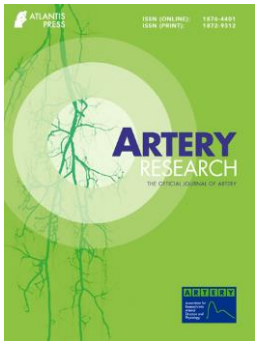

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1.1: GENOME WIDE ASSOCIATION SCAN IDENTIFIES LOCI FOR ARTERIAL STIFFNESS IN YOUNG HEALTHY ADULTS

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Oral Presentation Abstracts

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

Yasmin [a], C. McEniery [a], S. Cleary [a], B. Lam [a], H. Kuper [b], Y. Endo [b], S. Kinra [b], D. Chen [a], G. Chandak [c], J. Deanfield [d], D. Lawlor [e], J. Cockcroft [f], I. Wilkinson [a], K. O'Shaughnessy [a]
[a]*University of Cambridge, Cambridge, UK*
[b]*London School of Hygiene & Tropical Medicine, London, UK*
[c]*Centre for Cellular & Molecular Biology, Hyderabad, India*
[d]*University College London, London, UK*
[e]*Bristol University, Bristol, UK*
[f]*Cardiff University, Cardiff, UK*

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

O. Fedorova, Y. Grigorova, W. Wei, V. Zernetkina, O. Juhasz, E. Lakatta, A. Bagrov
NIH, Baltimore, USA

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

O. Mayer [a], J. Seidlerová [a], J. Filipovský [a], C. Vermeer [b]
[a]*Medical Faculty of Charles University and University Hospital, Pilsen, Czech Republic*
[b]*Maastricht University, Maastricht, The Netherlands*

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

P. Segers, L. Taelman, J. Degroote, J. Bols, J. Vierendeels
Ghent University, Gent, Belgium

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]
[a]*Maastricht University Medical Center, Maastricht, The Netherlands*