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Riding the Ferrous Wheel of Iron Supplementation in Pulmonary Arterial Hypertension

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Iron is an essential cofactor in numerous biological functions within aerobic organisms (1). As a component of hemoglobin, iron is crucial to oxygen transportation, and like oxygen, iron is required for optimal activity of many cellular processes and pathways (1). For example, iron serves a key role in regulating cellular metabolism, DNA synthesis, cell cycle, and cell death (2). In addition, iron inhibits HIFs (hypoxia-inducible factors), modulates BMP (bone morphogenic protein) signaling, regulates macrophage function, and increases oxygen delivery by raising hemoglobin levels (1, 3, 4). These biological properties make it a potential therapeutic target in pulmonary arterial hypertension (PAH), a disease characterized by uncontrolled pulmonary vascular remodeling and increased pulmonary artery pressures (Figure 1).

Of particular interest in PAH is iron's interaction with HIFs, major regulators of numerous biological processes (1, 5). PHDs (prolyl-hydroxylases) are a group of oxygen-dependent proteins that hydroxylate HIFs in the presence of oxygen and iron to induce HIF degradation via the proteosome. In the absence of oxygen or iron, PHDs are unable to hydroxylate HIF, allowing it to translocate to the nucleus and bind to hypoxia-responsive elements of its impressive array of target genes. Importantly, HIFs are major driving factors of metabolic alterations, pulmonary vascular remodeling, and vasoconstriction in pulmonary vascular disease (5). It therefore is not surprising that iron has been a matter of study in PAH and other forms of pulmonary hypertension.

Robust evidence exists that intracellular iron deficiency in pulmonary artery smooth muscle cells (PASMCs) can lead to the development of PAH in rodents and that iron repletion in this context attenuates the PAH phenotype (4, 6). At a biochemical level, iron deficiency is associated with increased lung expression of HIF-1α and HIF-2α as well as activation of NFAT (nuclear factor of activated T cells), survivin, and STAT3 (signal transducer and activator of transcription-3), all of which promote vascular cell proliferation and apoptosis resistance (4, 6). As a consequence of these alterations, iron deficiency has been linked to mitochondrial dysfunction and altered glycolysis (4, 6). Furthermore, intracellular iron depletion in PASMCs leads to upregulation of vasoconstrictive and proproliferative endothelin-1 signaling (4).

Iron infusion may decrease morbidity and mortality in patients with left heart failure (7), suggesting that such effects may also extend to patients with PAH and right heart failure. Indeed, one investigation found that 63% of patients with PAH were iron deficient (3). This correlated with inappropriately high hepcidin levels, suggestive of impaired iron absorption from the gastrointestinal tract (3). Iron deficiency in PAH associates with more severe disease and lower survival (3, 8). On the other hand, iron supplementation in PAH associates with improved exercise capacity and better quality of life, albeit in relatively small clinical studies (3, 8–10). Studies performed in the context of hypoxia exposure demonstrated lower pulmonary artery pressures with parenteral iron infusion and worsening hemodynamics after iron depletion (11). In light of these data, current treatment guidelines recommend correcting iron deficiency in PAH (12).

Building on this body of evidence, two double-blinded, randomized, placebo-controlled crossover studies sought to explore the effects of parenteral iron therapy in patients with PAH with patients with iron deficiency but without overt anemia. In this issue of *AnnalsATS*, Howard and colleagues (pp. 981–988) report the results from these investigations (13). In a study performed in Europe, ferric carboxymaltose or placebo was given as a single infusion at a dose of 1,000 mg (or 15 mg/kg if body weight was <67 kg) to 39 patients, and in a study conducted in China, iron dextran (20 mg iron/kg) body or placebo was given as a single infusion to 17 patients. All patients had idiopathic or heritable PAH. Iron deficiency at study enrollment was defined by a serum ferritin <37 μg/L, iron <10.3 μmol/L, or transferrin saturation <16.4%. Using an intention-to-treat analysis after a 12-week treatment period, the authors report that parenteral iron infusion restored iron levels and was well tolerated. However, iron administration was not associated with an improvement in exercise

