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IMPACT OF HEMORHEOLOGICAL AND ENDOTHELIAL FACTORS ON MICROCIRCULATION

Vera Turchetti*, Letizia Boschi, Giovanni Donati, Luca Trabalzini, and Sandro Forconi

1. ABSTRACT

Previous studies showed that endothelial alterations caused by physical stress worsened the hemorheological parameters mainly in patients affected by ischemic vascular diseases: major vascular alterations have been found in patients with very high endothelial dysfunction indexes: these indexes are given by the various substances produced by the endothelium, but it is very difficult to have a value which clearly identifies the real state of the endothelial alteration. The function of the NO, an endogenous vasodilator whose synthesis is catalyzed by NOs, can be determined by the Citrulline/Arginine ratio, which represents the level of activity of the enzyme. A very good index of the endothelial dysfunction is asymmetric dimethylarginine (ADMA), a powerful endogenous inhibitor of NOs; in fact several studies have demonstrated a strong relationship between ischemic vascular disease and high levels of plasmatic ADMA. Our recent studies on heart failure and on ischemic cerebrovascular diseases evaluate endothelial dysfunctions and hemorheological parameters.

2. BACKGROUND

Microcirculation is the most important vascular system component and, with blood and interstitial tissue, can be considered as a whole functional organ. Every vascular disease has repercussions on microcirculation and on tissular nutrition[1,2]. The worsening of the hemorheological parameters affects microcirculation: a lot of studies have shown that blood viscosity increase and erythrocyte deformability decrease can be found in ischaemic vascular diseases[3,4]. Hemorheological disturbances are present in vascular diseases, both in acute and in chronic conditions[5]. A reduction of blood fluidity, due either to increase of hematocrit or of fibrinogen concentration or of the rigidity of red cells is commonly considered a condition of high risk for acute or chronic brain

* Vera Turchetti, Dipartimento di Medicina Interna, Cardiovascolare e Geriatrica - Università degli Studi di Siena, Policlinico Santa Maria alle Scotte, 53100 Siena, Italy – e-mail: turchetti@unisi.it

ischemia [6,7]. Many studies have demonstrated these alterations in ischemic vascular diseases: in acute and chronic cerebrovasculopathies, in ischemic cardiac vasculopathies and especially in peripheral obliterating arteriopathy [8-12].

3. PHYSICAL EXERCISE AND HEMORHEOLOGY

We studied physical exercise in healthy subjects and in patients suffering from ischemic vascular diseases with different kinds of exercise, such as the cycloergometer test, treadmill test and isotonic stress test[13-15]. In our previous research, we found that hematic hyperviscosity was also present in the resting condition in the vasculopathic patients suffering from coronary heart disease or peripheral ischemic diseases compared to healthy subjects[16-18]. However, when stronger ischemia was provoked by means of general or specific exercise, the hemorheological decline increased and persisted after a recovery period in a significant way in patients suffering from ischemic vasculopathies compared to healthy people. Subsequently, together with increased viscosity and reduced erythrocyte deformability, we found a significant increase in erythrocytic cytosolic calcium which explained the reduced erythrocyte deformability and activation of the fibrinolytic system, as in conditions of hypercoagulability[16,17,19]. After devising a new method to evaluate erythrocyte morphology, (the Zipursky-Forconi method), we observed that the EMI was altered in the vasculopathic subject, with values <1 due to a higher number of discocytes, which are normal but more rigid than the bowls which are more abundant in healthy subjects[20,21]. The exercise further decreased the EMI which did not return to basal values even after 20 minutes of recovery. In those studies, we considered that the blood, in all its cellular and plasmatic components, and the vessel were involved in the phenomena that caused the ischemia during the stress test[22,23]. The rheological worsening, secondary to the ischemic pathology, was affected by, and in turn caused, a microcirculatory deterioration. Previous studies showed that endothelial alterations caused by physical stress worsened the hemorheological parameters mainly in patients affected by ischemic vascular diseases: major vascular alterations have been found in patients with very high endothelial dysfunction indexes[3,4,24].

4. HEMORHEOLOGY AND ENDOTHELIUM

In the last 20 years, there has been great interest in the study of the vascular endothelium. Today it is considered a true organ with a surface area of about 400 square meters, the same mass as 6 normal hearts with a weight of 1500 grams and containing more than 1 trillion cells[25]. It has many functions that are important in guaranteeing vascular homeostasis: it can modulate vascular tone, the proliferation of vascular smooth muscle cells, hemostasis, thrombolysis, platelet aggregation, adhesiveness of monocytes, inflammation, the immune response and the production of free radicals[26-28]. It secretes many substances which can be divided into vasodilators, such as nitric oxide (NO), prostacyclin, bradykinin and hyperpolarizing factors, and vasoconstrictors, such as endothelin-1, thromboxane and activation of angiotensin II[27,29]. The main vasodilatory factor is NO which also has an anti-platelet action and is an inhibitor of smooth muscle cells, of ET-1 synthesis, reduces the expression of molecular adhesion for inhibition of leukocytes[30,31]. The metabolic pathway of NO starts from l-arginine catalyzed by NO syntase and produces one molecule of NO and one molecule of l-citrulline. All the atherosclerotic risk factors for example hypercholesterolemia, hyperglycemia,