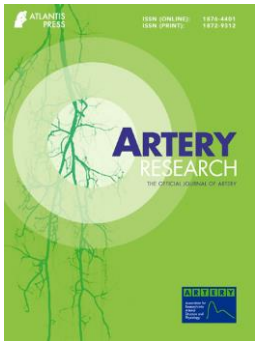

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1.5: THE EFFECT OF IVABRADINE ON PLAQUE SIZE, BIOMECHANICS, AND MICROVASCULATURE IN ATHEROSCLEROTIC RABBITS

E. Hermeling, R.H.M. Van Hoof, J. Salzmann, J.C. Sluimer, S. Heeneman, A. Hoeks, J. Roussel, H. Struijker-Boudier, J.E. Wildberger, M. Eline Kooi

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Oral Presentation Abstracts

1.1
GENOME WIDE ASSOCIATION SCAN IDENTIFIES LOCI FOR ARTERIAL STIFFNESS IN YOUNG HEALTHY ADULTS

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Background: Premature arterial stiffening is an important and independent predictor of cardiovascular risk. Stiffness is heritable, but the precise molecular pathways regulating it are poorly understood. We aimed to identify possible genetic risk loci for arterial stiffness in young healthy adults (<25 years) at low cardiovascular risk, and explore top signals in other populations.
Methods: Demographic and haemodynamic data including aortic pulse wave velocity (aPWV) were recorded. Genome wide association scan (GWAS) was performed in ACCT individuals at extremes of high and low aPWV (n=1200) using Illumina 610K beadarrays. Top 16 signals validated in age matched cohorts (ALSPAC: n=2963; Hyderabad: n=686; and remainder of ACCT: n=910). Taqman and Sequenom SNP assays used for replication studies. SNPs were tested for their association with aPWV after adjusting for covariates.
Results: GWAS analysis revealed a number of SNPs associating with aPWV. Overall, 7 SNPs reached GW significance ($p<10^{-8}$), 41 had threshold values of $p<10^{-7}$ $p<10^{-6}$ and 220 had nominal value of 10^{-5}. The beta value for strongest associations ranged from 0.38 to 0.17 per allele, and overall explained just under 5% of total variance; signals identified mapped to either intronic or intergenic regions. GWAS SNPs were successfully replicated in ALSPAC, Hyderabad and remainder of ACCT. The combined analysis of three studies revealed seven genetic loci associated significantly with aPWV ($p<10^{-9}$).
Conclusions: We identified, several genetic loci that, individually and in aggregate, substantially associate with risk of premature large artery stiffening (LAS). Fine mapping these signals will offer important insights into the patho-physiology of LAS.

1.2
MARINOBUFAGENIN (MBG), AN ENDOGENOUS STEROIDAL NA PUMP INHIBITOR, IS IMPLICATED IN CARDIOVASCULAR TISSUE REMODELING AND IN PRO-FIBROTIC SIGNALING IN OLD DAHL SALT-SENSITIVE (DAHL-S) RATS

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Marinobufagenin (MBG) initiated cardiovascular pro-fibrotic pathway in experimental uremic cardiomyopathy. Fibrosis is a hallmark of aging, so we hypothesized that MBG is a key player in pro-fibrotic signaling in aging. We immunoneutralized heightened MBG levels in **old** (12-mo) Dahl-S with anti-MBG monoclonal **antibody** (**OA**; n=6), and studied the pro-fibrotic gene expression in these rats in comparison to vehicle-treated 12-mo **old control** (**OC**; n=6) and to **young control** (**YC**; 3-mo; n=6) Dahl-S. All animals were kept on a low salt intake after weaning. Antibody was administered 3 times during 10 days to 12-mo old Dahl-S. Following 10 days of treatment, systolic blood pressure (SBP), 24-hr MBG excretion, mRNA expression (qPCR) in left ventricles (LV), and collagen and elastin abundance (histochemistry) in aortic media were assessed. In OC vs. YC, MBG level increased 3.6-folds ($p<0.01$), SBP elevated (175±3 vs. 117±6 mmHg; $p<0.001$), aortic elastin/collagen ratio decreased 3.3-fold, and expression of genes, implicated in TGFβ-signaling in LV were upregulated (TGFβ1 -3-fold; TGFβ2 -8-fold; CTGF-7.5-fold; SMAD4, SMAD5, MAPK3, and Collagen1 - 2-fold), and were down-regulated following immunoneutralization of MBG. The negative regulator of collagen1 synthesis Fli1 was 2-fold down-regulated in OC vs. YC, and restored in OA to the level of Fli1 in YC. In OA vs. OC, SBP decreased (156±5 mmHg; $p<0.05$), and aortic elastin/collagen ratio was normalized. Immunoneutralization of MBG produces anti-hypertensive and anti-remodeling effects associated with normalization of gene expression implicated in TGFβ- and Fli1-pro-fibrotic pathways initiated by MBG in aged Dahl-S. Restoration of elastin/collagen ratio indicates on normalization of vascular function by anti-MBG antibody in aging.

