14.01: MOLECULAR DETERMINANTS OF ARTERIAL STIFFNESS

S. Laurent*, C. Fassot, P. Lacolley, P. Boutouyrie

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13.01
C-REACTIVE PROTEIN LEVELS ARE GRADUALLY ASSOCIATED WITH ADIPOGENIN AND ARTERIAL STIFFNESS IN NEWLY DIAGNOSED UNTREATED ESSENTIAL HYPERTENSIVE SUBJECTS: A UNIFYING APPROACH TO ATHEROSCLEROSIS

K. Dimitriadis*, C. Tsiloufi, E. Taxarchou, D. Chatzis, M. Selima, D. Tsoukalis, C. Methanis, I. Kallikazaros. Department of Cardiology, Hippokration Hospital, Athens, Greece

Purpose: To examined the plausible correlations between hs-CRP levels, adiponectin and arterial stiffness in essential hypertensive patients.

Methods: In 148 newly diagnosed untreated non-diabetic essential hypertensive patients (98 men, mean age 49 years, office BP = 150/97 mmHg), aortic stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP). Venous blood samples were drawn for estimation of lipid profile and hs-CRP and adiponectin levels. All subjects according to hs-CRP values were divided into group A (hs-CRP > 2.39 mg/l), group B (hs-CRP: 1.3-2.39 mg/l) and group C (hs-CRP > 2.39 mg/l).

Results: Patients in group A (n = 51) compared to subjects in group B (n = 45) and C (n = 52) had lower office systolic BP and left ventricular mass index (p < 0.003 for all cases), while groups did not differ regarding lipid levels (p > NS). In the entire population, hs-CRP was positively correlated with body mass index (r = 0.32, p < 0.001) and c-f PWV (0.412, p < 0.0001), while it was negatively correlated with adiponectin (r = -0.231, p < 0.005). Furthermore, patients in group C exhibited lower levels of adiponectin compared to group B and A (7.0 ±4.0 vs 8.9±5.1 vs 9.4±4.9 µg/ml, respectively; p < 0.05 for all cases) and also increased PWV values (6.8 ±1.6 vs 8.2±0.9 vs 7.8±1.2 m/s, p < 0.05, for all cases). Analysis of covariance revealed that adiponectin and PWV values remained different between groups after adjustment for confounding factors (p < 0.05).

Conclusions: Low-grade inflammation is associated in a graded fashion with proatherogenic processes linked with hypoadiponectinemia and arterial stiffening, even in the early stages of essential hypertension.

13.02
EXPOSURE TO URBAN AIR POLLUTANTS ALTERS ENDOTHELIAL FUNCTION IN HEALTHY SUBJECTS

A. Tan *, E. Bozec, S. Laurent, P. Boutouyrie. European Hospital Georges Pompidou and INSERM U 652, Paris, France

Exposure to urban air pollution, ultrafine particles or gas, is associated with acute cardiovascular mortality and morbidity. We investigated the effects of ambient air pollution on endothelial function in 40 healthy Caucasian men, previously described in the KLL study (JCI 2005), who spontaneously breathed ambient air pollution in Paris.

Endothelial function was measured by the % of brachial artery dilatation (dDr) with proatherogenic processes linked with hypoadiponectinemia and arterial stiffening, even in the early stages of essential hypertension.

13.03
SYNERGISTIC EFFECT OF ANGIOTENSIN II TYPE 1 RECEPTOR AND ENDOTHELIAL NITRIC OXIDE SYNTHASE GENE POLYMORPHISMS ON ARTERIAL STIFFNESS

J. Filipovský*, O. Mayer Jr., M. Doležlová, L. Bolek. Charles University, Praha, Czech Republic

Angiotensin II and nitric oxide play an important role in the function of arterial system. We wondered whether the mutations of angiotensin II type 1 receptor (AGTR1) and endothelial nitric oxide synthase (eNOS) genes are associated with increased stiffness of large arteries. Two frequent polymorphisms, A1166C of AGTR1 and T786C of eNOS, were assessed in a random, population-based sample of 250 subjects aged 25 to 64 years. Pulse wave velocity was measured in the aorta (APWW, between carotid and femoral arteries) and on the lower extremity (peripheral pulse wave velocity, PPWV, between femoral and tibialis posterior/dorsalis pedis arteries). Both polymorphisms were significantly associated with PPWV: 12.4±0.7, 13.8±0.2, 15.2±1.7 m/s for AA, AC and CC genotypes of AGTR1, respectively, p < 0.01 for trend; 13.3±0.8, 13.4±1.0, 15.1±1.6 m/s for TT, TC and CC genotypes of eNOS, respectively, p < 0.05. The combined effect of the polymorphisms was further studied. Subjects with 3-4 mutant alleles (heterozygous + homozgyous + homozgyous, n=35) had signigicantly increased PPWV (17.9±2.4 m/s) than those with no mutant allele (12.4±1.2 m/s) or 1-2 alleles (12.3±0.5 m/s, p < 0.007 for difference). These associations remained highly significant in multiple regression models with adjustment on potential confounders. The polymorphisms did not influence APWW or blood pressure. In conclusion, both AGTR1 and eNOS gene polymorphisms are associated with increased stiffness of peripheral muscular-type large arteries and their effect is synergistic. This finding reflects an interaction between the renin-angiotensin and nitric oxide systems in their effect on arterial properties.

