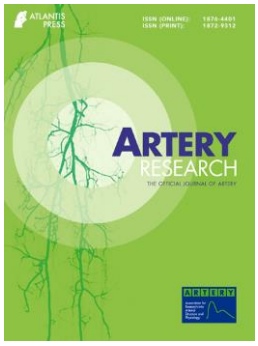

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2.2: DETERMINATION OF THE RESTENOSIS DEGREE INSIDE THE IMPLANTED STENT WITH INTEGRATED WIRELESS PULSE WAVE VELOCITY (PWV) SENSOR

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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 it's 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 ± 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±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 (≤50years) 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.

The short resonance inside the sensor circuit crosses the frequency of the externally applied field and shifts the impedance measured at the excitation coil. As the distance between the two sensors is known the PWV can be determined. The stiffer or the narrower a vessel is the higher is the PWV. A model based approach determines out of the PWV signal the restenosis degree inside the implanted stent. All further measurements are referenced to the first initial value done after the stent implantation. This approach is robust and has mean cross dependences because no absolute pressure measurement is required.

2.3
LOCAL STIFFNESS OF THE CAROTID ARTERY IS ASSOCIATED WITH INCIDENT CARDIOVASCULAR EVENTS AND ALL-CAUSE MORTALITY—A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: It has been suggested that local carotid stiffness is independently associated with cardiovascular (CV) events and mortality. However, consistent evidence for such an association is lacking. We therefore performed a systematic review and meta-analysis of longitudinal studies on the association between local carotid stiffness, incident CV events and all-cause mortality.
Methods: Medline and Embase were searched for articles published up to June 1, 2014. All studies were included which evaluated the association between local carotid stiffness (as determined by ultrasonography) on the one hand and incident CV events and mortality on the other. We used random-effects models to calculate hazard ratios (HRs) and 95% confidence intervals (95%CIs) for pooled data.
Results: We included 10 studies with data for 19,919 participants and 177,136 person-years of follow-up. The pooled HRs (95%CIs) for one SD higher carotid elastic modulus were: for CV events (fatal and nonfatal combined) 1.19 (1.06-1.33; 10 studies, n=19,496); for CV mortality 1.34 (1.15-1.55; 4 studies, n=3,083) and for all-cause mortality 1.26 (1.14-1.40; 5 studies, n=3,501). All results were adjusted for age, sex, blood pressure (SBP and/or MAP), and CV factors. Results were qualitatively similar when HRs were pooled for lower carotid distensibility and compliance instead of higher elastic modulus.
Conclusion: The present meta-analysis shows a strong association between local carotid stiffness and incident CV events, CV mortality and all-cause mortality. In a next step, we will do an individual participant meta-analysis to evaluate whether the association between local carotid stiffness and CV events and mortality is independent of carotid-femoral pulse wave velocity.

2.4
RELATIONSHIP BETWEEN ADULT TRANSFER FUNCTION DERIVED CENTRAL AORTIC SYSTOLIC PRESSURE AND MEASURED SYSTOLIC PRESSURE IN THE HEALTHY CHILDREN POPULATION

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Background: A non-invasive method, that used a general transfer function (TF), has been shown to accurately predict central aortic pressure from peripheral tonometry measurements in the adult population. However applying the same TF to estimate central aortic systolic pressure (aSP) in children has not yet been fully evaluated. This study aimed to assess the usage of adult TF to estimate aSP in children (aSP_{est_ch}) by establishing and testing different linear single/multivariate regression models between the adult TF estimated aSP (aSP_{TF_ad}) and the measured aSP (aSP_{meas_ch}).
Methods: 218 healthy, pre-pubescent children aged 8 years (113 male) had tonometer measured radial and carotid arterial pressure waveform recorded using the SphygmoCor device. Central aSP_{TF_ad} was estimated from the radial pressure using the TF (SphygmoCor, AtCor Medical), and the carotid systolic pressure taken as a surrogate for central pressure (aSP_{meas_ch}). The study group was divided into two groups: one to estimate the models (n=50, 19 male); another to test the models (n=168, 94 male). Models 1 and 2 were two simple linear regression models, whilst models 3 and 4 were two multivariate regression models.
Results: In the tested group, the aSP_{est_ch} from all models showed high correlations and low average differences with aSPmeas_ch (model 1 $R^2=0.88$, difference=1.6+2.6 mmHg; model 2 $R^2=0.88$ difference=1.8+3.4 mmHg; model 3 $R^2=0.89$ difference=-0.7+2.5 mmHg; model 4 $R^2=0.89$ difference=-1.2+2.7 mmHg, all $p<0.0001$).
Conclusion: Central aSP in children can be estimated accurately using the adult TF from the radial pulse by incorporating the now defined linear relationship between aSP_{TF_ad} and aSP_{meas_ch}.

