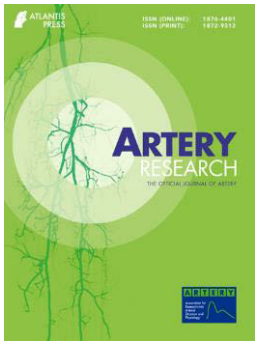

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06.01: THE INFLUENCE OF CARDIOVASCULAR DISEASE AND RISK FACTORS ON AGE-RELATED CHANGES IN AORTIC PULSE WAVE VELOCITY

C.M. McEniery, Y. Yasmin, M. Munnery, S.M.L. Wallace, B. McDonnell, K.M. Maki-Petaja, S. Hickson, J.R. Cockcroft, I.B. Wilkinson

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Background: We investigated in the same subjects, heritability and familial aggregation of various indexes of arterial stiffness and we partitioned the phenotypic correlation between these traits into shared genetic and environmental components.
Methods: Using a family-based random sampling frame, we recruited 204 parents (mean age, 51.7 years) and 290 offspring (29.4 years) from the population in Cracow, Poland (62 families), Hechtel-Eksel, Belgium (36), and Pilsen, the Czech Republic (50). We measured peripheral pulse pressure (PPp) sphygmomanometrically at the brachial artery; central pulse pressure (PPc), the peripheral (PAIx) and central (CAIx) augmentation indexes by tonometry at the radial artery; and aortic pulse wave velocity (PWV) by tonometry or ultrasound. In multivariate-adjusted analyses, we used the ASSOC and PROC GENMOD procedures as implemented in S.A.G.E. and SAS, respectively.
Results: All traits, with the exception of PPc ($P=0.79$) and PWV ($P=0.08$), showed significant heritability ($P\leq0.0001$), ranging from 0.37 for PPp to 0.41 for CAIx. The genetic correlation between PWV and the other arterial indexes were significant ($\rho_G\geq0.29$; $P<0.0001$). The corresponding environmental correlations were only significantly positive for PPp ($\rho_E=0.10$, $P=0.03$). Intrafamilial concordance was significant for all arterial indexes ($r\geq0.12$; $P\leq0.02$), with the exception of PPc ($r=-0.007$; $P=0.90$) in parent-offspring pairs. The sib-sib correlations were also significant for CAIx ($r=0.22$; $P=0.001$).
Conclusion: The observation in the same group of subjects of significant intrafamilial concordance and heritability of various indexes of arterial stiffness as well as the genetic correlations among arterial phenotypes strongly support the search for shared genetic determinants underlying these traits.

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05.03
OSTEOPROTEGERIN IS RELATED TO CAROTID-FEMORAL PULSE WAVE VELOCITY AND SURVIVAL IN HEMODIALYSIS PATIENTS

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Osteoprotegerin (OPG) is a marker and regulator of arterial calcification, and it is related to survival in hemodialysis patients. The link between OPG and aortic stiffening - a consequence of arterial calcification - has not previously been evaluated in this population, and it is not known whether OPG related mortality risk is mediated by arterial stiffening.

At baseline OPG and aortic pulse wave velocity (PWV) was measured in 98 hemodialysis patients who were then followed for a median of 18 months. The relationship between OPG and PWV was assessed by multivariate linear regression. The role of PWV in mediating OPG related mortality risk was evaluated by including both OPG and PWV in the same survival model.

At baseline mean (SD) PWV was 11.2 (3,3) m/s and median OPG (interquartile range) was 11.1 (7.5-15.9) nmol/L. There was a strong positive linear relationship between PWV and lnOPG (beta=1.48, p=0.009), independent of other covariates. During follow-up 28 patients died (mortality rate 18.4/100 patient years). In separate survival models both PWV and lnOPG were related to all cause mortality (hazard ratios 1.21[1.07-1.38] and 5.39 [2.16-13.43], respectively). When both PWV and lnOPG were entered into the same model, only OPG remained significantly associated with mortality (hazard ratios 1.12 [0.97-1.28] and 4.37 [1.62-11.80], respectively).

