

ABSTRACTS

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(EVBO)**

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Guest Editors

Marco Rossi, Pisa

Akos Koller, Budapest

Jozef Dulak, Krakow

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Plenary Lectures

MICROCIRCULATORY DYSFUNCTION: A CORE FEATURE OF THE METABOLIC SYNDROME – INSIGHTS FROM PHYSIOLOGY AND EPIDEMIOLOGY

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I shall review the evidence that microvascular rarefaction and microvascular endothelial dysfunction play key roles in the metabolic syndrome. First, microvascular dysfunction (MVD) increases peripheral vascular resistance and thus, other things being equal, blood pressure. Second, microvascular rarefaction and microvascular insulin resistance decrease insulin-mediated glucose uptake by impairing the timely access of glucose and insulin to muscle. Third, obesity causes MVD through dysregulation of adipokines derived from visceral and perivascular fat. Fourth, MVD worsens further in individuals with impaired glucose metabolism and otherwise uncomplicated type 2 diabetes, setting the stage for microvascular complications of diabetes. Finally, weight loss reverses obesity-associated microvascular dysfunction.

These data identify early, obesity-associated MVD as a novel target in the prevention of diabetes.

Award Lecture JVR / ESM

VASCULAR SMOOTH MUSCLE CELL SENEESCENCE IN VASCULAR DISEASE

Martin Bennett
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Aim: Cell senescence has been found in a variety of vascular diseases and affects a range of cells. However, the role of cell senescence in vascular disease pathogenesis is unproven. We examined the evidence for vascular smooth muscle cell (VSMC) senescence, and its functional consequences in atherosclerosis.

Methods: We examined VSMCs in human plaques and normal vessels both *in vitro* and *in vivo*, and generated novel transgenic mice with accelerated or inhibited VSMC senescence, or increased or decreased DNA damage.

Results: Plaque VSMCs showed typical features of cell senescence, including poor proliferation, telomere shortening, SA β G activity and G₁/S restriction point cell cycle regulator expression. Senescence was associated with DNA damage (particularly double-strand breaks), activation of the DNA damage response, and reduced expression of the telomere associated protein TRF2. Accelerating

VSMC senescence and increasing DNA damage by genetically inhibiting TRF2 or NBS1 respectively promoted atherosclerosis and plaque vulnerability, whilst inhibiting senescence and reducing DNA damage reduced these features.

Conclusions: Vascular smooth muscle cell senescence occurs in atherosclerosis, is due to both replication and DNA damage, and promotes plaque formation and features of vulnerable plaques.

Award Lecture Malpighi

FROM CAPILLARY TO END ORGAN DAMAGE

Angela Shore
University of Exeter Medical School

Tissue health relies on microvascular function which is appropriate for tissue demands. In disease such as hypertension, systemic sclerosis and diabetes, clinically evident abnormalities of the microcirculation are apparent. However these established abnormalities are the result of complex long term changes to the microcirculation some of which are due to an individual's lifecourse, their susceptibility to a disease [be that genetic or environmental], and some of which are altered by disease itself and its treatment. These overt clinically evident abnormalities are preceded by multiple more subtle alterations to the microcirculation which can be detected using detailed research techniques. Reductions in microvascular structure are common particularly due to prematurity, genetics, or disease. Vascular dysfunction occurs as the result of, for example, nutritional effects, increasing weight, hyperglycaemia, smoking and aging. Vascular permeability increases due to alterations in capillary hydrostatic pressure as well as reductions to the vascular barrier leading to increased albumin leakage. Many of these functional changes are reversible at least in the early stages. Mechanisms underlying these functional abnormalities and the relationships between preclinical microvascular abnormalities and the prediction of future disease will be discussed.

Symposium 16 - Hemorheology and microcirculation: the main mechanisms of interaction

DIABETES MELLITUS: EVALUATION OF ERYTHROCYTE AND POLYMORPHONUCLEAR LEUKOCYTE RHEOLOGY

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Aim: To explore red blood cells (RBC) and leukocyte rheology, that may be relevant in the pathophysiology of diabetes mellitus.

