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1.7: TLR4 SIGNALING MEDIATES SBP INCREASE WITH AGE—A TRANSLATIONAL INVESTIGATION

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Background: Atherosclerotic plaque development is associated with increased oxidative stress, that promotes angiogenesis, lipid oxidation and uptake, and ensues cell death. In addition, biomechanical stress, i.e. blood-pressure variations with every heart beat, may further enhance plaque vulnerability. Ivabradine, a heart-rate lowering drug, is associated with reduced oxidative stress and diminished atherosclerotic plaque formation in mice, yet its role on plaque microvasculature and biomechanical stress is unknown.

Methods: Endothelial denudation (balloon-injury) was performed on the abdominal aorta of 18 New-Zealand-rabbits fed with a high cholesterol diet for 14 weeks. Nine rabbits received ivabradine (17 mg/kg/d) within drinking water throughout the study. Dynamic contrast-enhanced MRI was performed to quantify plaque size and microvasculature (area-under-time-concentration curve, AUC). Blood pressure and relative distension were measured using a pressure catheter and high frame-rate ultrasound.

Results: Systolic, diastolic, and pulse pressure, and (relative) distension were similar between the ivabradine and control group (all $p > 0.25$). But, due to 15%-reduction in heart-rate ($p = 0.03$), the accumulated biomechanical stress on the plaque is lower in the ivabradine group. MRI plaque size was similar between the groups ($p = 1.0$). AUC was 25% lower for ivabradine-treated animals ($p = 0.03$). Linear regression showed a negative trend between heart-rate and AUC when adjusting for ivabradine ($p = 0.1$).

Discussion: Ivabradine led to lowered AUC on MRI, indicating decreased plaque microvasculature, which is thought to be an important determinant of reduced plaque vulnerability. Ivabradine did not lead to reduced plaque size, despite reduced accumulated biomechanical stress. Upcoming histological analysis might further unravel the effect of ivabradine on atherosclerosis.

1.6

AUGMENTATION PRESSURE INDEPENDENTLY ASSOCIATES WITH TIME TO PEAK SYSTOLIC MYOCARDIAL WALL STRESS

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Background: Central augmentation pressure (AP), an important component of central pulse pressure may be influenced by ventricular dynamics. We examined whether AP relates to time to peak systolic myocardial wall stress (MWS) independently of age, gender, body surface area (BSA), systolic blood pressure (SBP) and heart rate (HR) in subjects with a wide range of blood pressure.

Methods: We studied 133 subjects, evaluated for hypertension but otherwise free of clinically apparent cardiovascular disease aged 47.2 ± 16.9 (mean \pm SD) years with mean systolic blood pressure of 137 ± 21 mmHg. Carotid pressure, obtained by tonometry calibrated from peripheral mean and diastolic BP, was used to calculate AP (difference between the second and first systolic peaks of the aortic waveform). MWS, a function of left ventricle (LV) pressure, myocardial wall volume and cavity volume was obtained using carotid tonometry to estimate LV pressure and 2D transthoracic echocardiographic wall tracking analysis (Tomtec).

Results: Time to peak MWS increased as AP increased: 76.0 ± 2.4 , 87.4 ± 6.4 and 109.9 ± 7.4 ms (means \pm SE) for first, second and third tertiles of AP respectively ($p < 0.001$). After adjustment for age, gender, BSA, HR and SBP, time to peak MWS still positively associated with AP (standardized $\beta = -0.19$, $p < 0.001$).

Conclusions: Higher AP is associated with prolonged initial ventricular contraction in generating of peak MWS, independently of age, gender, BSA, HR and SBP. These results do not determine the direction of causality between AP and ventricular dynamics but are consistent with ventricular dynamics being a determinant of AP.

1.7

TLR4 SIGNALING MEDIATES SBP INCREASE WITH AGE—A TRANSLATIONAL INVESTIGATION

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Background: Systolic blood pressure (SBP) increases steadily with age. More than 50% of people aged 60+ are hypertensive. One suspected pathomechanism of SBP increase with age is aortic stiffness reflecting vascular aging. Oxidative stress contributes to aortic stiffness. An important regulator of oxidative stress is Toll-like receptor 4 (TLR4). We hypothesized that life-

long TLR4 mediated oxidative stress increases aortic stiffness and contributes to SBP increase with age.

