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P.061: A HAPLOTYPE AT THE MMP-9 LOCUS IS ASSOCIATED WITH HIGHER BLOOD PRESSURE AND GREATER ARTERIAL STIFFNESS IN PATIENTS WITH ESSENTIAL HYPERTENSION

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increase in this ratio was greater in physically trained than in untrained. CO ($p < 0.05$) and SV ($p < 0.01$) were significantly greater in trained individuals. SVR was constantly but insignificantly smaller in trained individuals.

The conclusion of our measurement is that physical training presumably changes CO, SV and SVR, but not BRS. Does that mean that BRS is not a valuable measure of the quality of blood pressure regulation?

P.061

A HAPLOTYPE AT THE MMP-9 LOCUS IS ASSOCIATED WITH HIGHER BLOOD PRESSURE AND GREATER ARTERIAL STIFFNESS IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Arterial stiffness is the result of a complex interplay between gene and environment. The metalloproteinases (MMPs) play an important role in vascular remodelling and plasma MMP-9 levels predict cardiovascular disease. We studied the effect of two MMP-9 polymorphisms; -1562C>T and -836G>A on blood pressure (BP) and arterial stiffness in essential hypertension.

We measured BP, pulse wave velocity (PWV) and augmentation index (Alx) in 217 untreated hypertensive patients (mean age 46 ± 1 years (108 male). MMP-9 polymorphisms were screened using RFLP. Haplotypes were determined using HAP analysis. Results analysed with JMP Version 5.0 and expressed as Mean \pm SEM, $p < 0.05$ considered significant.

Aortic PWV and BP were significantly higher in -1562T (TT homozygotes and CT heterozygotes) and 836 A allele carriers (AA homozygotes and GA heterozygotes). The predicted haplotypes were independently associated with aortic PWV and BP with a significant gene dose effect. In stepwise regression analysis, the -1562T and 836A alleles were independent determinants of PWV, in addition to age and BP. These polymorphisms were also independent determinants of both systolic and diastolic BP, either individually or when included together in the model.

Variation in the MMP-9 gene may modulate BP and aortic stiffness probably through accelerated turnover of vascular extracellular matrix. The significant gene-dose effect suggests that even one copy of the rare allele (A & T) may increase the risk of arterial stiffness and higher BP. A future challenge would be to use genotyping to identify high-risk individuals and to tailor anti-hypertensive treatment for achieving optimum BP control and reduced arterial stiffness.

P.062

ADIPONECTIN GENE POLYMORPHISM -276G>T CONTRIBUTES TO ARTERIAL STIFFNESS IN ESSENTIAL HYPERTENSION

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Adiponectin levels, the anti-inflammatory adipocytokine is reduced in hypertension and related to arterial stiffness¹. The adiponectin -276G>T polymorphism is associated with type 2 diabetes and insulin resistance. However, whether this polymorphism contributes to arterial stiffness is not known.

We measured pulse wave velocity (PWV) and index (Alx) in untreated hypertensive patients ($n = 221$, 109 Female). G>276T polymorphism was determined by RFLP. Fasting plasma insulin and adiponectin concentrations were determined using ELISA. Fasting lipids and glucose were measured by standard methods and insulin resistance estimated using HOMA index. Results expressed as Mean \pm SEM, $p < 0.05$ considered significant.

The genotypes frequencies were G/G 53%, G/T 37%, and T/T 10%. Adiponectin levels were significantly reduced and associated with insulin resistance in patients with GG genotype. Patients with GG genotype had significantly higher systolic blood pressure (BP) ($p = 0.01$) and pulse pressure ($p = 0.008$) with no difference in diastolic BP. The aortic PWV was significantly higher ($p = 0.004$) in patients with GG genotype compared with T allele carriers. In a stepwise regression model, the -276G>T polymorphism was an independent determinant of PWV, in addition to age and BP and explained 46% of the variability in PWV. However, there was no difference in Alx between the two genotypes. The -276G>T genotype is associated with

aortic stiffness and high BP as well as insulin resistance syndrome and may guide anti-hypertensive therapy in the future.