Methods and Results: Significant alterations have been observed in RBC behaviour using several filtration techniques, but the exploration of RBC deformability by laser diffractometry did not show any abnormality. We have also employed microrheological methods based on fluorescence spectroscopy: membrane microviscosity was evaluated in ghosts, while in intact RBC we explored the membrane polarity gradient using fluorescent fatty acids, the phospholipid and protein lateral mobility using respectively pyrene and pyrene-3-maleimide. Alterations emerged only using the latter methods. We also investigated the filterability of polymorphonuclear leukocytes (PMN), their membrane fluidity and cytosolic Ca^{2+} concentration, both at baseline and after in vitro activation. At baseline no difference was evident in PMN filtration parameters or in cytosolic calcium content between normals and diabetics; a difference was noted in membrane fluidity. In normals, activation only induced a decrease in filterability, whereas in diabetics of both types we also observed an increase in cytosolic Ca^{2+} content and, only in type 1 diabetics, a decrease in membrane fluidity. Moreover, PMNs showed an altered integrin pattern in diabetes.

Conclusions: The functional impairment observed in blood cells of diabetic subjects can play a role in the development of vascular complications.

VASCULOPATHY IN THALASSEMIA: NEW APPROACHES TO AN OLD PROBLEM

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Although the life expectancy of thalassemia patients has markedly improved, patients with thalassemia major and intermedia generally present many complications, such as vasculopathy. Several studies reported a high incidence of thromboembolic events in β -thalassemia, more common in thalassemia intermedia than in regularly transfused thalassemia major. Regular transfusions decrease the risk of thrombosis, whereas splenectomy increases the risk. A chronic hypercoagulable state is present as evidenced by platelet activation, impairment of the natural endothelial anticoagulant system, altered erythrocyte flow properties that facilitate micro-circulatory disorders as well as a marked elevation of adherence to endothelial cells. Procoagulant microparticles derived from endothelium, platelets, RBC and leukocytes result increased in thalassemia intermedia patients. Eterogeneous phenotypes exist within the homozygous and compound heterozygous states for β -thalassemia with a wide spectrum of clinical and laboratory abnormalities. In this study the

hemorheological profiles of patients with β -thalassemia major and intermedia have been characterized in order to point out new indices of vascular impairment. Blood viscosity, erythrocyte aggregation index and viscoelastic properties have been determined and the influence of splenectomy, transfusion and chelation therapies has been evaluated.

RED BLOOD CELL (RBC) MICRORHEOLOGY AND MICROCIRCULATION UNDER PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS: MOLECULAR CHANGE MECHANISMS

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The aim of this study was to investigate RBC microrheology and microcirculation under physiological and pathological conditions and to analyze some molecular change mechanisms.

Methods It was utilized three models: the long-term exercising (LTE), the bout of acute exercise (BAE) and hypertension. Blood viscosity (BV), RBC aggregation (RBCA) and deformability (RBCD) were measured. Laser Doppler Imagination (LDI, Aimago) and nail fold biomicroscopy were used in this research. RBC suspension was divided into several aliquots and exposed to: 1) Epinephrine; 2) Methaproterenol, 3) Prostacyclin; 4) Cilostazol. ATP concentration in RBCs was measured before and after the cell incubation with some drugs.

Results A decrease in BV and RBCA after BAE was found, whereas RBCD was increased. Individuals after LTE had more FCD and microvascular perfusion (MP) than at initial period. There was 80% in MP increase under BAE after period of LTE, whereas before BAE there was 29% only. It was found an increase of RBCD after cell incubation with above-mentioned drugs. Besides ATP concentration in RBCs was increased after LTE.

Conclusion In sum, an effective microvascular perfusion after LTE was accompanied by higher ATP concentration in RBCs and its increase after epinephrine, methaproterenol and cilostazol

HEMORHEOLOGICAL AND BIOCHEMICAL PARAMETERS IN AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) is a progressive, fatal disorder caused by dysfunction and