



## LETTER TO THE EDITOR

### Iron metabolism in heart failure: Mechanisms and therapeutic approaches



### Metabolismo do ferro na insuficiência cardíaca: mecanismos e abordagens terapêuticas

Anemia is frequent in heart failure (HF) patients, and is considered an independent factor for worse prognosis.<sup>1–3</sup> However, it is not known whether anemia causes worsening of the disease course or is only a sign of the patient's cardiac and systemic impairment. The definition of anemia according to the World Health Organization has the following criteria: for women, hemoglobin <12 g/dl (7.5 mmol/l) and for men, <13 g/dl (<8.1 mmol/l).<sup>4</sup> However, other criteria exist, and multicenter studies and meta-analyses have demonstrated that anemia is present in 22–37% of patients with HF.<sup>5</sup>

A recent meta-analysis studied anemia and mortality in more than 150 000 patients with HF.<sup>6</sup> It was observed that mortality in patients with anemia was nearly double that of nonanemic patients. The etiology of anemia in HF has been shown to be multifactorial, and can be caused by increased plasma volume or reduced red cell mass ("true anemia").<sup>7</sup> It is necessary to understand the factors that lead to decrease hemoglobin in patients with HF. Another plausible factor is the activation of pro-inflammatory cytokines (interleukin-6, interleukin-1, interferon-gamma and TNF-alpha),<sup>9</sup> that plays a fundamental role in the inhibition of hematopoiesis, reducing erythropoietin production.<sup>8,9</sup>

In a paper on renal transplant patients published in a recent issue of the Journal Rev. Port. Cardiol., Nunes et al. found that the levels of antibodies were associated with reduced left ventricular ejection fraction (LVEF). Based on their findings the authors report that inflammatory mediators such as antibodies (IgG and IgM) can be used as a marker of cardiac dysfunction.<sup>9</sup> This, by negative feedback, would lead to the inhibition of iron absorption at the duodenal level. Also, the drugs routinely administered to HF patients, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and carvedilol, have been known to inhibit the production of

erythropoietin.<sup>10</sup> Our research group performed a random double-blind study in 2007, assessing left ventricular systolic function in patients with chronic Chagas cardiomyopathy before any therapeutic intervention (Botoni et al.<sup>11</sup>). In preliminary studies as yet to be published, a negative correlation was observed between the serum hemoglobin level and the B-type natriuretic peptide (BNP), confirming a close neurohormonal relationship with the ventricular function. Nevertheless, in this study, there was a significant reduction in blood pressure, as well as in serum hemoglobin levels, but without any cases of anemia. This is important, since low hemoglobin levels increase cardiac work as well as the activity of the renin-angiotensin-aldosterone system, leading to increased cardiac remodeling.

Studies have shown the value of administering erythropoietin intravenously in patients with mild to severe congestive HF and in patients with chronic kidney failure. This treatment seems to be an efficient therapy that is largely responsible for improved prognosis as shown by New York Heart Association functional class, LVEF, left ventricular dilation and hypertrophy, BNP, exercise capacity and quality of life. Studies on therapeutic interventions performed in Italy and Greece, published in 2006 and 2008 respectively, show that the administration of erythropoiesis-stimulating agents (ESAs) such as darbepoetin alfa in patients with heart failure increase and maintain hemoglobin levels, leading to improvements in physical ability and in quality of life.<sup>12</sup> On the other hand, a study on 319 patients randomized to placebo or darbepoetin alfa showed no improvement in exercise capacity, but mortality and hospitalization were low (hazard ratio 0.68, 95% confidence interval 0.43–1.08,  $p=0.10$ ). However, patients with heart failure and anemia treated with ESAs present significantly increased risk of cardiovascular events, including myocardial infarction and thromboembolic events.

### Conclusion

Changes in the metabolism of iron and its relation to the inflammatory response appear to exert significant pathogenic role in patients with heart failure.

A better understanding of these changes and interrelationships may lead to the development of alternative treatments for these patients.

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