THE EFFECT OF BLOOD GLUCOSE LEVELS ON HEMORHEOLOGICAL PARAMETERS, PLATELET ACTIVATION AND AGGREGATION IN ORAL GLUCOSE TOLERANCE TESTS

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Rheological factors and increased platelet aggregation are convincingly implicated in the development of micro- and macrovascular disease associated with diabetes mellitus. The present examination has been designed to describe the effects of a standard oral glucose load on hemorheological parameters, platelet activation and aggregation in patients with normal and pathologic glucose tolerance. Oral glucose tolerance test (OGTT) was performed in 30 patients suspected to have diabetes mellitus. Hematocrit, erythrocyte aggregation, red blood cell filterability, plasma and whole blood viscosity, soluble P-selectin levels and platelet aggregation were tested paralelly with blood glucose measurements 1, 2, and 3 hours after glucose consumption. Patients were divided into two groups based on glucose tolerance. Patients with abnormal glucose tolerance (IGT/DM) showed significant elevation in red blood cell aggregability (Myrenne indices M and M1) at the 2- and 3-hour samplings ($p<0.01$ and $p<0.001$, respectively). Patients with normal glucose tolerance (NGT) showed significant elevation only in M1 index ($p=0.01$). Plasma viscosity decreased significantly compared to fasting values in IGT/DM patients in all samples, but remained unchanged in NGT patients. Hematocrit decreased in IGT/DM patients significantly from the 2-hour samplings on ($p<0.05$), in normoglycaemic patients its decrease reached a borderline significance at 3-hour measurements. No significant changes were detected in whole blood viscosity, red blood cell filterability and sP-selectin levels during OGTT in either examined groups. No examined parameters were significantly correlated to blood glucose levels at any sampling. Erythrocyte aggregation showed significant correlation with BMI ($p<0.01$). Our results demonstrate that after the intake of a standard amount of glucose the development of rheological alterations is not simultaneous with the elevation of blood glucose levels, and our data suggest that the observed elevation in erythrocyte aggregation during OGTT might be associated with hyperinsulinemia. **(Clin Hemorheol Microcirc 2006; 35:517-525).**

CLOPIDOGREL RESISTANCE?

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Clopidogrel is an effective inhibitor of platelet activation and aggregation due to its selective and irreversible blockade of the P2Y(12) receptor. Combination antiplatelet therapy with clopidogrel and aspirin is an important

strategy for patients with acute coronary syndromes and those undergoing percutaneous interventions. Despite significant benefits demonstrated with combination antiplatelet treatment in large clinical trials, the occurrence of adverse ischemic events, including stent thrombosis, remains a serious clinical problem. Recent studies have demonstrated distinct response variability and nonresponsiveness to clopidogrel therapy based on ex vivo platelet function measurements. Small scale investigations have suggested that nonresponsiveness may be associated with a heightened risk for adverse clinical events. The above findings have stimulated a close examination of clopidogrel metabolism. **(Thromb Res 2006 Nov 13).**

RELATION OF LEFT VENTRICULAR HYPERTROPHY WITH SYSTEMIC INFLAMMATION AND ENDOTHELIAL DAMAGE IN RESISTANT HYPERTENSION

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The relation between left ventricular hypertrophy (LVH) and unfavorable cardiovascular prognosis may involve systemic inflammation and endothelial dysfunction/damage. The aim of this study was to investigate in a cross-sectional design the relationships of LVH with C-reactive protein (CRP) levels (a marker of systemic low-grade inflammation) and with microalbuminuria (a marker of glomerular endothelial damage) in 705 patients with resistant hypertension. At baseline, all were submitted to a laboratory evaluation including 24-hour urinary albumin excretion, 2D echocardiogram, and 24-hour ambulatory blood pressure monitoring. A total of 463 patients also had high-sensitivity CRP levels determined. LVH was defined as an indexed left ventricular mass >110 g/m(2) in women and >125 g/m(2) in men. Microalbuminuria was evaluated in 3 categories: low normal (<15 mg/24 hours), high normal (between 15 and 29 mg/24 hours), and abnormal (between 30 and 299 mg/24 hours). CRP was dichotomized at the median value (3.7 mg/L). Associations with LVH were examined after adjustment for all of the potential confounders by multivariate logistic regression. A total of 534 patients (75.7%) had LVH. After full adjustment, both abnormal microalbuminuria (odds ratio: 1.97; 95% CI: 1.04 to 3.73) and high CRP (OR: 1.76; 95% CI: 1.06 to 2.93) were independently associated with LVH occurrence. The high-normal albuminuria was associated with a borderline significant 46% increased chance of having LVH. Furthermore, the association between high CRP and LVH was observed exclusively in the subgroup with normal albuminuria. In conclusion, both systemic inflammation and endothelial damage were associated with LVH occurrence. These relationships offer insight into the pathophysiological mechanisms linking LVH to atherosclerosis and to increased cardiovascular morbidity and mortality. **(Hypertension 2007 Jul 16).**

ESTIMATE OF WHITE-COAT EFFECT AND ARTERIAL STIFFNESS.