13.04
LACK OF ENDOTHELIAL DYSFUNCTION IN BURGER’S DISEASE

A. Bura*, P. Boutouyrie*, S. Peyrad*, J.N. Flessinger*, S. Laurent, M. Azizi1. European Hospital Georges Pompidou and INSERM U 652, Paris, France, 1European Hospital Georges Pompidou, Clinical Investigation Center, Paris, France

Objective: To compare the acute flow-dependent vasodilatation (FDV) to a hand warming test (from 28ºC to 44ºC) and endothelium-independent vasodilatation (IVD) to sublingual glyceryl trinitrate (GTN 150 µg) of the brachial artery (BA) in 10 patients with an acute-phase Buerger disease, defined by an ADAR score >4 and a recent ulcer of the lower limbs (7 current), and 10 age- and sex-matched non-smokers healthy subjects.

Methods: BA diameter and shear stress were recorded by high definition echotracking. FDV was estimated by the slope of diameter-shear stress relationship.

Results: See the table.

<table>
<thead>
<tr>
<th></th>
<th>median [IQR]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buerger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDA diameter</td>
<td>6.8 (0.1;8.1)</td>
<td>3.7 (1.1;6.5)</td>
</tr>
<tr>
<td>BDA shear stress</td>
<td>70 (32;100)</td>
<td>93 (57;125)</td>
</tr>
<tr>
<td>BVA diameter</td>
<td>30 (28;33)</td>
<td>17 (13;22)</td>
</tr>
<tr>
<td>BVA shear stress</td>
<td>98 (40;137)</td>
<td>117 (76;251)</td>
</tr>
<tr>
<td>BVA slope-diameter stress</td>
<td>0.89 (0.55;1.24)</td>
<td>0.28 (0.01;0.58)</td>
</tr>
</tbody>
</table>

Buerger’s patients had an enhanced flow-dependent response to the increase in shear stress due to hand warming by comparison with controls as shown by the higher slope of diameter-shear stress relationship.

Conclusions: Acute flow-mediated changes in brachial artery diameter during hand hyperemia and IVG to GTN were not impaired in patients compared to control, by contrast to what has been repeatedly suggested in the literature.

14.01
MOLECULAR DETERMINANTS OF ARTERIAL STIFFNESS

S. Laurent*, C. Fassot1, P. Lacolley2, P. Boutouyrie*. 1Department of Pharmacology and INSERM U662, Hôpital Européen Georges Pompidou, Université Paris-Descartes, Faculté de Médecine, Paris, France, 2INSERM U684, Vandoeuvre-lès-Nancy, France

Arterial stiffness has an independent predictive value for cardiovascular events. This review proposes an integrated view of the molecular determinants of arterial stiffness, based on a candidate gene approach, an analysis of the structure-function relationship in hypertension, and studies on gene expression profile in humans. In monogenic diseases of connective tissue (Marfan, Williams, and Ehlers-Danlos syndromes) and corresponding animal models, the precise characterization of arterial phenotype allows understanding the influence of abnormal, genetically-determined, wall components on arterial stiffness. These studies underline the role of extracellular matrix signaling in the vascular wall and the fact that elastin
and collagen have not only passive elastic or rigid properties, but also are implicated in the control of SMC function. In animal models of essential hypertension (SHR and SHR-SP), the structural modifications of the arterial wall include a higher number of elastin/SMC connections, and smaller fenestrations of the internal elastic lamina, which could redistribute the mechanical load towards elastic materials. Thus, the changes in arterial wall material which accompany wall hypertrophy in these animals are not associated with an increased stiffness. Taken together, these data afford strong arguments to consider that arterial stiffness is not only influenced by the amount and density of stiff wall material, but mainly by its spatial organization.

