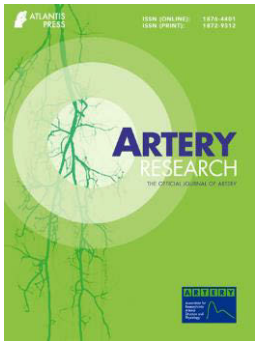

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WALL SHEAR STRESS REVISITED

Robert S. Reneman

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Career Development Lectures

NON-INVASIVE ASSESSMENT OF MECHANICAL PROPRERTIES AND COMPOSITION OF VULNERABLE CAROTID PLAQUES

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Background: Plaque rupture mechanisms are complex processes, which are dependent on plaque morphology and composition and mechanical characteristics. We have previously demonstrated that the higher risk of plaque complication reported in patients with diabetes and hypercholesterolemia may be due to a specific pattern of strain gradient between plaque and adjacent common carotid artery (CCA) (inward bending stress). In addition, previous studies have suggested that plaque echogenicity is related to the histological components of carotid plaques and that carotid plaque echolucency (low echogenicity) is associated with the development of neurological events.
Objective: of our study was to determine the difference in plaque composition according to the presence of an outward or an inward bending stress (ArtLab system) using an in vivo noninvasive approach with a software for videodensitometry analysis, the MIP system (Medical Image Processing, CNR Pisa), which yields the gray levels distribution of a region of interest (ROI).
Patients: The study included 24 patients with a recent cerebrovascular ischemic event and either a plaque on the far wall of CCA. We divided the patients into two groups according to strain behaviour: pattern A (larger strain at the level of plaque than at the level of CCA, outward bending strain), pattern B (plaque strain smaller than CCA strain, inward bending strain). In all patients digital images of plaques were analyzed offline with MIP.
Results: In 16 patients a pattern A and in 8 patients a pattern B strain behaviour were observed. Demographic and hemodynamic characteristics were similar in the two groups. The prevalence of hypercholesterolemia and diabetes were significantly higher in patients with a pattern B strain behaviour (respectively, 100% *vs* 56.3% $p=0.03$ and 62.5% *vs* 12.5%, $p=0.04$). Mean gray levels were significantly lower in patients with an inward bending strain compared to patients with an outward bending strain (65 ± 20 *vs* 95 ± 30, $p=0.018$).
Conclusions: These results suggest that the higher risk of plaque complication, reported in patients with diabetes and hypercholesterolemia, may be due to a specific pattern of strain gradient between plaque and adjacent CCA and to a different plaque composition.

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NEW INSIGHTS INTO CARDIOVASCULAR RISK FROM THE EXERCISE CENTRAL WAVEFORM

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Abstract: Numerous studies in healthy individuals with normal office blood pressure (BP) have shown that a hypertensive response to exercise predicts the future onset of hypertension, as well as cardiovascular morbidity and mortality, independent of office BP. The mechanisms underlying the predictive value of exercise BP are incompletely understood. However, it has been proposed that the additional cardiovascular stress imposed by exercise may unmask the presence of concealed hypertension. A new non-invasive method of exercise arterial pressure waveform analysis (and central BP estimation) may provide additional clinical information, as well as insight into mechanisms, beyond the BP obtained by traditional upper arm cuff methods.