In hemodialysis patients OPG is strongly related to PWV and OPG related mortality risk may, in part, mediated by increased PWV.

05.04
ACUTE EFFECTS OF PASSIVE SMOKING ON PERIPHERAL VASCULAR FUNCTION

D. Adamopoulos [1], J.F. Argacha [1], M. Gujic [1], N. Amai [1], D. Fontaine [2], G. Berkenboom [1], P. van de Borne [1]. *[1]Department of Cardiology, Erasme Hospital, Brussels, Belgium, [2]Laboratory of Pharmacology and Physiology, Erasme Hospital, Brussels, Belgium*

Background: Environmental tobacco smoke (ETS) acutely affects vascular function through many pathophysiological mechanisms including nicotine sympathoexcitatory effects and oxidative stress. However, a secondary vascular reflex following smoke sensory stimulation cannot be excluded, since the vascular effects of ETS exposure have never been compared to these of a non-tobacco smoke. We therefore tested the hypothesis that acute ETS exposure, when compared to non-tobacco smoke, is responsible for a specific increase in aortic wave reflection and that this is accompanied by an alteration of endothelium dependent microvascular function.
Materials and methods: We examined the vascular effects of one hour ETS exposure, compared to a non-tobacco smoke and a normal-air exposure, in 11 healthy non-smokers men, using a randomized, single blind cross over study design. Augmentation index (AIx), and wave transit time (Tr) have been used to assess aortic wave reflection, while skin microvascular response to a local heating stimulation has been measured with a laser doppler flowmeter to assess endothelial function.
Results: Air particle densities did not differ during the ETS and non-tobacco smoke sessions. We observed no effect of ETS or non-tobacco smoke on central and peripheral blood pressures. However, AIx increased both during ($p=0.01$) and after ($p<0.01$) the ETS session, but remained unchanged in the non tobacco smoke session as compared to normal air. A strong correlation between serum nicotine levels ($n=10$) after ETS exposure and Aix change ($r=0.84$, $p<0.01$) was also noted. Tr decreased both during ($p=0.02$) and after ($p<0.01$) ETS, but remained unchanged in the non tobacco smoke session as compared to normal air. ETS exposure reduced the skin blood flow response to heating ($p=0.03$), which was not seen during the non tobacco smoke and the normal air sessions.
Conclusions: Passive exposure to tobacco smoke increases aortic wave reflection and impairs endothelium dependent microvascular function as compared to passive inhalation of non tobacco smoke. The increase in wave reflection after ETS exposure is strongly related to the rise in serum nicotine levels.

Free Communications

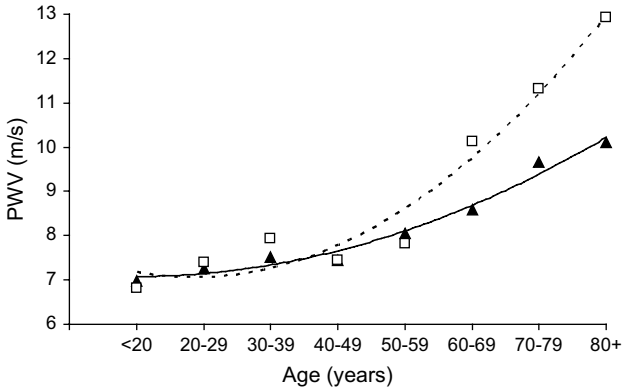
06.01
THE INFLUENCE OF CARDIOVASCULAR DISEASE AND RISK FACTORS ON AGE-RELATED CHANGES IN AORTIC PULSE WAVE VELOCITY

C.M. McEniery [1], Y. Yasmin [1], M. Munnery [2], S.M.L. Wallace [1], B. McDonnell [2], K.M. Maki-Petaja [1], S. Hickson [1], J.R. Cockcroft [2], I.B. Wilkinson [1]. *[1]University of Cambridge, Cambridge, United Kingdom, [2]Wales Heart Research Institute, Cardiff, United Kingdom*

We have demonstrated previously that age-related changes in aortic pulse wave velocity (PWV) are more prominent in individuals over the age of 50 years, suggesting that aortic PWV might provide a sensitive marker of risk in older subjects. Therefore, the aim of this investigation was to assess the impact of cardiovascular disease and risk factors on age-related changes in aortic PWV.

