



## Artery Research

ISSN (Online): 1876-4401

ISSN (Print): 1872-9312

Journal Home Page: <https://www.atlantispress.com/journals/artres>

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### **P2.03: THE PLASMINOGEN ACTIVATOR INHIBITOR-1 (4G/5G) POLYMORPHISM AFFECTS CENTRAL ARTERIAL BLOOD PRESSURE IN WOMEN**

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**To cite this article:** H.M. Björck, P. Eriksson, U. Alehagen, L.U. Ljungberg, R. DeBasso, K. Persson, U. Dahlström, T. Länne (2009) P2.03: THE PLASMINOGEN ACTIVATOR INHIBITOR-1 (4G/5G) POLYMORPHISM AFFECTS CENTRAL ARTERIAL BLOOD PRESSURE IN WOMEN, Artery Research 3:4, 177–178, DOI: <https://doi.org/10.1016/j.artres.2009.10.019>

**To link to this article:** <https://doi.org/10.1016/j.artres.2009.10.019>

Published online: 14 December 2019



# Poster Presentation Abstracts

## Epidemiology 1

### P2.01

#### INITIAL DATA ON THE NATURAL HISTORY OF aPWV IN WEST AFRICAN INFANTS

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**Introduction:** Aortic pulse wave velocity (aPWV) may measure vascular structure and function (distensibility) more precisely than blood pressure (BP). Few data exist on arterial distensibility in infancy; none on the effects of malaria in African children.

**Methods:** Healthy women with singleton pregnancies were recruited at Adeoyo Maternity Hospital, Ibadan, Nigeria. Measures of anthropometry, resting BP and aPWV using a Doppler device were taken on mothers and their babies at birth and three months later.

**Results:** 147 mother-baby pairs were measured at birth; 74 mothers had slide-positive malaria. 79 mother-baby pairs were measured at 3 months of age, but only 24 at both times. At birth, mean (SD) aPWV of infants whose mothers had malaria was 4.6 (1.6) m/s and SBP/DBP of 75.0/38.5 mmHg compared with those without 5.6 (1.6) m/s and 72.0/35.8 mmHg. Adjusting for birthweight, these differences were not significant.

By 3 months, children with maternal malaria had aPWV & BP of 7.2 (2.8) m/s and 88.2/47.8 mmHg compared to those without at 7.0 (3.0) m/s and 87.6/48.6 mmHg.

Neonatal aPWV was significantly related only to heart rate ( $R = 0.40$ ;  $p < 0.001$ ), but at 3 months to heart rate ( $R = 0.27$ ;  $p = 0.015$ ) and maternal age ( $R = 0.25$ ;  $p = 0.028$ ), independent of maternal and infant BP.

**Discussion:** aPWV on average increased during the first three months of life, uncorrelated between birth and 3 months. Children with maternal malaria had slightly lower aPWV at birth, catching up by 3 months. Whether higher aPWV develops sooner in babies with malaria than in those without malaria will be examined in follow-up.

### P2.02

#### THE METABOLIC SYNDROME IN MIDDLE AGED INDIVIDUALS IS ASSOCIATED WITH GREATER ELASTIC, BUT NOT MUSCULAR ARTERIAL STIFFNESS

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There is some evidence that in MetS increase of arterial stiffness may be distributed over muscular and the elastic arteries not uniformly.

**The purpose of this study** was to examine the association between the MS and arterial stiffness of both elastic and muscular arteries in middle aged individuals.

**Methods:** The cohort consisted of 951 individuals without MetS (females 338 and males 613), mean ages  $54.15 \pm 5.88$  and 604 with MetS (females 405 and males 199), mean ages  $54.41 \pm 5.97$  ( $p = 0.69$ ). For this investigation all those with diabetes were excluded. MetS defined according to the ATP III criteria. Following 10 min supine rest, blood pressure, carotid-femoral and carotid-radial PWV (using Sphygmocor v.7) and cardiovascular index CAVI (VaSera VS-100) were measured. All patients underwent detailed assessment of cardiovascular risk factors.

**Results:** Aortic PWV in the MetS group ( $9.02 \pm 1.53$  m/s) was significantly higher ( $P < 0.001$ ) than in patients without MetS ( $8.67 \pm 1.58$  m/s). There were no significant between-group differences of carotid-radial PWV (MetS  $8.92 \pm 1.21$  m/s, without MetS:  $8.95 \pm 1.4$  m/s;  $p = 0.53$ ) or CAVI (MetS:  $7.93 \pm 3.2$  m/s, non-MetS:  $8.18 \pm 6$  m/s;  $p = 0.46$ ) values. In this study multiple logistic regression revealed that aortic but not carotid-radial PWV and CAVI were independently related to MetS (standardized regression parameter  $r = -1.25$ ,  $p = 0.0049$  after adjusting for age, gender). **Conclusions:** the results therefore indicated that elastic arteries may stiffen preferentially over muscular arteries in middle aged individuals with the metabolic syndrome.

