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Marceau Quatredeniers, David Montani, Alain Cohen-solal, Frédéric Perros

Editorial

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Marceau Quatredeniers[1], David Montani[1], Alain Cohen-Solal[2] and Frédéric Perros[1]

[1]Université Paris–Saclay, AP-HP, INSERM UMR_S 999, Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital de Bicêtre, Le Kremlin Bicêtre, France; [2]Department of Cardiology, Lariboisière Hospital, University of Paris, INSERM UMR_S 942, Paris, France

Abstract

In left heart failure, iron supplementation (IS) is a first-line treatment option, regardless of anemia. Pulmonary arterial hypertension (PAH), a rare disease leading to right heart failure, is also associated with iron deficiency. While it is a much debated topic, recent evidence demonstrate that restoration of iron stores results in improved right ventricular function and exercise tolerance. Hence, IS may also be considered as an option in the treatment of PAH.

Keywords

right heart failure, hepcidin, iron supplementation

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Iron deficiency in cardiovascular diseases

Iron deficiency is a common comorbidity in chronic left heart failure (HF), with an estimated prevalence of 30%–40% in stable patients and more than 50% in hospitalized patients.[1] The causes of iron deficiency in HF patients are multiple and include low-grade inflammation, poor intestinal absorption, as well as anticoagulant-induced bleeding. Inflammation causes an increase in serum hepcidin, the master regulator of iron homeostasis, hence repressing iron release from storage sites and intestinal iron absorption.[1] Animal and human studies in HF have shown that iron deficiency impairs metabolism, contraction and relaxation of the left ventricle, negatively affects left ventricle remodeling, and that these effects may be improved by iron supplementation.[2] As a consequence, in a number of placebo-controlled studies in HF patients with reduced left ventricular ejection fraction (HFrEF) and iron deficiency, intravenous iron supplementation, even in the absence of anemia, improved physical performance (increased 6-minute walk distance (6MWD)), New York Heart Association functional class, and quality of life.[1,3,4] In CONFIRM-HF,[5] HF rehospitalizations were reduced. Large-scale mortality trials are currently ongoing. The 2016 ESC guidelines recommend that all newly diagnosed HFrEF patients are routinely tested for iron deficiency and that intravenous supplementation should be considered as a treatment option in symptomatic patients with HFrEF and iron deficiency (serum ferritin $< 100\,\mu g/L$, or ferritin 100–299 $\mu g/L$ and transferrin saturation $< 20\%$).[6] The deleterious effects of iron deficiency are also described in pulmonary arterial hypertension (PAH).[7] PAH is a progressive disorder characterized by increased mean pulmonary artery pressure ($\geq$20 mmHg) and increased pulmonary vascular resistance ($\geq$3 Wood Units)[8] as a result of endothelial dysfunction and obstructive remodeling of small pulmonary arteries. This leads to reduced cardiac output, right HF, and ultimately death.[9]

As observed in HF, iron deficiency is highly prevalent in PAH patients (40%–60%) and negatively correlates with exercise capacity (decreased 6MWD) and survival, regardless of the presence of anemia.[10] PAH and HFrEF share the common effect of an ongoing inflammatory stimulus, where the increase in cytokines such as interleukin 6 induces

Corresponding author:
Frédéric Perros, Inserm UMR_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, 92350, France.
Email: frederic.perros@inserm.fr

hepcidin release from the liver.[11,12] Unlike in HFrEF, iron deficiency in right ventricular failure is poorly documented so that concluding on the benefit of iron supplementation in PAH remains challenging.

Iron deficiency in PAH: undeniable limitations of clinical studies

Over the past two decades, PAH has evolved from a uniformly fatal condition to a chronic, manageable disease in many cases, the result of unparalleled development of new therapies[13] and the challenge of managing comorbidities such as iron deficiency.

The handful of clinical trials investigating the potentially useful therapeutic effect of iron supplementation in PAH patients present many limitations. When comparing them to studies carried out in chronic left HF, several key explanations appear and merit thorough analysis.

First, all trials with iron supplementation in PAH were uncontrolled, open-label investigations in small populations (15–21 patients with iron deficiency).[10,14,15] The diagnosis of PAH was not systematically confirmed by the gold standard right heart catheterization.[14] In addition, the published trials often combined PAH etiologies,[10,14,15] regardless of the World Health Organization's classification for PAH. Moreover, the degree of PAH-induced right HF may be very variable and it has been shown in left HF that the prevalence of iron deficiency was higher in the most severe ones.[16]

Secondly, the diagnostic evaluation of iron deficiency is critical. In the aforementioned studies, iron status in PAH patients was assessed by different methods: measurements of serum ferritin, transferrin, soluble transferrin receptor (sTfR), transferrin saturation, or iron itself; with or without second measurements such as vitamin D or C-reactive protein. However, these independent indicators cannot be compared, and assessment of iron status often relies on a combination of biochemical indicators.[14] The lack of standardized diagnostic method prevents from a final valuation of the impact of iron supplementation in PAH. In addition, neither inflammation nor hepcidin levels were evaluated systematically in the enrolled patients. Similarly, sTfR levels were not systematically measured, which may have led to incorrect interpretation of iron status in patients with inflammation.[14] Conversely, iron deficiency had a standardized definition in all HF studies: ferritin <100 μg/L, or 100–300 μg/L if transferrin saturation is $<20\%$.[4–6] Although ruling on a universal definition of iron deficiency is challenging, using these criteria may help comparing the relative prevalence of iron deficiency in PAH and in HFrEF. Further clinical trials enrolling more patients and considering all the confounding parameters would help to identify potential subgroups of responders to iron therapy.