Data from 4219 participants in the ACCT Study[†] cohort were analysed (aged 18-92 years). In all subjects, seated and supine brachial BP was measured following at least 10 minutes of rest. Central (aortic) BP was derived by pulse wave analysis, and aortic (carotid-femoral) and brachial PWV were recorded (SphygmoCor). Subjects were then divided into groups based on the presence of cardiovascular disease ($n=445$) or risk factors: diabetes ($n=311$), hypertension ($n=952$), hypercholesterolaemia ($n=196$) and smoking ($n=318$), leaving 1997 control subjects, all of whom were free of cardiovascular risk factors and medication. Peripheral and central blood pressure and aortic PWV all increased significantly with age ($P<0.001$). However, compared with healthy controls, there was a steeper age-related rise in aortic PWV after the age of 50 years in subjects with cardiovascular disease or risk factors ($P<0.001$, Figure), even after adjusting for differences in mean

pressure. In multivariate analyses, hypertension, diabetes, smoking and the presence of cardiovascular disease were independently associated with aortic PWV (R^2=0.65, P<0.001). In conclusion, aortic PWV appears to be a sensitive marker of cardiovascular risk in individuals aged over 50 years.



Age-related changes in aortic PWV in healthy controls (▲) versus diabetics (□)

† Anglo-Cardiff Collaborative Trial.

06.02

AORTIC AND CAROTID STIFFNESS IN OLDER ADULTS. THE ROTTERDAM STUDY

F.U.S. Mattace-Raso [1], N.M. van Popele [2], A. Hofman [2], J.C.M. Witteman [2]. *[1]Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Department of Epidemiology & Biostatistics, Erasmus University Medical Center, Rotterdam, Netherlands*

The purpose of this study is to describe aortic (aPWV) and carotid stiffness (DC) in older adults according to age, gender and blood pressure. Information on both measures was available for 2766 subjects. The mean value of both aPWV and DC was lower in women than in men. The difference (95% CI) in aPWV was -0.99 (-0.81 to -1.18) (m/s) and the difference in DC was -1.62 (-1.35 to -1.82) (10^{-3}/kPa) for women as compared for men. With aging, both aorta and carotid artery become stiffer but the increase attenuates at high age. Women under 80 years of age had a less stiff aorta and a stiffer common carotid artery as compared to men of the same age. The relations of both measures of arterial stiffness with SBP and PP were non-linear, flattening off at higher levels, whereas the relation with DBP was non-linear and resembled a J-shape. We found a quadratic relationship between DC and aPWV: DC = 27.4 - 1.9 * (aPWV) + 0.04 * $(aPWV)^2$ [p total model ≤ 0.001], (R^2= -0.41, P<0.001). Subjects with increased aortic stiffness had a 30-fold increased risk of also having increased carotid stiffness, OR 31.2 (95% CI 20.9-46.4) (Figure 1).

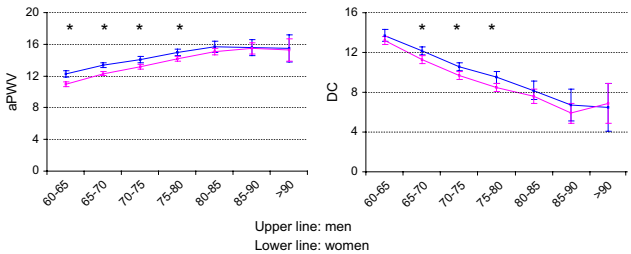


Figure 1. Mean (95% CI) aPWV and DC per 5-years age category in strata of gender. *p < 0.05 for difference between men and women.

06.03

NITRIC OXIDE AND ENDOTHELIUM-DERIVED HYPERPOLARIZING FACTOR REGULATE THE ADAPTATION OF HUMAN CONDUIT ARTERY MECHANICS TO CHANGES IN SHEAR STRESS

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The role of NO and endothelium-derived hyperpolarizing factor (EDHF), synthesized by cytochrome epoxygenases and acting through calcium-activated potassium (KCa) channels, in the flow-mediated regulation of human conduit artery mechanics has never been investigated.