### P2.03

#### THE PLASMINOGEN ACTIVATOR INHIBITOR-1 (4G/5G) POLYMORPHISM AFFECTS CENTRAL ARTERIAL BLOOD PRESSURE IN WOMEN

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Plasminogen activator inhibitor (PAI-1) is the key inhibitor of the fibrinolytic system, modulating cellular responses associated with vascular remodeling. Elevated plasma PAI-1 has been positively correlated to systolic- and diastolic blood pressure, measured in the brachial artery, and is increased in hypertensive patients. The (4 G/5 G) polymorphism in the PAI-1 promoter influences plasma concentrations, 4 G/4 G subjects having higher plasma PAI-1 levels than 5 G carriers. The effect of the (4 G/5 G) polymorphism on central arterial pressures is unknown. Hence, the aim of this study was to test whether the PAI-1 4 G/5 G polymorphism affects central arterial blood pressure.

400 subjects, 212 men and 188 women (70–88 years) were studied. Central pressures and waveforms were calculated from radial artery pressure waveforms by the use of the SphygmoCor device, using a generalized transfer function. The PAI-1 (4 G/5 G) genotype was determined. Central

aortic blood pressures were higher in female carriers of the 4 G/4 G genotype than female subjects carrying the 4 G/5 G and 5 G/5 G genotypes, ( $P = 0.014$ ,  $P = 0.004$  and  $P = 0.003$  for central systolic-, diastolic- and mean arterial pressure, respectively). Adjustment for variables related to hypertension (age, BMI, DM, smoking, LDL-cholesterol, fasting glucose) had no effect on the associations. No association was found between PAI-1 genotype and brachial blood pressure in either men or women.

Our findings show that the PAI-1 (4 G/5 G) polymorphism is associated with central arterial blood pressure in women. The genotype effect was independent of other risk factors related to hypertension, suggesting that impaired fibrinolytic potential may play an important role in the development of central arterial hypertension.

#### P2.04

### CALCIUM INTAKE IS INDEPENDENTLY ASSOCIATED WITH INCREASED AUGMENTATION INDEX: RESULTS FROM A CROSS-SECTIONAL FOLLOW-UP STUDY OF TWO RHEUMATOID ARTHRITIS COHORTS

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**Background:** Population studies have indicated that both the presence of osteoporosis and serum levels of calcium are associated with an increased risk of cardiovascular disease.

**Objective:** To investigate the association between bone loss, calcium intake and levels of the reactive hyperemia index (RHI) and augmentation index (AIx), two measures of endothelial function and surrogate markers of cardiovascular disease, in a cohort of patients with RA.

**Methods:** Two hundred and thirty eight patients with early RA were comprehensively examined at baseline with registration of clinical and radiographic data. At the 15-year follow-up these examinations were repeated in 153 patients and additionally the RHI (ITAMAR) and AIx (Sphygmocor) were recorded.

**Results:** Calcium substitution, ever vs never was associated with lower levels of RHI and higher AIx  $\beta$ (SE) -0.12 (0.05)  $p = 0.03$  and 4.03 (1.19)  $p = 0.001$  respectively, in models that were adjusted for age, sex and CVD risk factors. Measures of bone mineral density or rate of bone loss were not significantly related to AIx or RHI. In models that were adjusted for current CVD risk factors, RA disease activity and use of disease modifying anti-rheumatic drugs, current use of calcium substitution was a significant independent predictor of AIx  $\beta$ (SE) 5.21 (2.38)  $p = 0.03$ , model  $r^2$  0.56, but not of RHI.

**Conclusion:** Calcium supplementation was associated with increased arterial stiffness in this cohort of patients with RA. Residual confounding cannot be ruled-out.

#### P2.05

### CENTRAL HEMODYNAMIC PARAMETERS AND ARTERIAL STIFFNESS IN PAGET'S DISEASE

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**Background:** Paget's disease of bone (PDB) is a common disorder characterised by increased, disorganised bone turnover in affected areas with overgrowth of immature woven bone. An increased cardiovascular risk has been reported in some studies of PDB, possibly related to arterial wall calcifications. The aim of this study was to evaluate central hemodynamic parameters and arterial stiffness in PDB patients.

**Methods:** 11 PDB patients and 11 control subjects matched by age, weight, height and cardiovascular risk factors, were enrolled. Anthropometric measures, metabolic profile and information about PDB features (extension, therapy, and genetic alteration of disease) were made available for all subjects. Central hemodynamic parameters and carotid-femoral Pulse Wave Velocity (PWVcf) were assessed non-invasively by Sphygmocor.

**Results:** The PDB and the control group were comparable for age (PDB vs Control:  $59 \pm 8.0$  vs  $58 \pm 7.2$  yrs;  $M \pm SD$ , height:  $168 \pm 6.7$  vs  $168 \pm 6.0$  cm and body weight:  $78 \pm 14$  vs  $77 \pm 12$  kg). PDB patients presented a significantly higher PWVcf ( $9.8 \pm 1.8$  vs  $7.7 \pm 1.5$  m/s,  $p = 0.008$ ) and a trend toward higher central PP ( $48 \pm 19$  vs  $45 \pm 10$  mmHg,  $p = 0.60$ ). The difference in PWVcf was confirmed after adjustment for age, gender, heart rate and central mean pressure ( $9.6 \pm 0.54$  vs  $7.18 \pm 0.53$  m/s  $M \pm SE$ ;  $p = 0.006$ ).

