EDITORIAL COMMENT

Hemorheology, microcirculation and macrocirculation

Hemorreologia, microcirculação e macrocirculação

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The article by Cekirdeci and Bugan published in this issue of the Journal\textsuperscript{1} opens up new prospects for improving our knowledge of microvascular angina (MVA).\textsuperscript{1} Clinical characterization of MVA and coronary artery disease (CAD) shows them to be examples of endothelial dysfunction at the level of the microcirculation and macrocirculation, respectively. There is now general consensus about both coronary microcirculation and macrocirculation.

The authors selected biomarkers of hemorheology and inflammation and applied clinical methodology to diagnose and classify the patients and the control group. The latter were similar to the MVA and CAD patient groups regarding the presence of other associated diseases. The statistical computation performed confirmed the value of the control group used, which in my opinion is more realistic than other control groups selected without comorbidities.

As is well known, a compromised microcirculation leads to insufficient blood perfusion in arterioles, capillaries and venules, and hence poor oxygenation in tissues and organs. One cause could be a reduced ability of erythrocytes to reversibly deform (erythrocyte deformability) when they move into capillaries with a smaller diameter than the cell. Erythrocyte deformability is a hemorheological parameter which is affected by erythrocyte membrane composition, structure, internal viscosity, and signal transduction mechanisms resulting from exogenous and/or endogenous binding or compounds entering through the erythrocyte membrane.\textsuperscript{2}

A large number of disorders can change this hemorheological property of erythrocytes and hence reduce their ability to deliver oxygen to the tissue microcirculation. If such a situation is accompanied by diminished oxygen diffusion to endothelial cells, this may trigger cell hypoxia, leading to the generation of reactive oxygen species.\textsuperscript{3} In tissues where the oxygen partial pressure is lower than in the lungs, the efflux of nitric oxide (NO) from the erythrocyte through its membrane protein band\textsuperscript{4} is concomitant with oxygen delivery from the erythrocyte to cell tissues.\textsuperscript{3} In situations of abnormal microcirculation, reactive nitrogen species may be formed, leading to decreased concentrations of NO and loss of its physiological vasodilator function.\textsuperscript{3}

It is important to be aware of the possible existence of an inflammatory process in post-capillary venules where decreased rolling velocity and increased leukocyte adhesion retard blood flow. The presence of erythrocyte aggregates in post-capillary venules results in leukocytes remaining near the surface of the endothelium, promoting an acute inflammatory response.\textsuperscript{4} This effect was observed by us in an animal model of acute inflammation with labeled neutrophils using intravital microscopy.\textsuperscript{5} Impaired erythrocyte deformability and decreased NO efflux from erythrocytes during the acute phase of inflammation were observed.\textsuperscript{4} As the in vivo study was performed with mice, the quantity of blood was insufficient for whole blood viscosity (WBV) assessment, but according to other studies, WBV is likely to be increased.

In addition to its function as an acute phase protein in inflammatory diseases, fibrinogen is involved in the mecha-
nism of the coagulation cascade, the ability of erythrocytes to scavenge or donate NO, and erythrocyte aggregation.  

Erythrocyte aggregation and deformability are hemorheological parameters that influence WBV as a function of shear rates and hematocrit (HCT). In blood samples from healthy humans, when subjected to low shear rates erythrocyte aggregation takes place at higher WBV values in an HCT-dependent fashion, in contrast to erythrocyte deformability, which is increased by high shear rates and lower WBV values, and is little influenced by HCT.  

Cekirdekci and Bugan chose WBV and C-reactive protein (CRP) as hemorheological and inflammatory biomarkers, respectively, to cardiovascular disease, as has been previously demonstrated. The levels of both parameters were increased in the MVA and CAD groups, confirming the presence of a subclinical inflammatory state in patients with MVA. The present study illustrates the need for studies that include microcirculation observations. The microcirculation can be monitored non-invasively, the sublingual region being the area of choice to apply hand-held microscopy. In addition, assessment of NO efflux from erythrocytes obtained from patients with MVA and CAD will be helpful for monitoring the effects of drugs on the microcirculation and macrocirculation, respectively. Our team observed that NO efflux from erythrocytes of patients with systemic lupus erythematosus and rheumatoid arthritis is negatively associated with both intima-media thickness (IMT) and the presence of atherosclerosis plaques, and is an independent predictor of coronary IMT.  

Systemic inflammation occurs in both the macrocirculation and the microcirculation, and endothelial dysfunction in resistance coronary vessels contributes to coronary microvascular disease and vice versa. Before the achievement of this consensus we found that disturbances in microcirculation in the eye are associated with endothelial dysfunction in patients suffering from macrocirculatory diseases such as the accelerated phase of hypertension.  

The authors of the present article pointed out the need to quantify WBV by specialized equipment rather than through a formula based on a mathematical model.

WBV is a hemorheological parameter dependent on erythrocyte aggregation and deformability, as well as on plasma viscosity, and not only hematocrit. The intricacies of the vascular network, with variations in vessel length and diameter and number of ramifications, have implications for the differing values of HCT. All hemorheological parameters can be determined in appropriate laboratories with specialized equipment, which will help provide a better understanding of the pathophysiology. Follow-up studies conducted in patients with acute myocardial infarction demonstrated that patients with lower erythrocyte aggregation and CRP values at hospital discharge present higher recurrent event and mortality rates than patients with normal values.  

The development of new hemorheological microfluidic devices to be used at the bedside and microcirculatory apparatus means that MVA and CAD patients can be subdivided according to the associated pathology, and as well as WBV and HCT, erythrocyte deformability and aggregation, NO efflux from erythrocytes and microcirculatory parameters can be assessed. In the near future, new questions will be asked that will lead to multiple scientific discoveries.

Conflicts of interest
The author has no conflicts of interest to declare.

References