( $9.4 \pm 2$  vs  $8.0 \pm 1$  m/s) and lower transmitral E/A ratio ( $1.2 \pm 0.5$  vs  $1.4 \pm 0.4$ ,  $p < 0.01$ ); no significant differences were found for LV midwall shortening ( $116 \pm 13$  and  $119 \pm 13\%$ ), and EF ( $67 \pm 6$  and  $69 \pm 5\%$ ). In the overall population, transmitral E/A correlated inversely ( $p < 0.01$ ) with age ( $r = -0.60$ ), SBP ( $r = -0.37$ ), DBP ( $r = -0.50$ ), LVMI ( $r = -0.43$ ), and PWV ( $r = -0.51$ ). In multivariate analysis, PWV remained independent predictor of E/A, together with age, SBP and DBP (adjusted  $R^2$  0.43,  $p < 0.05$ ). E'/A' showed a similar correlation pattern as E/A. **Conclusion:** in subjects free of CV disease and with preserved LV systolic function, AS affects LV diastolic filling and longitudinal myocardial velocities independently of age, LVM and BP.

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#### 06.03

### COLLAGEN ACCUMULATION IS A SIGNIFICANT CONTRIBUTOR TO PULMONARY HYPERTENSION-INDUCED LARGE ARTERY STIFFENING

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Hypoxic pulmonary hypertension (HPH) leads to large pulmonary artery (PA) stiffening, which affects right ventricular afterload. We hypothesized that vascular collagen accumulation is the major cause of large PA stiffening in HPH. The hypothesis was tested with transgenic mice that synthesize collagen type I resistant to collagenase degradation (Col1a1<sup>R/R</sup>) and wild-type controls. Animals were exposed to hypoxia for 10 days and then allowed to recover. Main PAs were harvested for mechanical and biochemical tests. Effects of smooth muscle cells (SMCs) were examined using the vasoactive agents U46619 and Y27632. Pressure-diameter testing showed that left PAs of both Col1a1<sup>R/R</sup> and wild-type mice stiffened with hypoxia ( $p < 0.01$ ). Measurement of hydroxyproline biochemically confirmed that PA collagen content increased as well ( $p < 0.01$ ). After recovery, wild-type PAs were less stiff ( $p < 0.01$ ), whereas Col1a1<sup>R/R</sup> PAs remained stiffened; biochemically, collagen content tended to decrease in both strains although less so in the Col1a1<sup>R/R</sup>. Interestingly, after hypoxia, Col1a1<sup>R/R</sup> PAs were less stiffened than those of wild-type mice. We speculate that differences in mean PA pressure during the 10 days of hypoxia between strains are responsible. Consistent with our hypothesis, Col1a1<sup>R/R</sup> PAs also accumulated less collagen in response to hypoxia than wild-type mice. In the recovery group, stiffness and collagen content were comparable between strains. Quantitation for elastin showed no significant differences between groups. No significant differences between exposures and strains were observed in the mechanical effects of SMCs. The correlation between mechanical and biological properties suggests that collagen accumulation is critical to HPH-induced PA stiffening.

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#### 06.04

### THE COMBINED EFFECT OF HIGH PULSE WAVE VELOCITY AND AUGMENTATION INDEX PREDICTS MORTALITY IN AN ELDERLY POPULATION: THE PROTEGER STUDY

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**Objective:** Carotid – femoral aortic stiffness (PWV) and pressure wave reflections (AI), both markers of cardiovascular mortality, are considered to increase in parallel. A disassociation between PWV and AI has been described. In a cohort (PROTEGER study) of old population ( $85.4 \pm 0.5$ ) has been previously observed that neither PWV nor AI, were predictors of mortality. The aim of the present analysis was to investigate the association between PWV and AI as well as their combined effect on mortality.

**Methods:** Pulse wave analysis was applied in 259 subjects for the assessment of PWV and AI. The population was divided and analyzed according to tertiles of PWV and AI.

