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EDITORIAL COMMENT

Isn't it IRONic? In the era of complex cardiac procedures, the deficiency of a simple tiny cation makes a difference in acute coronary syndromes

Não é IRÔNICO? Na era dos procedimentos cardíacos complexos, a deficiência de um simples catião minúsculo faz a diferença nas síndromes coronárias agudas

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Iron is an essential micronutrient, well known for its role in oxygen transport and storage, in immune and neural functions, and also in basic cellular processes, including enzymatic reactions, mitochondrial function and oxidative metabolism. It is particularly important in metabolically active tissues such as cardiac muscle.[1]

It is therefore conceptually logical that iron deficiency affects myocardial performance.

However, in this era of enthusiastic advanced and complex cardiac technologies, the prognostic impact of this simple cation deficiency in cardiac conditions was proven only a little over a decade ago, and specifically in the context of heart failure (HF).[2]

In fact, iron deficiency (regardless of the presence of anemia) emerged as an important co-morbidity with independent prognostic value in HF, being associated with higher mortality, more HF hospitalizations and worse quality of life.[1,2] This finding led to the evaluation and subsequent confirmation of the positive prognostic impact of intravenous iron replacement, using ferric carboxymaltose, in patients with chronic HF with reduced ejection fraction.[3] Accordingly, the 2016 European Society of Cardiology HF guidelines recommend testing these patients for iron deficiency and treating it, preferably with that intravenous therapy.[4] More recently, this benefit was also proven in an acute HF setting.[5]

Acute myocardial infarction (AMI) is a major cause of HF. HF may occur early, frequently during hospital admission for AMI, or later, in subsequent months. There are multiple variables that account for the prognosis of patients with AMI, including successful revascularization, but it depends strongly on the extent of the infarction and the residual left ventricular function, which may be influenced by the iron status at the time of the acute coronary syndrome (ACS). In fact, since iron is critical in the citric acid cycle for adenosine triphosphate (ATP) generation, iron deficient ACS subjects may suffer adverse glycolysis and increased lactate formation, in order to compensate for decreased ATP production, enhancing ischemic stress and increasing the loss of cardiomyocytes.[6] Also, there are data indicating that iron has immunomodulatory effects on macrophages. These cells accumulate in the infarcted myocardium and take up iron, which shifts their profile into an anti-inflammatory phenotype, resulting in improved infarct healing and beneficial remodeling.[6,7] Therefore, iron deficient ACS patients might be prone to more myocardial loss and more adverse remodeling, and subsequently, HF.

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However, the impact of iron deficiency on outcomes in patients with ACS has not been well established.[8]

Meroño et al. reported in a study including 244 patients that iron deficiency was a determinant of functional capacity and quality of life 30 days after an ACS, but mortality and hospitalization data were not reported.[9]

Zeller et al. studied 836 ACS patients, 29.1% of whom had iron deficiency, and this was shown to be a strong predictor of non-fatal AMI and cardiovascular death on follow-up. In fact, the risk of these events in the four years after ACS was 73% higher in those who were iron deficient at the time of ACS.[6]

Very recently, Reinhold et al. published a systematic review and meta-analysis of studies including patients with ACS stratified by iron status.[8] This meta-analysis included seven studies (n=2821 patients), all of them reporting a high prevalence of iron deficiency in the ACS population. Short-term outcomes were heterogeneous across studies, but all the studies that assessed long-term prognosis found it was worse in the iron deficiency population, reporting higher all-cause mortality or higher combined endpoint of non-fatal myocardial infarction and cardiovascular mortality. The authors concluded that patients with iron deficiency presenting with ACS may have a worse long-term prognosis, but more studies are required for confirmation.

In this issue of the Journal, Carina Silva et al. present an observational, retrospective, single center study of 817 patients admitted for ACS,[10] 95% of whom had AMI, allocated into two groups according to the presence (n=298) or absence (n=519) of iron deficiency at admission, which was defined as ferritin <100 ug/L or ferritin >100 ug/L and <300 ug/L and transferrin saturation <20%, accounting for both absolute and functional iron deficiency. Groups were then compared regarding the clinical endpoint of death or severe HF in long-term follow-up (medium 738 days), and independent predictors of prognosis were determined with logistic regression analysis. Authors reported that iron deficiency affected a significant proportion of ACS patients (36%), and that iron deficient ACS patients presented more frequently with moderate and severe depression of LV function and depression of RV function and higher Killip classes. At follow-up, patients of the iron deficient group had a higher rate of events, namely higher mortality, more severe HF (NYHA III-IV), and higher hospital readmission rate (9.8% vs. 13.7%, p=0.048). Iron deficiency was found to be an independent predictor of death or HF on follow-up, along with anemia, left ventricular dysfunction, renal dysfunction and the absence of revascularization. It also enabled further prognostic stratification of ACS patients without anemia for the occurrence of death or severe HF, and of those ACS patients with lower Killip classes ($\leq$2) in terms of the occurrence of death.

As the authors pointed out, this study has several limitations: it is a single center retrospective study; there was no therapeutic follow-up assessment, nor evaluation of anti-thrombotic or optimal medical treatment for HF, nor regarding possible iron supplementation, and many patients (159 of the 976 patients admitted for ACS in the timeframe considered) were excluded because of absence of iron status parameters or other reasons, which might constitute bias. Additionally, only one set of iron kinetic parameter tests was used and only at admission, raising therefore the possibility that clinical outcomes at long-term follow-up depend on the known effect of iron deficiency in HF and not on its effect in ACS.

So, more robust studies are needed to confirm these results.

Nevertheless, this study highlights the value of a simple, cheap and easy prognostic tool, supporting the inclusion of iron status parameters in the laboratory routine panel for patients admitted for ACS.

Additionally, these results raise the expectations of a window of opportunity to easily improve the prognosis of ACS patients, since iron deficiency is a potentially treatable condition. Prospective controlled trials are needed to assess the possible benefit of iron supplementation in ACS.

Hopefully in the near future, we shall have more evidence and maybe not a new but a very simple way of further improving prognosis of ACS patients and potentially contributing to the prevention of ischemic HF.

Conflicts of interest

The author has no conflicts of interest to declare.

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