1.3
THE ASSOCIATION BETWEEN CIRCULATING UNDECARBOXYLATED MATRIX GLA PROTEIN AND ARTERIAL STIFFNESS IN GENERAL POPULATION

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Background: Matrix Gla protein (MGP), a natural calcification inhibitor, strongly correlated with the extent of coronary calcification. Vitamin K is the essential cofactor for activation of MGP. We aimed to establish whether there is also any association between dephosphorylated-uncarboxyled isoform of MGP (dp-ucMGP) and pulse wave velocity (PWV) in random sample of general population.
Methods: 1003 general population subjects (a subsample of postMONICA study undertaken in 2008) were analyzed in cross-sectional study. Aortic and peripheral PWV were quantified using Sphygmocor device, dp-ucMGP concentrations form frozen samples by ELISA methods using inaKtif pre-commercial kist developed by VitaK (Maastricht, Netherlands)
Results: Aortic, but not peripheral PWV significantly (with $p<0.0001$) increased among dp-ucMGP quartile. Using multiple logistic regression, subjects in top quartile of dp-ucMGP (≥ 675 pmol/L) shows about two-times higher risk of having high aPWV (≥ 9.3 m/sec) or an absolute increase of PWV by 1 m/sec, even if adjusted for potential covariates (age, history of vascular disease, obesity, raised blood pressure and overt diabetes also entered significantly the regression model).
Conclusion: Increased dp-ucMGP as circulating biomarker of vitamin K status and vascular calcification independently predicts high central-type , large artery stiffness. In contrast, peripheral muscular-type arteries remain uninfluenced.
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1.4
THE AORTIC RESERVOIR-WAVE AS A PARADIGM FOR ARTERIAL HEMODYNAMICS: INSIGHTS FROM 3D FLUID-STRUCTURE INTERACTION SIMULATIONS IN A MODEL OF AORTIC COARCTATION

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The reservoir-wave paradigm considers aortic pressure as the superposition of a "reservoir pressure", directly related to changes in reservoir volume, and an "excess pressure" ascribed to wave dynamics. The change in reservoir pressure is assumed to be proportional to the difference between aortic inflow and outflow (i.e. aortic volume changes), an assumption that is virtually impossible to validate in vivo. The aim of this study is therefore to apply the reservoir-wave paradigm to aortic pressure and flow waves obtained from 3D fluid-structure interaction simulations in a model of (a) a normal aorta, (b) aortic coarctation (narrowed descending aorta) and (c) stented coarctation (stiff segment in descending aorta). We found no unequivocal relation between the intra-aortic volume and the reservoir pressure for any of the simulated cases. When plotted in a pressure-volume diagram, hysteresis loops are found that are looped in a clockwise way indicating that the reservoir pressure is lower than the pressure associated with the change in volume. The reservoir-wave analysis leads to very high excess pressures, especially for the coarctation models, but to surprisingly little changes of the reservoir component despite the impediment of the buffer capacity of the aorta. In conclusion, with the observation that reservoir pressure is not related to the volume in the aortic reservoir in systole, an intrinsic assumption in the wave-reservoir concept is invalidated and, consequently, also the assumption that the excess pressure is the component of pressure that can be attributed to wave travel and reflection.

1.5
THE EFFECT OF IVABRADINE ON PLAQUE SIZE, BIOMECHANICS, AND MICROVASCULATURE IN ATHEROSCLEROTIC RABBITS

E. Hermeling [a,c], R. H. M. Van Hoof [a,c], J. Salzmann [b], J. C. Sluimer [a,c], S. Heeneman [a,c], A. Hoeks [a,c], J. Roussel [b], H. Struijker-Boudier [a,c], J. E. Wildberger [a,c], M. Eline Kooi [a,c]
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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.