Thirdly, iron was differently administered among the different PAH trials. Oral iron supplementation was not able to increase serum iron in PAH patients.[14] Such negative results were already reported in trials on chronic left HF[17] where they are explained by hepcidin-related absorption defect.[1] Indeed, although oral iron supplementation is convenient, readily available and inexpensive, oral iron is not effectively absorbed, particularly in HF and PAH patients due to the resulted effects on the gastrointestinal tract and the elevated hepcidin levels.[18,19] Despite these valuable insights from the left heart, an ongoing open-label phase III clinical trial is currently studying the effects of oral iron supplementation in a larger cohort of PAH patients (*clinicaltrials.gov; ID: NCT03371173*). On the other hand, intravenous iron supplementation improved quality of life and skeletal muscle exercise capacity, due to better peripheral oxygen supply by increased hemoglobin levels.[14,15] In addition, a randomized, placebo-controlled crossover study is currently investigating the effect of intravenous iron supplementation on cardiopulmonary hemodynamics, exercise capacity, and quality of life in iron-deficient PAH patients (*clinicaltrials.gov; ID: NCT01447628*).

Reassessment and correction of iron status may become part of the regular follow-up of PAH patients, but the long-term benefit remains to be determined, since the duration of follow-up was limited to 4–12 weeks in all studies.[14,15] Moreover, the available findings cannot answer the question of whether iron deficiency is a cause of more advanced symptoms with possible correction by iron supplementation, or if it corresponds to a marker of PAH severity. A very recent study suggested that iron deficiency is likely a secondary marker for the progression of PAH. This led the authors to the invidious conclusion that treating iron deficiency in PAH would then be unnecessary.[20] However, iron deficiency is not responsible for HFrEF in the left heart either and yet, iron supplementation is recommended to improve iron-deficient patients.

Despite beneficial in treating PAH patients when injected intravenously, iron supplementation resulted in conflicting effect among preclinical studies. Iron chelation by desferrioxamine prevented experimental PH development in mice, but the authors did not report on iron status after 2 weeks.[21] Another study showed that a low iron diet prevented the development of monocrotaline-induced PH in the rat, while these rats do not show any iron deficiency.[22–24] By contrast it has been shown in rats that an iron-deficient diet resulted in the development of PH and pulmonary vascular remodeling.[25] Overall, there is still a lack of experimental evidence and consensus on iron in experimental PH.

To summarize, the right heart could benefit from the extensive knowledge accumulated from studies on iron deficiency in the left heart, considering the following criteria: PAH diagnosis by right heart catheterization, standardized iron measurements for a standard definition of iron deficiency, benefits of iron supplementation according to the different clinical phenotypes of PAH, intravenous iron supplementation, rather than *per os* administration.

In addition, functional assessment of the patients (e.g. improved quality of life and increased skeletal muscle exercise capacity) could be the primary endpoints of these iron supplementation studies. The use of rigorous morphological or hemodynamic criteria of the disease such as pulmonary artery pressure, but also of modern parameters evaluating RV remodeling (by cardiac magnetic resonance) and RV function (by echocardiographic deformation imaging) might be useful for future studies.

The World Symposium on Pulmonary Hypertension holds every 5 years and is one of the key drivers of progress in PAH.[26] Its tasks forces bring consensus opinions on diagnosis, prognosis, therapy, and future perspectives of pulmonary hypertension. Their forthcoming directives will guide future research studies in the field of iron deficiency and PAH.

Conclusion

Very few studies examined the therapeutic potential of iron supplementation in PAH with iron deficiency, and the current available data are not robust enough to convince on the expected beneficial effect of such a treatment. This explains why the screening of iron deficiency in PAH patients is not mentioned in the PAH guidelines. The first trials suffered from methodological limitations. Further studies, taking advantages of left heart trials, are required to confirm the potential benefits of iron supplementation in PAH. Moreover, additional investigations are needed to identify potential subgroups of iron-deficient PAH patients in respect of PAH etiologies and hepcidin expression levels. The mechanistic links between iron deficiency and PAH remain unclear. A recent study reported a direct cause-and-effect relationship between vascular iron deficiency and PAH.[27] The authors of that study showed that intracellular iron deficiency in pulmonary arterial smooth muscle cells (PASMCs) leads to increased expression of the endogenous vasoconstrictor endothelin-1 (ET-1), known to be elevated in the lung and circulation of PAH patients.[12] In addition, they provided evidence that deregulation of this cell-autonomous pathway may be an etiological factor in familial PAH. Indeed, PASMCs from patients with mutations in bone morphogenetic protein receptor 2 (heritable PAH) have decreased hepcidin expression, increased ferroportin levels, reduced intracellular iron levels, and increased levels of ET-1.[27] Together, these data enhance the idea that iron levels in the pulmonary vasculature may be considered as a target in the treatment of PAH, and that targeting the hepcidin/ferroportin axis in PASMCs may hold therapeutic potential.

Authors' contributions

MQ, DM, ACS, and FP drafted the article or revised it critically for important intellectual content.

Conflict of interest

Pr MONTANI reports grants and personal fees from Actelion, grants and personal fees from Bayer, personal fees from GSK, personal fees from Pfizer, grants, personal fees and non-financial support from MSD, personal fees from Chiesi, personal fees from Boehringer, non-financial support from Acceleron, personal fees from Incyte Biosciences France, outside the submitted work. Dr PERROS reports personal fees from MSD outside the submitted work.

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