**Conclusions:** PDB patients presented evidence of higher arterial stiffness as compared with control subjects. These results support the hypothesis

that PDB is a systemic condition associated with increased cardiovascular risk.

#### P2.06

### ENDOTHELIAL DYSFUNCTION IS ASSOCIATED WITH ARTERIAL STIFFNESS IN HYPERTENSIVE PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Both endothelial dysfunction and arterial stiffness are considered as independent predictors of cardiovascular mortality, but their interrelationship has been poorly explored. Therefore we evaluated the relationship between endothelial function and pulse wave velocity (PWV) in essential hypertensive patients with (DM+) or without (DM-) diabetes mellitus, on chronic pharmacological treatment.

51 DM+ patients and 51 DM- patients matched for age, gender and BP were included. Applanation tonometry (Sphygmocor®) was used to determine aortic (carotid to femoral) PWV. Brachial artery endothelium-dependent flow-mediated dilation (FMD), and endothelium-independent dilation by 25  $\mu$ g sublingual glycerol trinitrate (GTN) were assessed by high resolution ultrasound and computerized edge detection system.

In DM+ patients was higher ( $9.9 \pm 1.8$  vs  $8.4 \pm 1.4$  m/s,  $p = 0.0001$ ) and FMD was lower ( $3.1 \pm 1.7$  vs  $6.3 \pm 3.5$ ,  $p < 0.0001$ ) than DM-. In DM+, PWV was related to BMI ( $r = 0.47$ ,  $p = 0.0007$ ), triglycerides ( $r = 0.54$ ,  $p = 0.00006$ ), systolic BP ( $r = 0.54$ ,  $p = 0.00006$ ) and FMD ( $r = -0.47$ ;  $p = 0.0005$ ). In multivariate analysis, only FMD ( $r^2 = 0.10$ ,  $p = 0.003$ ), systolic BP ( $r^2 = 0.17$ ,  $p = 0.002$ ), BMI ( $r^2 = 0.22$ ,  $p = 0.009$ ) resulted significant independent predictors of PWV. On the contrary in DM-, PWV was related to age ( $r^2 = 0.35$ ,  $p = 0.01$ ), systolic BP ( $r^2 = 0.45$ ,  $p = 0.001$ ), but not to FMD. In multivariate analysis, only SBP ( $p = 0.02$ ) was an independent predictor of PWV ( $r^2 = 0.23$ ).

In hypertensive type 2 diabetic subjects on chronic pharmacological treatment, a decline in endothelial function seems to be independently associated with increased aortic stiffness, possibly suggesting a cause-effect mechanism. The association is not present in hypertensive euglycemic patients, who have lower aortic stiffness and endothelial dysfunction.

#### P2.07

### MASKED HYPERTENSION IS "UNMASKED" BY LOW INTENSITY EXERCISE BLOOD PRESSURE

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**Background:** Masked hypertension (MH) independently predicts mortality but cannot be diagnosed from clinic blood pressure (BP). We sought to determine if MH could be identified from BP or pressure waveform analysis (PWA) at rest or during low intensity exercise.

**Methodology:** Brachial and estimated central BP (by PWA; Sphygmocor) were recorded at rest and during  $\approx 10$  minutes of cycling exercise (60-70% of age-predicted maximal heart rate) in 77 untreated subjects with a hypertensive response to exercise (HRE) (aged  $54 \pm 8$  years) and 61 patients with hypertension (HT) receiving therapy (aged  $62 \pm 8$  years). All subjects underwent 24 hour ambulatory BP monitoring (24hrABPM) and MH was defined as clinic systolic BP (SBP)  $< 140$  mmHg and 24hrABPM SBP  $\geq 130$  mmHg.

**Results:** There were 44 (57%) HRE and 32 (52%) HT patients with MH. For the HRE group at rest, there were no significant differences between MH and normotensive subjects in any haemodynamic variable except brachial systolic BP, which was higher in MH subjects ( $127 \pm 9$  vs.  $120 \pm 9$  mmHg;  $p < 0.05$ ). After correction for resting SBP, MH subjects had significantly higher brachial ( $187 \pm 22$  vs.  $168 \pm 15$  mmHg;  $p < 0.05$ ) and central SBP ( $154 \pm 17$  vs.  $141 \pm 12$  mmHg;  $p < 0.05$ ) during exercise, with greater changes in both from baseline ( $p < 0.05$ ). No differences were observed in the HT group. Exercise brachial SBP predicted the presence of MH independent from all resting hemodynamic variables ( $\beta = 0.35$ ;  $p < 0.001$ ), and if  $> 190$  mmHg, identified MH with 97% specificity ( $p < 0.001$ ).

**Conclusions:** MH can be identified in untreated individuals from low intensity exercise brachial SBP. Exercise BP testing may be indicated in patients with borderline raised clinic brachial SBP.