2.5
COMPARISON OF NON-INVASIVE AND INVASIVE MEASUREMENTS OF CENTRAL BLOOD PRESSURE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Background: The blood pressure (BP) in the ascending aorta can be estimated non-invasively by pulse wave analysis using commercially available devices such as the SphygmoCor. However, this device has not been validated for use in patients with chronic kidney disease (CKD).
Objectives: Comparison of non-invasively obtained estimates of central BP with invasively measured central BP in CKD patients.
Methods: Patients with stable CKD stage 3-5 corresponding to an estimated glomerular filtration rate (eGFR) under 60 ml/min undergoing elective coronary angiography were included. Central BP was estimated by the SphygmoCor using four different calibrations: Invasive aortic diastolic and mean BP (invasive), systolic and diastolic brachial BP (sys-dia), brachial diastolic and mean arterial BP (form factor 0.33) (ff-0.33), and brachial diastolic and mean arterial BP (form factor 0.4) (ff-0.4). Brachial artery BP was measured simultaneously with a validated oscillometric BP device.
Results: Forty-nine patients, 65% males, age 61±13 (mean±SD) with a median eGFR of 18 ml/min (range 5-59 ml/min) were enrolled. Invasive BP was 150.8±22/ 75.4±11 mmHg while brachial BP was 147.3±19 /86.0±10 mmHg (mean differences: -3.6±9.3/10.6±7.9 mmHg ($P<0.012$).
Mean differences (invasive minus estimated central BP) with the four calibrations used were: -5.9±6.1/1.3±1.0 mmHg, $P<0.001$ (invasive); -16.0±9.3/11.5±8.0 mmHg, $P<0.001$ (sys-dia); -17.5±10.5/11.5±7.9 mmHg, $P<0.001$ (ff-0.33); -7.5±10.2 /11.6±7.9 mmHg, $P<0.001$ (ff-0.4).
Conclusion: In CKD patients, we found a systematic difference between estimated and invasively measured central BP. Surprisingly, brachial systolic BP was very close to invasively measured central systolic BP and was even more accurate than estimates based on calibration with invasively obtained BP.

2.6
NON-INVASIVE ESTIMATION OF EXERCISE CENTRAL BLOOD PRESSURE BY RADIAL TONOMETRY MAY BE UNDERESTIMATED DUE TO BRACHIAL-TO-RADIAL-SYSTOLIC-BLOOD-PRESSURE-AMPLIFICATION AND IS RELATED TO UPPER LIMB BLOOD FLOW VELOCITY

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Objectives: Both central blood pressure (BP) and light-moderate exercise BP are independently associated with cardiovascular risk, and measuring central BP during exercise may have clinical relevance. Brachial-to-radial-systolic-blood-pressure-amplification (B-R-SBP_{AMP}) could influence the accuracy of central SBP estimation by radial tonometry during exercise. This study aimed to determine the influence of light-moderate exercise on B-R-SBP_{AMP} and consequent central SBP estimation. Independent correlates of B-R-SBP_{AMP} were also explored.
Methods: Sixty healthy participants (39±16 years, 50% male) underwent testing during light-moderate intensity (40W, 50RPM) semi-recumbent cycling. SBP was identified by brachial and radial ultrasound (1st Doppler flow inflection = 1st Korotkoff sound during cuff deflation). Haemodynamics were recorded by ultrasound and tonometry. Bra-Rad-SBP_{Amp} was defined as radial minus brachial SBP.
Result: Exercise radial SBP was significantly higher than brachial SBP (144±21 versus 134±17 mmHg; $p<0.001$). Exercise Bra-Rad-SBP_{Amp} was 10±11 mmHg and increased with advancing age ($r=0.360$, $p=0.005$). Exercise central SBP was significantly higher when radial tonometry was calibrated with radial SBP (accounting for Bra-Rad-SBP_{Amp}) versus brachial SBP (117±16 versus 110±13 mmHg, $p<0.001$). Low brachial peak flow velocity relative to radial velocity was negatively associated with exercise B-R-SBP_{Amp} ($r=-0.439$, $p=0.001$), independent of age, sex, heart rate and mean arterial pressure ($\beta=-0.389$, adjusted $R^2=0.273$, $p=0.003$).