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

Eduardo Barge-Caballero, David Couto-Mallón

Complejo Hospitalario Universitario de A Coruña (CHUAC), Instituto de Investigación Biomédica de A Coruña (INIBIC), Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), A Coruña, Spain

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
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 β2 adrenergic receptors activate sarcolic 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.

Conflict of interest: none declared

References
1. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol. 1992; 20(1): 248–254, indexed in Pubmed: 1351488.
2. Van Linthout S, Tschöpe C. Inflammation — cause or consequence of heart failure or both? Curr Heart Fail Rep. 2017; 14(4): 251–265, doi: 10.1007/s11897-017-0337-9, indexed in Pubmed: 28667492.
3. Biegus J, Zymliński R, Sokolski M, et al. Elevated lactate in acute heart failure patients with intracellular iron deficiency as an identifier of poor outcome. Kardiol Pol. 2019; 77(3): 347–354, doi: 10.5603/KP.a2019.0014, indexed in Pubmed: 30740644.
4. Andersen LW, Mackenauer J, Roberts JC, et al. Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc. 2014; 88(10): 1127–1140, doi: 10.1016/j.mayocp.2013.06.012, indexed in Pubmed: 24079662.
5. Biegus J, Zymliński R, Sokolski M, et al. Clinical, respiratory, haemodynamic, and metabolic determinants of lactate in heart failure. Kardiol Pol. 2019; 77(1): 47–52, doi: 10.5603/KP.a2018.0240, indexed in Pubmed: 30566223.
6. Zymliński R, Biegus J, Sokolski M, et al. Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion. Eur J Heart Fail. 2018; 20(6): 1011–1018, doi: 10.1002/ejhf.1156, indexed in Pubmed: 29431284.
7. Couto-Mallón D, González-Vilchez F, Almenar-Bonet L, et al. Prognostic Value of Serum Lactate Levels in Patients Undergoing Urgent Heart Transplant: A Subanalysis of the ASIS-TC Spanish Multicenter Study. Rev Esp Cardiol (Engl Ed). 2019; 72(3): 208–214, doi: 10.1016/j.recesp.2018.02.021, indexed in Pubmed: 29859897.
8. Örn S, van Hall G. Does a normal peripheral lactate value always indicate an aerobic tissue metabolism? Eur J Heart Fail. 2017; 19(8): 1034–1035, doi: 10.1002/ejhf.663, indexed in Pubmed: 28547836.
9. Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol. 2014; 2(4): 339–347, doi: 10.1016/s2213-8587(13)70154-2, indexed in Pubmed: 24703052.
10. Theurl I, Aigner E, Theurl M, et al. Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications. Blood. 2009; 113(21): 5277–5286, doi: 10.1182/blood-2008-12-195651, indexed in Pubmed: 19293425.
11. Dzięgala M, Kobak KA, Kasztura M, et al. Iron depletion affects genes encoding mitochondrial electron transport chain and genes of non-oxidative metabolism, pyruvate kinase and lactate dehydrogenase, in primary human cardiac myocytes cultured upon mechanical stretch. Cells. 2018; 7(10): 175, doi: 10.3390/cells7100175, indexed in Pubmed: 30347796.
12. Isoda M, Hanawa H, Watanabe R, et al. Expression of the peptide hormone hepcidin increases in cardiomyocytes under mechanical stretch. Cells. 2018; 7(10): 175, doi: 10.3390/cells7100175, indexed in Pubmed: 30347796.
13. Jankowska EA, Malyszko J, Ardehali H, et al. Iron status in patients with chronic heart failure. Eur J Heart J. 2013; 34(11): 827–834, doi: 10.1093/eurheartj/ehs377, indexed in Pubmed: 23178646.
14. Levy B. Lactate and shock state: the metabolic view. Curr Opin Crit Care. 2006; 12(4): 315–321, doi: 10.1097/01.ccx.0000225528.77450.15, indexed in Pubmed: 16810441.
15. Moliner P, Enjuanes C, Tajes M, et al. Association Between Norepinephrine Levels and Abnormal Iron Status in Patients With Chronic Heart Failure: Is Iron Deficiency More Than a Comorbidity? J Am Heart Assoc. 2019; 8(4): e010887, doi: 10.1161/JAHA.118.010887, indexed in Pubmed: 30760062.
16. Maeder MT, Khammy O, dos Remedios C, et al. Myocardial and systemic iron depletion in heart failure implications for anemia accompanying heart failure. J Am Coll Cardiol. 2011; 58(5): 474–480, doi: 10.1016/j.jacc.2011.01.059, indexed in Pubmed: 21777743.