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Objectives: Blood pressure (BP) measured in the office is usually higher than the average ambulatory BP, a difference generally taken as an estimate of the white-coat effect. This study was designed to assess whether such a difference is associated with impairment of the conduit arterial system. **Methods:** We calculated the difference between office and average daytime peak systolic blood pressure (DeltaSBP) in 2778 hypertensive participants (1240 women) of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale cohort. Arterial stiffness was evaluated using an adjusted office pulse pressure to stroke volume ratio (PP/SV), measured at rest, which has previously been shown to predict cardiovascular outcome independent of echocardiographic left ventricular hypertrophy. Effective arterial elastance was also estimated. **Results:** Across quintiles of PP/SV, significant linear, positive trends were found with age, the proportion of women, plasma glucose and triglyceride levels ($0.05 > P < 0.0001$). Heart rate measured in the office increased mildly with quintiles of PP/SV ($P < 0.05$). After adjusting for age, sex, body weight and office heart rate, DeltaSBP progressively increased with increasing quintiles of PP/SV (P for trend < 0.0001), whereas stroke volume decreased, paralleling the increase in left ventricular relative wall thickness (both $P < 0.0001$) and left ventricular mass index ($P < 0.05$). The significant increase in effective arterial elastance with quintiles of PP/SV was also independent of peak systolic BP, in addition to age, sex, heart rate and body weight. **Conclusions:** The difference between office BP and ambulatory BP, an estimate of the white-coat effect, is strongly associated with increased arterial stiffness, evaluated by a two-element fluid system accumulator. **(J. Hypertension 2007;25(4):827-831).**

HAEMATOCRIT LEVELS AND LEFT VENTRICULAR GEOMETRY: RESULTS OF THE MONICA AUGSBURG ECHOCARDIOGRAPHIC SUBSTUDY.

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Background: Extreme alterations in blood count such as anaemia or polycythemia are known to cause circulatory changes and, if these alterations persist, adaptations of cardiac geometry. **Objectives:** To investigate further the association between haematocrit levels and left ventricular geometry in a population-based sample. **Methods:** We examined 687

women and 648 men, aged 25-74 years, participating in the third population-based MONICA Augsburg study. Anthropometry, blood pressure, laboratory measurements and M-mode echocardiography were obtained using standardized methods. **Results:** Haematocrit levels were inversely related to end-diastolic diameters ($P < 0.001$). By contrast, septal and posterior wall thickness displayed parabolic association curves with nadirs at physiological haematocrit levels ($P < 0.001$). These associations remained significant after adjustment for age, sex, body fat, hypertension, diabetes mellitus, cardiovascular disease, heart failure, serum creatinine, and were likewise found for haemoglobin levels or numbers of erythrocytes. These correlations appeared to be secondary to changes in blood pressure and stroke volume that correlated either positively (blood pressure) or inversely (stroke volume) with haematocrit levels. Consequently, a concentric pattern of left ventricular hypertrophy, i.e. a relative wall thickness of 0.45 or greater, was significantly more prevalent in subjects with high haematocrit levels than in those with intermediate haematocrit levels. By contrast, an eccentric left ventricular hypertrophy, i.e. relative wall thickness less than 0.45, was more common in subjects with low haematocrit levels. **Conclusion:** In the general population, the variability of haematocrit levels and its haemodynamic consequences translates to distinct patterns of left ventricular geometry. **(J. Hypertension 2007;25(6):1301-1309).**

THREE ENDOTHELIAL NITRIC OXIDE (NOS3) GENE POLYMORPHISMS IN HYPERTENSIVE AND NORMOTENSIVE INDIVIDUALS: META-ANALYSIS OF 53 STUDIES REVEALS EVIDENCE OF PUBLICATION BIAS.

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Background: Studies on the relationship between endothelial nitric oxide (NOS3) gene variants and hypertension have been conflicting. To explore this hypothesis further, we performed a meta-analysis and re-evaluated the relationship between the three most widely studied NOS3 polymorphisms and hypertension status and blood pressure levels. **Methods:** Data on 40 413 subjects from 53 studies were combined in five distinct meta-analyses, and heterogeneity and publication bias were explored. **Results:** Heterogeneity was observed in all meta-analyses. By a random-effects model, carriers of the four 27-basepair repeat variable number of tandem re-

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peats in intron 4 were associated with a 28% increase in the risk of hypertension compared with those homozygous for the 5 repeat: odds ratio (OR) 1.28, 95% confidence interval (CI) 1.11-1.47, P = 0.001. In Asian individuals, Asp allele carriers displayed a similar association: OR 1.28, 95% CI 1.06-1.54, P = 0.01, as well as a 2 mmHg increase in both systolic (P = 0.04) and diastolic (P = 0.009) blood pressure levels. Furthermore, meta-regression analysis indicated that the effect of the Glu298Asp genotype on the risk of hypertension might be dependent on total cholesterol status. No effect of the T-786C variant on hypertension was detected. There was evidence that such findings might be a result of selectively reporting/publishing positive reports. **Conclusion:** Our results suggest that current data on the relationship between NOS3 variants and hypertension are subject not only to important heterogeneity but also to publication bias. Future research should preferentially focus on gene-environment interactions as well as haplotype analyses. **(J. Hypertension 2007;25(9):1763-1774).**