Poster Presentations

P.001 ASSOCIATION OF BETA-THALASSEMIA MAJOR WITH IMPAIRED ENDOTHELIAL FUNCTION AND INCREASED LEVELS INFLAMMATION MARKERS

C. Cosma1, G. Giannopoulou, C. Aggel, E. Christoforatou, D. Tousoulis, V. Lasid, C. Stefanadis. 1st Cardiology Dept., School of Medicine, University of Athens, Athens, Greece

Objective: We examined endothelial function and serum levels of inflammatory mediators in transfusion-dependent patients with beta-thalassemia major (BTM).

Methods: The study population consisted of 85 patients with BTM (age: 25.0 ± 6.6) with normal left ventricular function and 71 healthy age- and sex-matched controls. Forearm blood flow was measured with gauge-strain plethysmography. Forearm vasodilatory response to reactive hyperemia (RH%) or to nitrate (NTG%) were assessed. Serum levels of interleukin 6 (IL-6), soluble vascular cell adhesion molecule (sVCAM-1) and soluble intercellular adhesion molecule (sICAM-1) were determined with ELISA.

Results: Patients had significantly lower levels of total cholesterol (124 ± 4.5 vs. 208 ± 7 mg/dl, p < 0.01), ApoA1 (122 ± 3 vs. 129 ± 4 mg/dl, p < 0.05), ApoB (62 ± 3 vs. 97 ± 4 mg/dl, p < 0.01) and Lp(a) (8.1 ± 1.4 vs. 15.5 ± 4 mg/dl, p < 0.01) than controls. IL-6 levels were significantly higher in patients (3.1 ± 0.31 pg/ml) than controls (1.14 ± 0.16 pg/ml, p < 0.01). Similarly, sVCAM-1 and sICAM-1 levels were significantly higher in patients (915 ± 30 and 362 ± 24 ng/ml, respectively) than controls (331 ± 12.6 and 268 ± 1.05 ng/ml, respectively, p < 0.01 for both). Maximum hyperemic forearm blood flow and RH% were lower in patients (7.1 ± 0.4 ml/100 ml tissue/min and 48 ± 2.5%, respectively) than controls (8.6 ± 0.2 ml/100 ml tissue/min and 85 ± 5.4%, respectively, p < 0.01 for both).

Conclusions: BTM is associated with impaired endothelial function and increased levels of IL-6, sVCAM-1 and sICAM-1, suggesting a potential role of inflammation and endothelial dysfunction in the cardiovascular complications of the disease. These observations concerned subjects with normal left ventricular ejection fraction, which implies an early implication of these mechanisms in the pathophysiology of heart insult in BTM.

P.002 VASCULAR BED PROPERTIES IN MULTISYSTEMIC LANGHERS-CELL HISTIOCYTOSIS

K. Alexandraki1, P. Makras2, A. Protergerou2, A. Stathopoulou3, K. Dimitriou2, D. Papadopoulou3, E. VoidoniKoi3, G. Pladitsis1, C. Papamichal2, G. Kaltas3. 1. Division of Endocrinology, Department of Pathophysiology, Laiko University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 2. Department of Endocrinology & Diabetology, 251 Air Force Athens General Hospital, Athens, Greece, 3. Vascular Laboratory, Alexandra University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 4. Department of Endocrinology, G. Genimatas Hospital, Athens, Greece

Introduction: Langerhans-cell histiocytosis (LCH) is a rare disorder that combines features of carcinogenesis and chronic inflammation with specific predisposition for the Langerhans-Pituitary system. Chronic inflammation, insulin resistance (IR) and hypopituitarism have been associated with increased cardiovascular risk for cardiovascular disease. The purpose of this study was to investigate structural and functional vascular properties in treated patients with multisystemic LCH and their associations with inflammation markers and insulin resistance indices.

Methods: We studied 8 patients with multisystem LCH (age: 38.38 ± 4.49 yrs; BMI: 25.99 ± 1.26 kg/m²) and 24 controls (age: 37.92 ± 2.50 yrs; BMI: 25.03 ± 0.80 years; BMI: 25.99 ± 1.26 kg/m²) matched for sex, age and BMI. Structural properties were assessed by intima media thickness estimation in common carotid artery (mean value right and left, MCCA, mm) and functional by endothelial flow-mediated dilatation (FMD, %) on the brachial artery.

