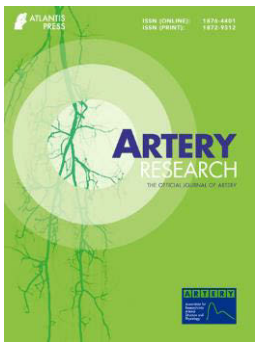

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14.01: MOLECULAR DETERMINANTS OF ARTERIAL STIFFNESS

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

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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 $\leqslant$ 1.29 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 ($p < 0.005$ for all cases), while groups did not differ regarding lipid levels (p = NS). In the entire population, hs-CRP was positively associated 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 more augmented PWV values (8.6 ± 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

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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 KLK study (*JCI 2005*), who spontaneously breathed ambient air pollution in Paris.
Endothelial function was measured by the % of brachial artery dilatation (dDr) and the absolute variation of shear stress (dSS) after hyperhemia following 5 min hand ischemia and after 150 μg of TNT sublingual, using RF-bases echotracking device, at two visits 2 weeks apart. Air pollution level, (CO, NO, NO_2, SO_2, PM 2.5) were extracted from "Airparif" database, the day of vascular measurement (J0"Pollutant") and 5 days before (mean "pollutant"). The ranks of pollutants were added to form SPOL score.
Baseline dDr was significantly and negatively correlated with mean and J0 NO ($P < 0.001$ for both), mean and J0 SO2 ($P < 0.0001$ for both), mean and J0 CO ($P < 0.0001$ for both), and SPOL($P < 0.001$). SPOL explained 19% of the variance of baseline dDr. Baseline dSS was significantly correlated with mean NO2 ($P = 0.003$), mean SO2 ($P = 0.004$), J0 SO2 ($P = 0.05$), and J0 PM 2.5 ($P = 0.02$). Changes in dDr between the two visits was significantly correlated with delta NO ($P = 0.001$) and delta SPOL ($P = 0.006$). Delta SPOL explained 8% of the variance of Delta DdLir. Changes in diameter or shear stress after TNT were not correlated with changes in air pollutants levels.
Endothelial function is significantly impaired by ordinary levels of pollutant in healthy young males, in urban area.

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

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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, $A^{1166}C$ of AGTR1 and $T^{786}C$ 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 (APWV, 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 ± 2.7 m/s for AA, AC and CC genotypes of AGTR1, respectively, $p < 0.02$ for trend; 12.3 ± 0.8, 13.4 ± 1.0, $15.1\ \pm1.6$ 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 + homozygous or homozygous + homozygous, 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 APWV 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 BUERGER'S DISEASE

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Objective: To compare the acute flow-dependent vasodilatation (FDV) to a hand warming test (from 28ºC to 44ºC) and endothelium-independent vasodilatation (EIV) 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 $\geqslant$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.

	median [IQR]		P value
	Buerger	Control	
FDV: Δ BA diameter (%)	6.8 (0.1;8.1)	3.7 (1.1;6.5)	ns
FDV: Δ shear stress (%)	70 (32;100)	93 (57;125)	ns
EIV: Δ BA diameter (%)	30 (28;33)	17 (13;22)	ns
EIV: Δ shear stress (%)	98 (40;137)	117 (76;251)	ns
Slope diameter-stress	0.89 (0.55;1.24)	0.28 (–0.01;0.58)	0.025

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 hyperhemia and EIV 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[1]*, C. Fassot[1], P. Lacolley[2], P. Boutouyrie[1]. [1]*Department of Pharmacology and INSERM U652, Hôpital Européen Georges Pompidou, Université Paris-Descartes, Faculté de Médecine, Paris, France,* [2]*INSERM U684, Vandoeuvre-les-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

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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 (aged 25±0.6) 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/ml, $p < 0.01$), ApoA1 (122±3 vs. 129±4 mg/ml, $p < 0.05$), ApoB (62±3 vs. 97±4 mg/ml, $p < 0.01$) and Lp(a) (8.1±1.4 vs. 15.5±4 mg/ml, $p < 0.01$) 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 (515±30 and 362±24 ng/ml, respectively) than controls (331±12.6 and 268±13.05 ng/ml, respectively, $p < 0.01$ for both). Maximum hyperemic forearm blood flow and RH% were lower in patients (7±0.4 ml/100 ml tissue/min and 48±2.5%, respectively) than controls (8.6±0.2 ml/100 ml tissue/min and 88.5±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 LANGERHANS-CELL HISTIOCYTOSIS

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Introduction: Langerhans-cell histiocytosis (LCH) is a rare disorder that combines features of carcinogenesis and chronic inflammation with specific predilection for the Hypothalamic-Pituitary system. Chronic inflammation, insulin resistance (IR) and hypopituitarism have been associated with increased 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/m^2) and 24 controls (age:37.92±2.50 yrs; BMI:25.03±0.68 kg/m^2) 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 function, using flow-mediated dilatation (FMD, %) on the brachial artery. Nitrate-induced dilatation (NID) was applied to exclude smooth muscle cells injury. C-reactive protein (CRP), fasting glucose, insulin, total cholesterol, HDL, triglycerides were measured; Waist-to-hip ratio (WHR), LDL and IR indices (glucose-to-insulin ratio, HOMA, QUICKI) were calculated.
Results: No difference in IMT ($p = 0.11$) and FMD ($p = 0.74$) values was detected among LCH patients and controls. Higher CRP ($p = 0.003$) and insulin levels ($p = 0.035$), and higher WHR ($p = 0.017$) and lower glucose-to-insulin ratio ($p = 0.003$) values were observed in LCH patients.
Conclusions: Treated patients with multisystemic LCH do not present alteration in vascular bed properties. However, such patients should be followed with caution as higher values of chronic inflammatory markers and insulin resistance indices were detected. Further larger scale studies are required to clarify whether these findings are inherent to the disease process or secondary to treatment.

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

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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 glycemia, 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/m^2) and 27 control women (age: 27.33±0.83 years; BMI: 25.05±1.19 kg/m^2) 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%, $p = 0.98$) values. The 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 glycemia, lipidemia and blood pressure, without evidence of of structural arterial impairment.

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

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Introduction: Flavonoid-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.