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EDITORIAL

Acute heart failure, iron deficiency, and hyperlactataemia: a high-risk combination

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Article Biegus et al., see p. 347

Heart failure (HF) represents a complex syndrome beyond a simplified haemodynamic concept. In HF pathogenesis, there is a close relationship between neurohormonal dysregulation, sympathetic activation, and overexpression of several cytokines, leading to a proinflammatory status [1, 2]. HF has two major pathophysiological consequences, congestion and hypoperfusion, that result in the metabolic impairment of peripheral tissues and end-organ dysfunction. These disturbances activate several compensatory biological responses, some of them not completely explained yet.

In the current issue of the journal, Biegus et al. [3] reported a high prevalence of elevated lactate levels and iron deficiency in patients with acute decompensated HF. Furthermore, the authors observed that the simultaneous presence of both iron deficiency and hyperlactataemia in this population identifies a high-risk subgroup with increased risk of death. The authors tried to explain their results with a provocative hypothesis that both pathophysiological pathways connect at some point.

The metabolism of lactate is complex and not well known. Lactate increase was traditionally considered a consequence of tissue hypoxia caused by hypoperfusion [4], but this simple interpretation was progressively modified when it was demonstrated that hyperlactataemia in patients with acute HF was not related to blood pressure, arterial oxygen saturation, or cardiac output, even in the sickest population [5–7]. Instead, lactate accumulation is better explained by an imbalance between its production and clearance, which itself may be caused by several mechanisms, such as peripheral hypoperfusion due to low cardiac output, high central venous pressure or vasoconstriction, sympathetic activation, hypoxaemia, anaemia, and liver or renal dysfunction [8].

The liver seems to play a central role in the connection between hyperlactataemia and iron deficiency. Hepatocytes are the main site where lactate is cleared, and the liver is also a major determinant of iron metabolism through the production of hepcidin. The authors, in accordance with previous reports, showed that patients with hyperlactataemia and iron deficiency presented a significant alteration in liver function expressed by increased values of transaminases and bilirubin. Liver dysfunction is believed to contribute to hyperlactataemia via decreased lactate clearance and accelerated glycolysis [9]. On the other hand, inflammatory stimuli observed in patients with HF induce hepatic production of hepcidin, decreasing iron absorption and levels of circulating iron [10].

Iron deficiency may itself aggravate the alteration of lactate metabolism. In cardiac myocytes, iron constitutes an indispensable cofactor for the sequential oxidation-reduction reactions, which yield oxidative production of ATP. Limitation of aerobic metabolism shifts the cardiac energy production to a less favourable anaerobic glycolysis, leading to lactate production. Recently, it has been shown that an iron-deficient environment increases lactate production of human cardiomyocytes in mechanical effort conditions. Myocardial hepcidin expression is increased in experimental models of myocardial ischaemia, myocarditis, and HF [11, 12].

In the liver, iron is an important element in the formation and availability of the enzymatic complexes NAD and NADH, which are necessary for hepatic conversion of lactate into pyruvate. Iron deficiency may therefore lead to lactate overproduction and accumulation, and unfavourable effects may be observed in the myocardium, the skeletal muscle, and the haematopoietic system [13].

Patients with HF usually present a pathological reduction of oxygen consumption, which is aggravated by iron deficiency and anaemia, as well as neurohormonal activation. Both factors explain why HF patients could quickly switch from aerobic

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to anaerobic metabolism, thus favouring the coexistence of both hyperlactataemia and iron deficiency during episodes of acute decompensation.

Adrenergic hyperstimulation might also play a role in the high prevalence of both iron deficiency and hyperlactataemia observed in patients with acute HF. On one hand, the increase in circulating catecholamines and subsequent chronic stimulation of $\beta 2$ adrenergic receptors activate sarcolemic ATPase Na/K activity, enhancing glycogenolysis and aerobic glycolysis [14], and on the other hand, patients with chronic HF with a greater sympathetic activation expressed by higher norepinephrine levels have an impaired iron transport (transferrin saturation < 20%) and increased iron demand (elevated levels of soluble transferrin receptor) without an increase in ferritin levels [15]. Additionally, sympathetic activation leads to cardiomyocyte iron deficiency via downregulation of type 1 transferrin receptor expression [16], which is also observed with the aldosterone exposure contributing to cardiac remodelling. Thus, sympathetic activation can lead to a metabolic disturbance that can cause both lactate accumulation and iron deficiency, independently of blood pressure, cardiac output, impaired iron absorption, or comorbidities.

In conclusion, the study by Biegus et al. [3] opens a window for a better understanding of the metabolic disturbances observed in the acute HF population. Both hyperlactataemia and iron deficiency are well-known determinants of a worse prognosis in HF patients, apparently with additive effects. The integration of both alterations in a common pathophysiological pathway is an interesting exercise that may lead to future therapeutic targets.

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