**Results:** Eighty-seven subjects died during the follow up (2 years). No association was found between PWV and AI. The subjects with combined high PWV (3<sup>rd</sup> tertile) and high AI (2<sup>nd</sup> and 3<sup>rd</sup> tertiles) [group a] had significantly higher mortality compared to the rest of the population [group b] (27/56: 48.6% vs 61/203: 30.1%,  $p < 0.05$ , Kaplan Mayer log-rank  $p = 0.003$ ). No significant differences

were found between group a and b regarding cardiovascular (CV) risk factors. Cox regression analysis showed that group a had higher mortality independently from age, gender, cardiovascular (CV) history and classical CV risk factors.

**Conclusion:** PWV and AI were not independent predictors of mortality. However, those subjects with combined increase of PWV and AI have higher mortality suggesting that: (i) the effect of PWV is more prominent in the presence of increased AI and (ii) that the disassociation between PWV and AI may be related to reduced mortality.

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#### 06.05

### PULSE WAVEFORM CHARACTERISTICS OR CENTRAL PRESSURE INDICES TO PREDICT ADVERSE CARDIOVASCULAR OUTCOMES IN CORONARY PATIENTS

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**Background:** Pulse waveform characteristics (Augmentation Index – AIx, Pressure Augmentation – AP, Pulse wave transit time – Tr) as well as central pressure indices (aortic pulse pressure – aoPP, pulse pressure amplification – PPamp, pulsatility – aortic PP/mean blood pressure) have been shown to predict cardiovascular events. We aimed to determine their relative predictive value.

**Methods:** We prospectively assessed AIx, AIx@75, AP, Tr as well as aoPP, PPamp and pulsatility, using radial applanation tonometry and a validated transfer function, in 520 male patients undergoing coronary angiography. Primary endpoint was a composite of all cause mortality, myocardial infarction, stroke, cardiac, cerebrovascular and peripheral revascularization. Statistics used were Cox proportional hazards regression models.

**Results:** Mean age was 63 years, 66.7% were hypertensives, 79.2% had CAD. During a follow up of 49.4 months, 170 patients reached the primary endpoint.

All pressure waveform characteristics and central pressure indices predicted the primary endpoint: When divided into tertiles according to the various indices, patients in the first tertile had an unadjusted HR for the combined endpoint of 0.477 (0.328-0.727) for AIx, 0.492 (0.339-0.744) for AIx@75, 0.468 (0.314-0.698) for AP, 0.435 (0.302-0.647) for Tr, 0.468 (0.331-0.685) for aoPP, 0.586 (0.406-0.858) for PPamp, and 0.585 (0.407-0.839) for pulsatility, when compared to patients in the third tertile. However, after adjustment for age, extent of coronary disease, and brachial blood pressures, only AIx, AIx@75, and Tr remained significant predictors of the combined endpoint.

**Conclusion:** In male patients undergoing coronary angiography, pulse waveform characteristics, but not central pressure indices, consistently and independently predict cardiovascular events.

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#### 06.06

### EVIDENCE OF AUGMENTATION OF SYSTOLIC CORONARY BLOOD FLOW BY RETROGRADE WAVE REFLECTION TRAVELLING-BACK FROM THE PROXIMAL AORTA

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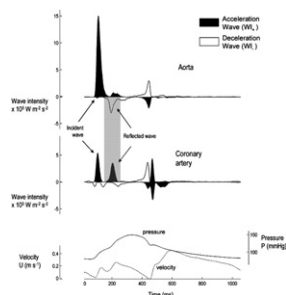
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**Background:** It has been proposed that blood flow in coronary arteries is augmented by waves travelling-back from the distal aorta. However, these waves have never been identified. We used wave intensity analysis to time and quantify reflected waves travelling from the proximal aorta into coronary arteries, and assess their contribution to changes in coronary blood flow with ageing and hypertension.

