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REVIEW ARTICLE

Anemia and iron deficiency in heart failure☆

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Abstract Heart failure is a common problem and a major cause of mortality, morbidity and impaired quality of life. Anemia is a frequent comorbidity in heart failure and further worsens prognosis and disability. Regardless of anemia status, iron deficiency is a common and usually unidentified problem in patients with heart failure. This article reviews the mechanisms, impact on outcomes and treatment of anemia and iron deficiency in patients with heart failure.

PALAVRAS-CHAVE
Anemia;
Deficiência de ferro;
Insuficiência cardíaca;
Terapêutica com ferro

Anemia e deficiência de ferro na insuficiência cardíaca

Resumo A insuficiência cardíaca é uma patologia comum e uma causa importante de mortalidade, morbilidade e deterioração da qualidade de vida. A anemia é uma comorbilidade frequente na insuficiência cardíaca e agrava o seu prognóstico e capacidade funcional. Independentemente da presença ou não de anemia, a deficiência de ferro é um problema associado à insuficiência cardíaca muitas vezes não identificado. Este artigo revê os mecanismos, impacto prognóstico e tratamento da anemia e deficiência de ferro.

Case study

A 72-year-old woman with a history of poorly controlled hypertension under diuretic therapy for the previous 10 years was assessed for fatigue and dyspnea on minimal exertion (NYHA class III). Her blood pressure was 150/85 mmHg and her heart rate was 88 bpm; she had faint crackles in the lung bases and ankle edema. The ECG showed voltage criteria for left ventricular hypertrophy. Her hemoglobin (Hb) level was 11.0 g/dl and her mean corpuscular volume was 85 fl, blood glucose 102 mg/dl, total cholesterol 190 mg/dl and creatinine 1 mg/dl. She was medicated with furosemide, a renin-angiotensin system inhibitor and a beta-blocker, and was referred for echocardiographic assessment.

What role did the patient's Hb of 11 g/dl play in her clinical setting?

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Table 1 Factors associated with anemia in patients with heart failure.

1. Nutritional deficiency
2. Intestinal malabsorption
3. Hypovolemia with hemodilution
4. Renal failure
5. Hypothyroidism
6. Bleeding
7. Inflammation: increased serum cytokines (IL-6, TNF-α) and acute phase proteins (CRP)
8. Treatment with ACE inhibitors

ACE: angiotensin-converting enzyme; CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha.

Introduction

The prevalence of heart failure (HF) is 1–2%, but may exceed 10% in individuals aged over 70.[1,2] In Portugal, the prevalences of HF with systolic dysfunction and HF with preserved systolic function have been estimated at 1.3% and 1.7%, respectively, in a primary health care context.[3]

HF is associated with a marked decline in quality of life and high morbidity and mortality.[4] Although treatment with renin-angiotensin-aldosterone system inhibitors and beta-blockers can be effective, one-year mortality is up to 20% and rehospitalizations for HF can reach 30%.[5] However, the clinical course of HF is variable, due to the interaction of diverse demographic and clinical characteristics that affect prognosis, among them anemia and iron deficiency.[6–8]

Anemia in heart failure

Anemia is a frequent comorbidity in HF. Its prevalence ranges between 4% and 55% depending on the study population and the cutoff values of Hb defined as the lower limit of normal.[9] In a large cohort study published in 2003 of 12 065 patients with new-onset HF in 138 centers in the Canadian state of Alberta, the prevalence was 17%.[10] It is more common in women, the elderly and individuals with renal failure.

Anemia is associated with increased morbidity and mortality, as well as significant reductions in functional capacity, which is already impaired by HF.[6–8,11,12] In the largest observational registry published, anemia was an independent indicator of prognosis after correction for numerous confounding factors.[12]

There are various causes of anemia in association with HF (Table 1), including renal failure and hypothyroidism, and occasionally low levels of vitamin B_{12} and folic acid.[13] Another factor may be hemodilution, which can cause anemia due to expansion of plasma volume without any effective reduction in red blood cells. Angiotensin-converting enzyme inhibitors, which are commonly used in HF treatment, can be associated with low Hb, probably by suppression of erythropoietin, while inflammatory cytokines such as interleukin-1 and -6 and tumor necrosis factor alpha, which are elevated in severe HF, can reduce production of erythropoietin or increase resistance to its action. Finally, antiplatelet or anticoagulant therapy can cause gastrointestinal bleeding.[14]

Although all of the above factors can play a part, iron deficiency anemia (IDA) is the most common form in HF.

IDA associated with HF may be absolute or functional. The following mechanisms are presumed to be involved in the development of absolute IDA, in which iron stores are depleted as indicated by serum ferritin <30 μg/l[15]: (i) insufficient dietary iron supply, (ii) intestinal malabsorption, impaired duodenal iron transport, drug interactions (e.g. omeprazole), or food reducing absorption, and (iii) gastrointestinal bleeding.

In a 2006 study of the causes of anemia in HF patients, de Silva et al. found low iron or ferritin levels in 43% of patients but microcytosis in only 6%.[16] However, Nanas et al. detected iron deficiency in bone marrow in their study population, despite normal serum iron, ferritin and erythropoietin.[17] This may be explained by diversion of iron from the marrow to storage sites of the reticuloendothelial system, where it is unavailable for erythropoiesis despite normal or high iron and ferritin levels, as seen in chronic disease.[18]

An important factor is transferrin saturation (TSAT). Normal TSAT ranges between 20% and 50%; values below 20% are seen in IDA and inflammation anemia. In a study of 157 patients with chronic HF, TSAT <20% was associated with higher NYHA functional class, lower peak oxygen consumption and greater mortality in two-year follow-up.[19]

Functional IDA is defined as insufficient iron supply to meet demands, despite abundant iron stores, because iron is locked within cells of the reticuloendothelial system and is unavailable for cell metabolism. One mechanism in functional IDA appears to be related to hepcidin, a protein that is central to regulation of iron metabolism. Hepcidin levels are elevated in the initial stages of HF but fall as the disease progresses; low levels are an independent marker of worse prognosis.[15] Hepcidin binds to ferroportin, the only protein able to export intracellular iron, which is thereby degraded, preventing iron from re-entering cells.[15] This reduces iron absorption in the duodenum and causes iron to be retained in the reticuloendothelial system, reducing its concentration and availability in target tissues. Hepcidin also plays a part in erythropoiesis and in the innate immune response to pathogens.

Iron is essential for normal hematopoiesis; most of it is taken up by erythroblasts and reticulocytes for Hb synthesis. Iron deficiency results in resistance to hematopoietic growth factors (e.g. erythropoietin), and impairs the differentiation and maturation of all types of hematopoietic cells.[15]

Treatment of anemia in heart failure

There is no universally agreed definition of anemia. The World Health Organization considers anemia to exist when Hb levels are lower than 13 g/dl in men and 12 g/dl in women.[20] Others define it as hematocrit less than 35–39%.[21] The target Hb level in patients with anemia is also not agreed, but 12 g/dl is regarded as safe.[22]

The association of anemia with worse prognosis, functional capacity and quality of life in HF has prompted efforts to correct this comorbidity. Besides blood transfusion, which is recommended for severe anemia,[23] there are two main types of treatment of anemia in HF: erythropoietic stimulating agents (ESAs) and iron supplementation.