Nitric oxide status in sickle cell anemia

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In this issue of the *Revista Brasileira de Hematologia e Hemoterapia*, Elias et al.[1] show the negative correlation between nitrite serum levels and the concentration of fetal hemoglobin (Hb F) in adult patients with sickle cell anemia. Hb F is a predictor of good prognosis in sickle cell anemia suggesting that the nitrite concentration might be used as a biomarker of the disease prognosis[1]. Decreased levels of nitrite can indicate a better prognosis as it may be related to an increased production of NO via Hb F[2] .

Sickle cell disease (SCD) is an inherited disorder of hemoglobin synthesis. The cause of SCD is a point mutation in the β-globin gene. This genetic abnormality leads to the production of sickle hemoglobin, a protein that has the unique property of polymerizing into long fibers when deoxygenated, thereby decreasing red blood cell deformability and damaging the cell membrane. Sickle cell anemia is characterized by episodes of vaso-occlusion and hemolysis, which are responsible for the clinical manifestations of the disease[3] .

This disease is a chronic inflammatory condition that diminishes the reserves of nitric oxide (NO). NO is normally produced by the endothelium and regulates the basal vessel tone, inhibits platelet and hemostatic activation, inhibits adhesion molecules and reduces reactive oxygen species (ROS) levels. The potential importance of NO in SCD has been the subject of much research over the last decade. It is now accepted that the decreased availability of NO is an important mechanism in the pathophysiology of SCD[3].

Serum levels of L-arginine, the precursor of NO, are decreased in patients with sickle cell anemia, particularly during vaso-occlusive and acute chest syndrome episodes; these levels are inversely proportional to painful crisis. In the vascular compartment, the hemolytic process causes the release of large amounts of free hemoglobin, heme and arginase. Free plasma hemoglobin, in addition to generating ROS, such as the hydroxyl and superoxide radicals, is also a potent scavenger of nitric oxide. The hydrophobic heme enters the plasma membrane of endothelial cells, releasing iron, which damages the cells causing the release of ROS[3]. Arginase, released in plasma L-arginine acts in transforming it into urea and ornithine. The increase in plasma L-ornithine competes with low levels of L-arginine uptake in cellular compartments and may generate pulmonary hypertension and the production of ROS. The half-life of NO in the blood is extremely short because of its rapid reaction with hemoglobin to form methemoglobin and nitrate[4].

In conclusion the analysis of the metabolism of NO is important to monitor patients with SCD and biomarkers may be associated with disease progression. This represents the most important advance in understanding the pathogenesis, contributing to a more accurate management of patients[5].

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