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MacDonald Lecture

WALL SHEAR STRESS REVISITED

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Wall shear stress (WSS), the drag of the flowing blood exerted on the endothelial cells, is an important determinant of endothelial function, structure and gene expression. It also plays a role in atherogenesis. Based upon theory WSS is considered to be constant along the arterial tree and similar in a particular artery across species.
In vivo measurements in humans and animals, however, show that the theoretical assumptions regarding WSS and its calculation are far from valid. In humans mean WSS is higher in the common carotid artery (1.1-1.3 Pa) than in the brachial (0.4- 0.5 Pa) and femoral (0.3-0.5 Pa) arteries; te latter values being substantially lower than the theoretically predicted value of $1.5\pm50\%$. The lower mean WSS in these conduit arteries can be explained by the high peripheral resistance in these arteries, reducing mean volume flow and inducing reflections. In the femoral artery, adaptation of the peripheral resistance during vasodilatation results in mean WSS values close to those in the common carotid artery. Mean WSS also varies within the carotid and femoral artery bifurcations. Also in animals mean WSS varies along the arterial tree. Mean WSS was found to vary between 2.0 and 10.0 Pa in mesenteric arterioles and between 2.0 and 3.0 Pa in cremaster arterioles, the values being dependent on the site of measurement along the arteriolar tree. Across species mean WSS in a particular artery decreases linearly with increasing body mass. For example, in the descending aorta from 8.8 Pa in mice, to 7.0 Pa in rats and to 0.5 Pa in humans; the flow velocities in these artery being similar in these species.
The observation that mean WSS is far from constant along the arterial tree indicates that Murray's cube law on flow-diameter relations in bifurcations cannot be applied to the whole arterial system. At the present state of the art, it may be concluded that the exponent of the power law varies along the arterial tree, from 2 in the major branches of the aortic arch to 3 in arterioles. The *in vivo* findings also imply that in *in vitro* investigations on endothelial gene expression and cellular adhesion the endothelial cells derived from different vascular areas or from the same artery from different

species cannot be exposed to an average calculated shear stress value. The cells have to be studied under the shear stress conditions they are exposed to in real live.

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Abstracts

ORAL PRESENTATIONS

01.01
LOW BONE MINERAL DENSITY IS ASSOCIATED WITH GREATER AORTIC PULSE-WAVE VELOCITY IN WOMEN: THE NORTHERN IRELAND YOUNG HEARTS PROJECT (NIYHP)

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Background & Aims: Associations between low bone mineral density (BMD) and increased arterial stiffness have been suggested as a potential mechanism explaining the increased cardiovascular risk observed in osteoporosis. We have therefore examined, in a population of young adults: 1) whether BMD was associated with stiffness of central (i.e. aorta) and peripheral (i.e. upper and lower limbs) arterial segments; and 2) whether any such associations were similar in men and women.
Methods: Subjects were 274 (128 women) young adults (mean age of 23 yrs), participating in the NIYHP. BMD (in g/cm^3) of the lumbar spine and the femoral neck were measured by means of DXA. Arterial stiffness was assessed by measuring pulse wave velocity (PWV, in m/s) in 3 arterial segments using a non-invasive optical method.
Results: After adjustment for potential confounders (i.e. age, height, MAP, physical activities' peak strain, smoking and alcohol, calcium and vitamin D intake) BMD of both the lumbar spine [β=-0.67 (95%CI:-1.27;-0.07), p=0.029] and the femoral neck [β=-0.69 (-1.16;-0.22), p=0.005] were inversely associated with aortic PWV in women, but not in men; further adjustment for other cardiovascular risk factors did not attenuate these associations [β=-0.61 (-1.19;-0.04) and β=-0.58 (-1.04;-0.13), for BMD of the lumbar spine and femoral neck, respectively]. No significant associations were found between BMD and PWV of the upper and lower limbs, however.
Conclusions: Young women, but not men, with lower BMD have increased aortic stiffness. Pathophysiological mechanisms underlying these associations, notably already observed in young age, need to be further explored.

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01.02
GEOMETRIC AND ELASTIC PROPERTIES OF THE COMMON CAROTID ARTERY IN VASCULAR EHLERS-DANLOS SYNDROME PATIENTS WITH IDENTIFIED COL3A1 MUTATIONS

