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Letter to the Editor

Albumin cobalt binding and ischemia modified albumin generation: An endogenous response to ischemia?

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Myocardial ischemia has become the leading cause of mortality in western countries and this unfavorable trend is unlikely to reverse in the near future. The events progression leading to acute coronary syndrome involves a physiological continuum that traditionally spans from plaque instability to rupture, intracoronary thrombus, reduced blood flow, myocardial ischemia, reversible damage and necrosis [1]. From this biological perspective, myocardial necrosis is time-dependent and occurs when the action of the endogenous mechanisms of response to ischemia is finally overwhelmed. During acute ischemic conditions, the metal binding capacity of albumin for transition metals, like copper, nickel and cobalt is reduced, generating a metabolic variant of the protein, commonly known as ischemia modified albumin (IMA). IMA measurement has recently been proposed as the first US FDA-cleared sensitive marker for the diagnosis of myocardial ischemia in patients presenting with typical acute chest pain [2]. The precise mechanism for IMA generation is yet unknown, though it appears that reactive oxygen species, produced during ischemia, might generate highly reactive hydroxyl free radicals, resulting in site-specific modification to the N-terminus of the albumin moiety, especially at the *N*-Asp-Ala-His-Lys sequence [3,4].

It has been recently reported that cobalt chloride administration might promote delayed cardiac preconditioning through selective activation of the HIF-1, AP-1 and iNOS signaling [5]. Cobalt is a relatively rare transition metal with properties similar to iron, chromium and nickel. Cobalt chloride, a water-soluble compound traditionally employed to treat anemia in pregnant women, infants and chronic anemia patients undergoing long-term haemodialysis [6], is a well-established chemical inducer of hypoxia-like responses, such as erythropoiesis and angiogenesis in vivo, likely involving an increased DNA binding activity of hypoxia-inducible factor-1α (HIF-1α) to its target genomic sequences. Genes modulated by the HIF-1α binding include those encoding for angiogenetic growth factors (angiopoietin, erythropoietin, vascular endothelial growth factor, insulin growth factor-2, placental growth factor, platelet-derived growth factor β), cytokines (transforming growth factors α and β), survival factors and proapoptotic proteins (RTP801, NIX) [7]. It has been speculated that cobalt might stabilize HIF-1α through generation of reactive oxygen species (ROS) by a nonenzymatic, nonmitochondrial mechanism. Under normoxic conditions, the main mediator HIF-1α is rapidly degraded by the proteasome. However, at lower oxygen conditions, HIF-1α undergoes a stabilization process and induces activation of genetic sequences that promote efficient adaptations to hypoxia. On the basis of the evidence provided by the article of Xi et al. [5], the in vivo generation of IMA might thus be interpreted as an efficient endogenous mechanism of response to ischemia, preventing myocardial damage or limiting the extent of myocyte necrosis. The decreased albumin affinity for transition metals, as it occurs during acute ischemia, generates IMA and increases the concentration of biological active free

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cobalt in plasma, which might finally exert a beneficial effect, limiting the extent of the ischemic injury, by modulating the HIF pathway. In this perspective, we believe that this evidence might provide a reliable explanation for the in vivo generation of IMA during acute ischemia.

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