## S30: From Rheology to Microcirculation: New Insights

### S30-1 Red blood cell rheology under different pathological conditions

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Blood viscosity and erythrocyte deformability play a key role in maintaining and regulating microcirculation. Hemorheological changes due to alterations of blood cells and plasma components lead to hyperviscosity, which may slow blood flow and facilitate occlusive events through erythrocyte rouleaux formation and platelet aggregation. Hemorheological alteration have been described in Sickle Cell Anemia (SCA) and Thalassemia. SCA is characterized by sickle red blood cells which do not easily flow through the microcirculation, causing frequent vaso-occlusive episodes, with resulting red cell rigidity, poor microvascular blood flow, tissue ischemia and infarction. In Thalassemia a high incidence of thromboembolic events, a hypercoagulable state and an increased risk of thrombosis have been demonstrated which can result in significant morbidity and mortality. The molecular and cellular mechanisms contributing to hypercoagulability are diverse and include chronic platelet activation, alteration of red blood cell membranes, abnormal expression of adhesion molecules on vascular endothelial cells, and dysregulation of hemostasis.

In this study the hemorheological profiles of patients with SCA and Thalassemia have been characterized in order to point out new indices of vascular impairment. Blood viscosity,

### S30-2 Role of hemorheological alteration in skin ulcers

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Several diseases are associated with both hemorheological alterations and skin ulcers. The most important conditions include hematological diseases such as plasma cell disorders (multiple myeloma and Waldenstrom's macroglobulinemia), cryoglobulinemia, fibrinogen alterations (cryofibrinogenemia, dysfibrinogenemia) and hereditary anemias (spherocytosis, thalassemia, sickle cell disease). Also connective tissue diseases can be complicated by hyperviscosity and skin lesions. Morevover, a hemorheological impairment can contribute to the skin lesions observed in diabetes mellitus (diabetic foot syndrome), critical limb ischemia, arterial hypertension (Martorell's ulcer) and venous insufficiency. The mechanisms of the rheological alteration vary in different clinical conditions, being related to an altered behaviour of circulating cells or a variation in quantity or quality of plasma proteins. The circulating cells involved in the pathophysiology of skin lesions are primarily erythrocytes but in some instances, and particularly in chronic venous diseases, leukocytes can play a major role. As regards plasma factors, the main point is the prominent influence of fibrinogen on plasma viscosity, much larger than what expected on the basis of its concentration. This effect, resulting from the molecular characteristics in physiological conditions, is amplified when circulating fibrinogen is abnormal. The most relevant site of intervention of rheological factors is microcirculation, where rheology interacts with hemodynamics and vessel wall function. Hemorheological impairment, besides having a pathophysiological role in skin ulcers, may have implications for their treatment.

**S30-3 Hemorheology in kidney disease**

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Patients in renal replacement therapy (RRT), namely dialysis and renal transplantation, present a cardiovascular risk substantially higher than the general population, due to both traditional and non-traditional risk factors. Hemorheological alterations have been extensively described in hemodialysis patients (HD), while little data exist about peritoneal dialysis patients (PD) and kidney transplant recipients (KT). We characterized the hemorheological profile of 49 PD and 108 KT patients, and compared these data with hemodialysis patients (HD). PD showed lower plasma viscosity, whole blood viscosity at 1-Hz, erythrocyte aggregation index and yield stress (parameters related to macro-circulation) when compared to HD, while microcirculatory function resulted severely impaired, as expressed by high values for whole blood viscosity 200-Hz shear rate and lower erythrocyte deformability (ED). KT, when compared to HD, showed lower plasma viscosity, whole blood viscosity at 1-Hz and 200-Hz shear rate, erythrocyte aggregation index and yield stress. Nevertheless, KT show a markedly reduced ED. Low ED in PD patients may be due to exposure to high-glucose dialysis fluids in PD; although we suspect a role for immunosuppressive treatment for ED reduction in KT, we found no differences among hemorheological parameters between the different classes of immunosuppressive drugs used. In conclusion, we found several hemorheological alterations in patients in RRT, which may contribute as a non-traditional risk factor to the high burden of cardiovascular disease in this population. More specifically, we confirm profound hemorheological dysfunction in HD patients; KT and, in part, PD patients showed a lower plasma viscosity and whole blood viscosity, but had an important defect in ED.

**S30-4 Rat pial microvascular changes during brain hypoperfusion and reperfusion injury: role of antioxidant substances**

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Our studies were aimed to evaluate the in vivo polyphenol protective effects on damage induced by 30 min cerebral blood flow decrease (CBFD) and subsequent 60 min cerebral blood flow recovery (CBFR) in rat pial microcirculation. In particular, we tried to detect changes in ROS production after different polyphenol administration.

Rat pial microcirculation was observed using fluorescence microscopy through a closed cranial window. In all animals, pial arterioles were classified in five orders of branching according to Strahler's method. Furthermore, neuronal damage and radical oxygen species (ROS) formation were detected by 2,3,5- triphenyltetrazolium chloride staining and 2'-7'-dichlorofluorescein-diacetate assay, respectively.

After 30 min of CBFD, induced by bilateral common carotid artery occlusion, and 60 min of CBFR, hypoperfused rats showed a decrease in arteriolar diameter, an increase in microvascular leakage and leukocyte adhesion, accompanied by decreased capillary perfusion. Moreover, marked neuronal

damage and evident ROS generation were detected. Conversely, rats treated with different polyphenols, such as oleuropein, malvidin and apigenin, showed a dose-related arteriolar dilation, a reduction in microvascular permeability as well as leukocyte adhesion compared to hypoperfused rats; moreover, capillary perfusion was protected. Finally, ROS generation and neuronal damage were reduced in animals treated with these antioxidant substances.

Polyphenols, intravenously infused, showed dose-related protective effects on rat pial microcirculation during CBFD and subsequent CBFR, preventing blood-brain impairment and neuronal loss. Furthermore, a significant reduction in ROS generation was observed.

**S30-5 Bridging the gap from basic microcirculation to the clinical world**

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In recent years the research on microcirculation has received a significative impulse. Numerous clinical studies have emphasized the role of microcirculation in the pathophysiology of several diseases. At the same time basic research has produced a huge number of observations that have broadened the knowledge of microcirculatory function (MF), providing clinicians with additional elements to be used for diagnostic and therapeutic purposes. However, basic and clinical research do not still succeed in dialogue. The assessment of the cutaneous hemodynamic by laser Doppler fluxmetr (LDF) with Wavelet Analysis (WA) may be considered an example.Between the 1998 and 2003 the WA has been applied for calculating the frequency spectrum of the human cutaneous LDF flowmotion waves.

Although the application of the WA to the LDF signal would allow a detailed evaluation of the MF by selecting each individual component the use of this metodology does not seem to be yet widespread, remarking a gap between basic research and clinical world.

In a systematic review of the literature on WA its application to the LDF cutaneous signal over the last 20 years,seems to be scarce Between 1998 and 2017, on 98 documents, 45 with 45,9 % (95%CI 36.3-55.7 %) pooled rate, reported data on 1679 patients (PTS) and 53, with 54.0% (95%CI 44.2-63.6) pooled rate, have been performed on 892 healthy subjects (HS). No significant difference between the two groups pooled rates has been found (p0.84)

The reasons of the poor application of WA to the LDF are not easy to find., but the constitution of a common language between basic and real clinical world could bridge the gap. Scientific societies may play a significant role