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Background: Vascular Ehlers-Danlos syndrome (vEDS), an autosomal dominant inherited disorder of connective tissue, results from mutations in the gene encoding type III procollagen (COL3A1), can present with spontaneous arterial rupture or dissection. Diagnostic is based on the clinical criteria. Mutations of COL3A1 gene may be identified in about 60% case. Our study is to compare arterial geometric and elastic properties in vSED patients with identified COL3A1 mutations (COL3A1+) to unidentified COL3A1 mutations (COL3A1-).
Methods: 53 vEDS patients diagnosed by clinical criteria with no previous β-blocker were included in the cross-sectional study. Mutations of COL3A1 gene was identified in 32 patients. Arterial parameters were determined with high-resolution echo-tracking system coupled with applanation tonometry. Quantitative variables were compared by general linear model ANOVA.
Results: Demographic data did not differ between COL3A1+ and COL3A1- patients. Patients with COL3A1- were significantly older than COL3A1+ patients (+7 yrs, p<0.05). Heart rate, SBP, MBP, brachial PP, central PP, carotid diameter, distensibility, Young's elastic modulus, carotid-femoral pulse-wave velocity were not significantly different between two groups. Carotid intima-media thickness (IMT) was significantly lower (-18%, p<0.001) in COL3A1+ than COL3A1- patients. Carotid circumferential wall stress ($\sigma\theta$) was higher (+35%, p<0.001) in COL3A1+ than COL3A1- patients. After adjustment for age and blood pressure, these differences remained significant.
Conclusions: vSED patients with COL3A1+ have a lower carotid IMT associated with a higher $\sigma\theta$ than COL3A1- patient. These results reveal the role of $\sigma\theta$ in the pathogenesis of the vascular lesions and confirm the gold-standard of identifying COL3A1 mutations in the diagnostic of this syndrome.

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01.03
CAROTID-FEMORAL PULSE WAVE VELOCITY IS NOT INDEPENDENTLY RELATED TO INTIMA-MEDIA THICKNESS IN MIDDLE AGED WOMEN

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Carotid-femoral pulse wave velocity (PWV), a measure of central arterial stiffness and carotid intima-medial thickness (CIMT), thought to be a measure of subclinical atherosclerosis, are predictors of future cardiovascular events, recommended for risk stratification. Their relationship, however, remains poorly characterised. We sought to determine the association between PWV, CIMT and atherosclerotic plaque at the carotid and femoral artery and the heritability of PWV and CIMT. The study population consisted of 496 female twins (112 monozygotic (MZ), 135 dizygotic (DZ), mean age (interquartile range) 58 (53-64) years, from the TwinsUK cohort. PWV was determined using the SphygmoCor system (Atcor Australia) and CIMT measured 1 cm proximal to the flow divider by B-mode ultrasound. Plaque was quantified according to its presence at the carotid and femoral artery. Multiple regression analysis was used to examine the relation between PWV, CIMT and plaque. Heritability was determined from intra-class correlations. In multiple regression analysis incorporating age, mean arterial pressure (MAP) and heart rate (HR), PWV was not significantly positively correlated with CIMT, indeed there was a weak but significant negative correlation between PWV and CIMT (standardised regression coefficient β=-0.13, P<0.05). PWV was weakly positively associated with plaque (β=0.13, P<0.01). Heritability of PWV (adjusted for HR and MAP) and CIMT (adjusted for MAP, total cholesterol and HDL-cholesterol) was 0.34 and 0.57 respectively. These results confirm high heritability of CIMT but suggest that it is largely independent of PWV which may be influenced more by environmental factors. Combining measures of CIMT and PWV might improve risk stratification.

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01.04
REFERENCE VALUES FOR ARTERIAL STIFFNESS

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Objectives: The implementation of arterial stiffness measurements in clinical practice is hampered by methodological differences in PWV definitions and the absence of reference values. This study reports reference values for pulse wave velocity (PWV) in a population of 24,482 subjects originating from 13 European centres.
Methods: PWV values presented are valid for direct carotid-femoral distance measurement (L_{direct})and transit time determined by the algorithm of intersecting tangents ($\Delta t_{intersecting\ tangent}$). PWV was converted using statistical models for estimation of L_{direct} and $\Delta t_{intersecting\ tangent}$ if required. PWV relevant clinical data were available in 13,919 without curent antihypertensive therpay. Subjects were divided into age deciles (<30, 30-39, 40-49, 50-59, 60-69, 70-79, >=80 years) and for each age category a box-percentile plot was constructed.
Results:
Conclusions: The data presented form a solid base for establishing reference values according to age group valid for a European population.