**Method and Results:** In 19 subjects (age 35-73 years) sensor-tipped intra-arterial wires were used to measure pressure and Doppler velocity in the coronary arteries and at proximal aortic root. Separated wave intensity analysis was used to identify and quantify incident and reflected waves. The reflected wave in the proximal aorta occurred in systole in all subjects ( $159 \pm 12$ ms after the ECG-R-wave) and could be seen later in the coronary arteries: left main stem ( $186.8 \pm 10.7$  ms), circumflex ( $188.8 \pm 7.4$  ms) and left anterior descending ( $194.4 \pm 7.7$  ms). In the coronary arteries the mean reflected wave represented  $20.3 \pm 2.1\%$  of the incident wave magnitude, and elicited a  $38.9 \pm 8.4\%$  instantaneous increase in systolic coronary blood flow velocity ( $0.2$  to  $0.28$  m/s,  $p < 0.002$ ). This augmentation was seen to increase with increasing age ( $r = 0.51$ ,  $p < 0.03$ ), probably

due to an increase in aortic stiffening (pulse wave velocity,  $r=0.77$ ,  $p<0.001$ ). **Conclusions:** Reflected wave can be followed travelling-back from the proximal aorta into the coronary arteries. These reflected waves augment coronary systolic blood flow. With increasing age the degree of augmentation of systolic coronary blood flow is increased.



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### 07.01

#### OUTWARD HYPERTROPHIC REMODELING AND INCREASED CAROTID ARTERY WALL STIFFNESS IN PATIENTS WITH RUPTURED INTRACRANIAL ANEURYSMS

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Because an underlying arteriopathy might contribute to the development and rupture of intracranial aneurysms (IAs), we assessed the elastic properties of proximal conduit arteries in 27 patients with antecedent of ruptured IAs (delay:  $4.8\pm 0.6$  years) and 27 control subjects. Arterial pressure, diameter, intima-media thickness (IMT), circumferential wall stress (CWS) and elastic modulus were determined in the common carotid arteries using applanation tonometry and echotracking. Moreover, carotid augmentation index (AIx) and carotid-to-femoral pulse wave velocity (PWV) were assessed.

Compared to controls, patients with IA exhibit higher carotid systolic ( $108\pm 2$  vs.  $122\pm 3$  mmHg), diastolic ( $73\pm 1$  vs.  $81\pm 1$  mmHg) and pulse pressures ( $35\pm 1$  vs.  $41\pm 2$  mmHg), an increased IMT ( $0.55\pm 0.01$  vs.  $0.64\pm 0.01$  mm, all  $P<0.01$ ) without difference in diameter. IMT was correlated with pulse pressure in controls ( $r=0.539$ ,  $P<0.001$ ) but not in patients ( $r=0.152$ ,  $P=0.2$ ). Despite a similar CWS between groups, patients display an increased elastic modulus ( $0.21\pm 0.02$  vs.  $0.37\pm 0.03$  kPa. $10^3$ ,  $P<0.001$ ). These increased IMT and modulus were still observed in patients matched with controls for carotid arterial pressures ( $n=17$  in each group). Furthermore, patients with IAs have higher PWV ( $7.8\pm 0.2$  vs.  $8.3\pm 0.2$  m. $s^{-1}$ ,  $P<0.05$ ) which contributes to the increase in arterial wave reflections (AIx:  $15.8\pm 2.1$  vs.  $21.1\pm 1.6\%$ ,  $P<0.05$ ) and thus in systolic and pulse pressures.

This study demonstrates that patients with IAs display a particular carotid artery phenotype with a partly pressure-independent outward hypertrophic remodeling and altered elastic properties which might contribute together with the fatiguing effect of increased pulsatile stress on the arterial wall, to the pathogenesis of IAs.