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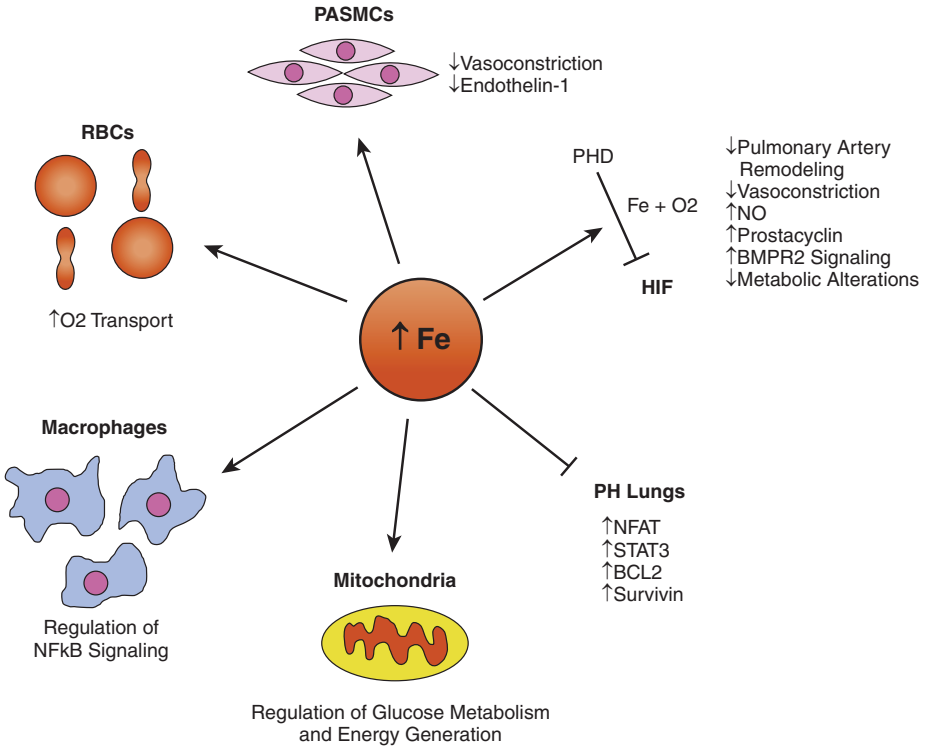

Figure 1. Overview of the various roles of iron in pulmonary hypertension. Iron favorably affects numerous processes in different organs, cells, and cellular compartments that are implicated in the development of pulmonary hypertension. Note that while several of the effects and pathways listed are HIF dependent, iron's effects on PHDs and HIF are shown separately for clarity. Consequences of attenuated HIF signaling in pulmonary hypertension are depicted on right side of the figure. BCL2 = B-cell lymphoma 2; BMPR2 = bone morphogenic protein receptor 2; Fe = iron; HIF = hypoxia-inducible factor; NFAT = nuclear factor of activated T cells; NFκB = nuclear factor κ-light-chain-enhancer of activated B cells; NO = nitric oxide; PASMCs = pulmonary artery smooth muscle cells; PHD = prolyl hydroxylase; RBCs = red blood cells; STAT3 = signal transducer and activator of transcription-3.

capacity (assessed by cardiopulmonary exercise testing or 6-min-walk test) or cardiopulmonary hemodynamics. These results held up no matter if the studies were analyzed separately or combined.

In the European study, the original primary endpoint was a change in pulmonary vascular resistance (PVR). However, recruitment was slow, and an unplanned blinded analysis of the PVR endpoint after enrollment of 15 patients revealed insufficient power to detect a statistically significant effect. Because a prior study of ferric carboxymaltose administration demonstrated an improvement in endurance time, the primary endpoint was therefore modified to a change in endurance time during cardiopulmonary exercise testing. Ultimately, the study was stopped after 39 patients because of slow recruitment. In the Chinese trial, change in PVR was maintained as the primary endpoint, but the trial had to be stopped after 17 patients because of slow recruitment.