¹ Mahmud A, Feely J. Adiponectin and arterial stiffness. *Am J Hypertens*. 2005 Dec;18:1543-8.

P.063

INDUCIBLE NITRIC OXIDE SYNTHASE ACTIVITY IS ASSOCIATED WITH INCREASED AORTIC STIFFNESS AND ENDOTHELIAL DYSFUNCTION

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Background: *In vitro* studies suggest that inducible nitric oxide synthase (iNOS) activity mediates endothelial dysfunction, but the role of iNOS in the process of arterial stiffening (AS) and endothelial function (EF) *in vivo* is unknown. Rheumatoid arthritis (RA) is a chronic inflammatory condition and as such can provide an interesting model to study this. The aim was to establish the contribution of iNOS to AS and EF.

Methods: Forearm blood flow (FBF) was measured during intra-arterial infusions of acetylcholine (ACh), sodium nitroprusside (SNP), N-monomethyl-L-arginine (L-NMMA) and aminoguanidine (AG), a selective iNOS inhibitor, in 12 RA patients and 13 control subjects. Aortic pulse wave velocity (aPWV) was also assessed.

Results: FBF response to ACh was reduced in RA patients compared to controls (384 ± 72 v. $179 \pm 29\%$, respectively; $P = 0.01$), whereas SNP response was preserved ($P = 0.5$). AG reduced FBF in RA patients, but not in controls ($-15 \pm 2\%$ v. $13 \pm 4\%$, $P < 0.001$), while the response to L-NMMA was not different between the groups ($P = 0.4$). RA patients had higher aPWV than controls ($P = 0.01$). In multiple regression models logCRP, LDL and AG response were found to be independent predictors of EF ($R^2 = 0.617$, $P < 0.001$), and EF, AG response, and age independently predicted aPWV ($R^2 = 0.616$, $P < 0.001$).

Conclusion: RA patients have increased aPWV and iNOS activity, and blunted EF in comparison to controls. iNOS activity independently predicts aPWV and EF. Additionally, aPWV is independently associated with EF. However, the causal relationship between these conditions remains unclear; possibly they exist in parallel, driven by common risk factors, such as inflammation.

P.064

AMBULATORY ARTERIAL STIFFNESS INDEX, PULSE WAVE VELOCITY AND AUGMENTATION INDEX—INTERCHANGEABLE OR MUTUALLY EXCLUSIVE MEASURES

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The ambulatory arterial stiffness index (AASI) has been proposed as a novel measure of arterial stiffness and has been prospectively shown to predict stroke and cardiovascular death, but not cardiac death. This index has prompted considerable controversy as to whether it is a true measure of arterial stiffness.

The aim was to examine three different measures of arterial stiffness, i.e., pulse wave velocity (PWV, Complior), wave reflection (augmentation index, Alx) and AASI in a large hypertensive population, comparing their determinants and inter-correlations, both unadjusted and adjusted for confounders and using Bland Altman analysis to determine 95% confidence intervals for the ability of the AASI to predict PWV, the proposed gold standard of arterial stiffness.

The AASI correlated univariately with both PWV and Alx in subjects overall ($r = 0.28$ for PWV and 0.24 for Alx; $p < 0.001$ for both) and in those with untreated or treated hypertension. Adjustment for age in the current study negated entirely the positive correlation between AASI, PWV and Alx. Additional adjustment for confounders did not significantly alter these non-significant relationships. Furthermore, the 95% prediction limits for AASI to predict PWV were ± 4.18 meters/second and for AASI to predict Alx were $\pm 25.4\%$, suggesting that the methods would not be interchangeable in a clinical setting. Direct comparative studies would be required to establish the relative predictive strength of each measure and whether combining measures can provide additional risk prediction. Until such data become available, we propose that the measures should not be considered interchangeable.