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### 07.02

#### TOWARDS NON-INVASIVE ASSESSMENT OF RENAL ARTERY STENOSIS SEVERITY IN THE INDIVIDUAL PATIENT WITH THE AID OF NUMERICAL COMPUTER SIMULATIONS

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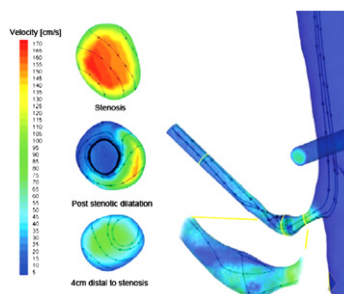
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**Introduction:** Severe renal artery stenosis is responsible for 5% of all hypertension cases. Treatment of the stenosis is often decided upon catheterisation, with a pressure gradient (DP) of 10mmHg used as cut-off, thus requiring invasive measurements. The aim of the present study was to

assess the feasibility and accuracy of a non-invasive estimate of DP through numerical simulation in a patient-specific model.

**Methods:** We constructed a computer model of the abdominal aorta, coeliac trunk, mesenteric superior aorta and two renal arteries from a patient with unilateral renal stenosis (77% area stenosis). Images were obtained from MR angiography scans and segmented to obtain the 3D patient-specific model. Blood flow was simulated assuming an aortic inflow rate of 2.7l/min and prescribed outflow rates at the different arterial outlets. The calculated DP was compared to in vivo measurements.



**Results:** The numerical calculations yielded a DP of 11.7mmHg, which was in excellent agreement with the value of 10.5mmHg measured in vivo in the same patient (with pressure guide-wires) and with values measured in a silicon hydraulic bench model of the same geometry. A parameter study demonstrated a rapid increase in DP beyond 60% stenosis. In the post-stenotic dilatation zone, secondary flow patterns with recirculation were observed. **Conclusion:** These promising results demonstrate the feasibility and utility of patient-specific computer simulations in the diagnosis of individual patients, although further steps will be necessary to include pulsatile blood flow, distensible walls and patient-specific boundary conditions.

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### 07.03

#### FETUIN-A IS INDEPENDENTLY ASSOCIATED WITH PROGRESSIVE AORTIC STIFFNESS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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**Background:** There is a disproportionate burden of vascular disease in patients with chronic kidney disease (CKD). Both aortic stiffness, as measured by carotid-femoral pulse wave velocity (C-F PWV), and deficiency in inhibitors of vascular calcification, such as Fetuin-A, have been implicated in the higher rates of cardiovascular mortality observed in this population. We sought to determine whether Fetuin-A concentration was inversely associated with progressive aortic stiffness.

**Methods:** 54 stable outpatients enrolled in a prospective cohort study of cardiovascular risk in CKD stages 3 and 4 underwent measurement of C-F PWV using Complior under standardized conditions at baseline and 12 months. Baseline plasma Fetuin-A concentration was determined using the Biovendor ELISA kit.

**Results:** The population was aged  $68.0\pm 10.4$  years, 80% male, 11% diabetic with a mean eGFR of  $32.0\pm 11.5$ . Baseline Fetuin-A did not correlate with patient age, eGFR, mean arterial blood pressure, albumin, calcium-phosphate product, parathyroid hormone or CRP. Baseline Fetuin-A was inversely correlated with the change in PWV over 1 year ( $\rho=-0.52$ ,  $p<0.001$ ). After adjustment for change in mean arterial pressure between visits, age, eGFR and presence of diabetes the correlation was maintained ( $r_p=-0.54$ ,  $p<0.001$ ). Using stepwise multiple linear regression with a model including age, change in eGFR, parathyroid hormone, CRP and diabetic status, Fetuin-A was the only independent predictor of change in aortic stiffness adjusted for change in MAP ( $\beta$ -coefficient  $-0.61$ ,  $p<0.001$ ;  $R^2$  total 0.36).

**Conclusion:** In a cohort of patients with CKD stages 3 and 4 there is an independent negative association between Fetuin-A and progressive aortic stiffness.

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