In 11 healthy volunteers, whole blood viscosity, arterial pressure, radial artery diameter, wall thickness and flow (echotracking) were measured during hand skin heating in the presence of saline and the NO-synthase inhibitor, L-NMMA, infused alone and combined with the inhibitors of KCa channels, tetraethylammonium, and cytochrome epoxygenases, fluconazole. Wall shear stress, the flow-dependent stimulus, was calculated (Poiseuillean model). Arterial compliance, elastic wall modulus were calculated and fitted as functions of midwall stress (wall loading conditions) to suppress the confounding influence of changes in geometry.

Heating induced in all cases an increase in radial artery flow, diameter, shear stress and midwall stress and a decrease in wall thickness without change in arterial pressure. The increase in diameter with shear stress was reduced by L-NMMA and, in a more extent, by both combinations. Heating induced an upward shift of the compliance-midwall stress curve and a downward shift of the modulus-midwall stress curve under saline demonstrating an associated decrease in smooth muscle tone and wall stiffness with the shear stress increase. The shifts of these curves were decreased by L-NMMA and abolished by both combinations.

These results demonstrate that NO and EDHF regulate the adaptation of conduit artery mechanics to shear stress variations in humans suggesting the major role of the endothelium in maintaining arterial conductance and adjusted cardiac load.

06.04

NON-ALCOHOLIC FATTY LIVER DISEASE IS ASSOCIATED WITH IMPAIRED SECRETION OF FAT PRODUCED HORMONES AND INCREASED CARDIOVASCULAR RISK

K. Baou [1], C. Vlachopoulos [1], E. Manesis [2], N. Ioakeimidis [1], G. Papatheodoridis [2], J. Koskinas [2], A. Archimandritis [2], C. Stefanadis [1]. *[1]1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece, [2]2nd Department of Medicine, Athens Medical School, Hippokration Hospital, Athens, Greece*

Purpose: Adipocytokines may provide a link between metabolic syndrome, inflammation and cardiovascular disorder in non-alcoholic fatty liver disease (NAFLD) patients. We investigated whether NAFLD is associated with fat produced hormones and if this relation can affect the impaired endothelial structure and function.

Methods: We studied 34 patients (age 55 ± 13 years, 20M) with biopsy evidence of NAFLD, and 34 control subjects adjusted for classical risk factors. The changes in the diameter of the brachial artery were measured in response to reactive hyperemia and nitroglycerin. Mean IMT of common carotid arteries and carotid-femoral PWV were determined as markers of atherosclerosis and aortic stiffness respectively. Adipocytokines were measured by ELISA kit.

Results: NAFLD subjects had significantly reduced flow-mediated vasodilation (1.1 ± 1.9% vs 4.3± 3%, p<0.05), and mean value of carotid IMT (0.98 ± 0.3 vs 0.77 ± 0.2 mm, p<0.05) and PWV (8.4 ± 1.6 vs 7.3 ± 1.7 m/s, p<0.01) were increased compared to controls. NAFLD subjects had increased levels of leptin (21.81± ng/ml vs 12.12 ± 10 ng/ml, p<0.01), and resistin (5.174 ± 1.6 ng/ml vs 3.5 ± 1.28 ng/ml, p<0.01) and reduced levels of adiponectin (7.96 ± 5.19 μg/ml vs 13.17 ± 12.4 μg/ml, p<0.05) compared to controls. After adjustment for confounding factors, resistin levels were independently associated with impaired endothelial function (p<0.05, t=7.53, coefficient st=0.883) and leptin levels were independently associated with the increased mean IMT (p<0.01, t=6.92, coefficient st=0.888), and PWV (p< 0.05, t=2.258, coefficient st=0.32) in NAFLD patients.

Conclusion: Although the initiating events that trigger the development of atherosclerosis in NAFLD patients cannot be ascertained, the role of adipocytokines may identify a potential basis.