Methods: We investigated adult (3-6 months of age) aged (9-12 months of age) and advance aged (15-18 months of age) male C57Bl/6j and TLR4 null-mice mice. We assessed SBP, aortic stiffness (aortic pulse wave velocity, aPWV) and aortic oxidative burden with malondialdehyde (MDA) in aging. In a translational study we analyzed in a cohort of 2679 patients with myocardial infarction the effect of TLR4 896A/G single nucleotide polymorphism on SBP, pulse pressure and hypertension in dependency on age.

Results: C57Bl/6j and TLR4 null-mice had in adulthood similar SBP, aPWV and similar oxidative burden. During aging in C57Bl/6j mice SBP, aPWV and MDA increased (15mmHg, 2m/s, 30%, respectively). Aged TLR4 null-mice did not show these changes. In the upper age tertile of the patient cohort (age > 70 years), patients with a TLR4 896A/G single nucleotide polymorphism had lower SBP and pulse pressure (7mmHg) and less hypertension (79% versus 60%). The TLR4 SNP remained a significant predictor for SBP in univariate and multivariate regression analysis.

Discussion: We propose that TLR4 signaling participates in SBP increase with age by inducing vascular aging.

2.1

24 HOUR CENTRAL AMBULATORY BLOOD PRESSURE: USUAL VALUES AND RELATIONSHIP WITH MARKERS OF CARDIOVASCULAR RISK

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Brachial ambulatory blood pressure monitoring (ABPM) provides greater predictive value for cardiovascular (CV) events than clinic blood pressure (BP). However, 24hour ambulatory central BP (central ABPM) may be more closely related to surrogate markers of CV risk than brachial ABPM. The aims of this study were to determine usual values of central ABPM in apparently healthy, unmedicated individuals and to determine whether these relate to two established markers of CV risk, left ventricular (LV) mass and carotid intima-media thickness (cIMT).

24hour brachial and central ABPM was undertaken in 730 healthy individuals aged 18-88 years, using the Mobil-O-Graph device, together with clinic-based measurements of BP. A sub-set of individuals underwent assessment of LV mass ($n = 356$) and cIMT ($n = 483$), by ultrasound.

Central pulse pressure (PP) increased and PP amplification decreased significantly at night ($P < 0.001$ for both). Daytime central, but not brachial, ABPM was significantly and independently associated with cIMT ($R^2 = 0.37$, $P = 0.01$) and, in general, correlations between central or brachial ABPM parameters and cIMT were stronger in younger (≤ 50 years) than older individuals. The association between 24hour central ABPM and LV mass was of borderline significance ($R^2 = 0.16$, $P = 0.05$). However, the associations between central or brachial ABPM parameters and LV mass were only significant in older individuals.

The variation in PP amplification within individuals over 24hours, indicates that brachial and central BPs are differentially affected by the activities of daily living. Moreover, central, rather than brachial ABPM is more strongly related to surrogate markers of CV risk.

2.2

DETERMINATION OF THE RESTENOSIS DEGREE INSIDE THE IMPLANTED STENT WITH INTEGRATED WIRELESS PULSE WAVE VELOCITY (PWV) SENSOR

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Patients with implanted stents were often (approx. 30 %) faced with the restenosis. By now no alternative to clinical examination is known to get a quick diagnosis for the actual state of possible and probable in-stent-restenosis. At Fraunhofer IPA in Stuttgart a simple method to measure and to determine the restenosis degree was invented and implemented. The Proof of principle was conducted on the experimental rig on an artery model. The approach is based on an inductive coupling between the external detection unit and implanted sensors. Two passive sensors were integrated in a stent and consist of a capacitive pressure sensor and an air-coil. Connected they form an oscillating circuit, the resonance frequency of which functionally depends on the local pressure. The extra-corporal detection unit generates an alternating magnetic field by 35 MHz. The spreading pulse wave changes the resonance frequency of the passive oscillating circuits inside the vessel.