Results: No difference in FMD (p = 0.011) and nitroglycerin (p = 0.74) values was observed among PCOS women and controls. Similarly, patients had significantly lower levels of total cholesterol (124 ± 4.5 vs. 208 ± 7 mg/dl, p < 0.01), ApoA1 (122 ± 3 vs. 129 ± 4 mg/dl, p < 0.05), ApoB (62 ± 3 vs. 97 ± 4 mg/dl, p < 0.01) and Lp(a) (8.1 ± 1.4 vs. 15.5 ± 4 mg/dl, p < 0.01) than controls. IL-6 levels were significantly higher in patients (3.1 ± 0.31 pg/ml) than controls (1.14 ± 0.16 pg/ml, p < 0.01). Similarly, sVCAM-1 and sICAM-1 levels were significantly higher in patients (915 ± 30 and 362 ± 24 ng/ml, respectively) than controls (331 ± 12.6 and 268 ± 1.05 ng/ml, respectively, p < 0.01 for both). Maximum hyperemic forearm blood flow and RH% were lower in patients (7.1 ± 0.4 ml/100 ml tissue/min and 48 ± 2.5%, respectively) than controls (8.6 ± 0.2 ml/100 ml tissue/min and 85 ± 5.4%, respectively, p < 0.01 for both).

Conclusions: BTM is associated with impaired endothelial function and increased levels of IL-6, sVCAM-1 and sICAM-1, suggesting a potential role of inflammation and endothelial dysfunction in the cardiovascular complications of the disease. These observations concerned subjects with normal left ventricular ejection fraction, which implies an early implication of these mechanisms in the pathophysiology of heart insult in BTM.

P.003 FUNCTIONAL AND STRUCTURAL VASCULAR BED PROPERTIES IN YOUNG WOMEN WITH POLYCYSTIC OVARY SYNDROME AND NORMAL LIPIDEMIC, GLYCEMIC AND BLOOD PRESSURE PROFILE


1. Division of Endocrinology, First Department of Medicine, Laiko University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 2. Vascular Laboratory, Department of Clinical Therapeutics, Alexandra University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 3. Laboratory of Biological Chemistry, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 4. Endocrine Unit, 2nd Department of Obstetrics and Gynecology, Aretaean Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 5. Division of Endocrinology and Human Reproduction, Second Department of Obstetrics and Gynecology, Aristotele University School of Medicine, Thessaloniki, Greece

Introduction: Cardiovascular risk factors and endothelial dysfunction have been shown to be present early in life in women with Polycystic Ovary Syndrome (PCOS). The aim of the present study was a global assessment of abnormalities in the arterial bed of young women with PCOS and normal profile of glycaemia, lipidemia and blood pressure by non-invasive, reproducible methods.

Methods: 27 women with PCOS (age: 25.41 ± 0.80 years; BMI: 27.42 ± 1.12 kg/m²) and 27 control women (age: 27.33 ± 0.83 years; BMI: 25.05 ± 1.19 kg/m²) of comparable age, body mass index and waist-to-hip ratio were studied. Macrovascular function was assessed by flow-mediated dilatation (FMD) on the brachial artery. Nitrate-induced dilatation (NID) was applied to exclude smooth muscle cells injury. Microvascular function was assessed by venous occlusion plethysmography studying forearm blood flow. Arterial structure was evaluated by ultrasonographic assessment of intima-media thickness (IMT) of the carotid artery.

Results: FMD values were lower in women with PCOS compared to controls (PCOS: 3.84 ± 0.74% vs. controls: 9.83 ± 0.97%, p < 0.001), but no difference was observed in NID (PCOS: 16.59 ± 1.84% vs. controls: 16.64 ± 2.05%, p = 0.98). The values time required for reactive hyperemia to reach peak value, a plethysmography parameter, was longer in PCOS women (PCOS: 20.63 ± 4.67 s vs. controls: 10.38 ± 5.11 s, p = 0.02). No difference was observed in the combined IMT among the studied groups (PCOS: 0.49 ± 0.01 mm controls: 0.51 ± 0.02 mm, p = 0.19).

Conclusions: Using non invasive methodologies endothelial dysfunction in the macrocirculation and evidence of early impairment in the microcirculation were demonstrated in young women with PCOS who had normal profile of glycaemia, lipidemia and blood pressure, without evidence of structural arterial impairment.

P.004 HABITUAL CHOCOLATE CONSUMPTION IS ASSOCIATED WITH IMPROVED ARTERIAL ELASTIC PROPERTIES AND CENTRAL HEMODYNAMICS

N. Alexisapolou1, C. Vlahopoulos, K. Aznauaurid, N. Ioakeimidis, I. Dima, P. Xaplanteris, C. Stefanadis. Athens Medical School, Hippokration Hospital, Athens, Greece

Introduction: Flavanoid-rich chocolate has been shown to improve endothelial performance, but its impact on blood pressure (BP) is inconsistent. The effect of habitual chocolate consumption on arterial elastic properties and central (aortic) hemodynamics, which are important predictors of cardiovascular risk, has not been investigated.