Although the two studies failed to reach their primary endpoints, the authors are to be commended for reporting these data, as it brings up several aspects that will help the field learn and move forward. The first is the question of the appropriate indicator(s) of iron deficiency and store repletion. As mentioned above, iron deficiency in these studies was defined by decreased serum ferritin, iron, or transferrin saturation. However, the log sTFR (soluble transferrin receptor)/ferritin ratio may be a better measure of iron deficiency (14). Although sTFR levels are not routinely measured in most patients, inclusion of this parameter in research studies may be of benefit. In addition, in light of data by Lakhal-Littleton and colleagues demonstrating the effects of intracellular iron depletion in PASMCs (4), one could speculate that iron stores need to be specifically increased in PASMCs and that markers of global iron store repletion may not reflect iron availability at the PASMC level.

Along those lines, mutations in *BMPR2* are associated with higher levels of the iron transporter ferroportin in PASMCs (4), a finding associated with intracellular iron deficiency and increased endothelin-1 levels. The studies by Howard and colleagues included patients with heritable PAH, but it is unknown if these patients exhibited different responses than patients with idiopathic PAH. However, because BMPR2 signaling can also be decreased in idiopathic PAH, it is tempting to speculate whether reduced BMPR2 signaling may negatively affect PASMC iron homeostasis and whether iron repletion strategies may need to differ in patients with PAH as compared with other patient populations.

Third, since iron is required for PHDs to inhibit HIFs, an interesting question is how much HIF activation was present in the cohorts studied by Howard and colleagues. Although there is evidence of normoxic HIF activation in PAH (even in absence of hypoxemia) (15), it would be of interest to know if this was the case in the patients studied and, if so, whether the degree of HIF activation was associated with the response to iron repletion. Also, since HIF signaling may be protective in the right ventricle, potential beneficial effects of iron-mediated HIF inhibition in the pulmonary vasculature may have been counteracted by unwarranted effects in that organ (16). Lastly, iron has a wide range of biological effects, and iron therapy may have negative effects such as worsening oxidative stress (17). Although iron treatment was well tolerated in the current studies, it is unknown if some of its beneficial effects were neutralized by unwarranted oxidative stress responses.

Taken together, even though the studies reported by Howard and colleagues did not affect their primary endpoints, the rationale for studying iron homeostasis in PAH is sound. Studies like these make us ask questions and generate new hypotheses. Ultimately, riding the Ferrous wheel of iron supplementation in PAH hopefully will lead to better outcomes for our patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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The Long and the Short of It: Is "Long COVID" More Than Slow Resolution of the Acute Disease?

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To date, the coronavirus disease (COVID-19) pandemic has taken millions of lives and sickened well over 100 million (1). We cannot yet measure the full impact of this ongoing outbreak on the health of the world, but it certainly has been impactful. Although the acute phase of COVID-19 represents a fearsome health threat, this disease can also cause symptoms that persist long after the acute phase of illness has resolved (2–10). This set of symptoms has been termed "long COVID" when persisting beyond 4 weeks, and distinctions between 4–12 weeks and greater than 12 weeks after diagnosis have also been proposed (11). Nomenclature aside, these syndromes are of the utmost importance; as was seen with postencephalitis Parkinsonism after the 1918 Spanish Flu pandemic (12), this aspect of COVID-19 could be a major factor long after the pandemic resolves. However, medium- and long-term outcomes from COVID-19 remain poorly defined, and persistent COVID-19 symptoms are poorly understood with respect to risk factors, prognosis, and etiology.

In this issue of *AnnalsATS*, Townsend and colleagues (pp. 997–1003) report a well-conducted cross-sectional study of a cohort of survivors of COVID-19 that adds important information on this topic (13). This cohort included survivors across disease strata with respect to the acute phase of illness. Of the entire group, 56% did not