SHORT COMMUNICATION

In patients with pulmonary hypertension caused by chronic lung disease, iron deficiency is linked to more severe pulmonary vascular disease

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ABSTRACT

Group 3 Pulmonary Hypertension (PH) is the second most frequent type of Pulmonary Hypertension (PH), although it has the greatest mortality rate of all PH illnesses. Group 3 PH patients have few therapy options; while inhaled treprostinil improves exercise capacity, patients nevertheless have a high morbidity and mortality rate. As a result, more research into the pathophysiologic findings of group 3 PH is needed, in the hopes of identifying possible treatment targets to battle the high symptom burden and poor outcomes experienced by these individuals. Parenteral iron treatment has been proven to enhance exercise capacity, New York Heart Association functional class, and patient wellbeing in chronic left heart failure, where iron deficiency is frequent and deleterious. The significance of iron in the natural history of Pulmonary Arterial Hypertension is gaining popularity (PAH). The availability of iron influences the pulmonary vasoconstrictor response to hypoxia, and growing evidence suggests that iron deficiency is common in both idiopathic and heritable forms of PAH, with iron status being linked to exercise capacity, symptoms, and a poorer prognosis in patients with Idiopathic PAH (IPAH). Inhibition of dietary iron intake by the master iron regulator hepcidin is one possible cause for iron shortage in IPAH. Chronic illness anemia is caused by high hepcidin levels. In preclinical models, iron deficiency promotes pulmonary vascular remodeling and is linked to worse outcomes in pulmonary arterial hypertension. The effects of iron deficiency in patients with pulmonary hypertension caused by chronic lung illness (Group 3 PH) are yet to be studied. Because of its prognostic and therapeutic potential, iron's importance in cardiopulmonary disease is gaining traction. At least one-third of PH patients have Iron Deficiency (ID). ID causes a higher symptom load, higher Mean Pulmonary Artery Pressure (mPAP), lower cardiac index, and a higher mortality rate in Pulmonary Arterial Hypertension (PAH), regardless of anemia. IV iron repletion improved body iron stores, exercise endurance time, aerobic capacity, and quality of life in 15 PAH patients in a single-arm study. However, a more recent randomized, double-blind, placebo-controlled crossover experiment in patients with ID PAH found that IV iron had no effect on cardiopulmonary exercise capacity or Pulmonary Vascular Resistance (PVR).

Key Words: *Pulmonary arterial hypertension*

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The therapeutic mechanisms of iron therapy in cardiopulmonary patients are still being researched; however they may include pulmonary vascular tone modulation [1]. Given the role of hypoxia and secondary hypoxic vasoconstriction in the development of group 3 PH, ID may be even more harmful than other PH causes in this group. However, the clinical importance of ID in group 3 PH has yet to be determined. As a result, we looked into the incidence of ID in group 3 PH and its relationship to the severity of pulmonary vascular disease, exercise capacity, and survival. A prolonged increase in pulmonary artery pressure (>25 mmHg) and normal pulmonary capillary wedge pressure (15 mmHg) with normal or reduced cardiac output characterizes Pulmonary Arterial Hypertension (PAH). PAH

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can be Idiopathic (IPAH), hereditary, or linked to other illnesses such congenital heart disease (especially systemic-to-pulmonary shunts), connective tissue disease, and chronic haemolytic anemias like sickle cell disease. Increased pulmonary vascular resistance, right ventricular failure, and premature death are all symptoms of this progressive vascular illness [2]. Iron deficiency is also common in IPAH, according to recent research, and may be linked to morbidity and mortality. In addition to the effects of iron on pulmonary vascular tone and CHF symptoms, studies of prognostic biomarkers have linked iron to the aetiology of pulmonary hypertension [3]. The variability of red blood cell size is measured by Red Cell Distribution Width (RDW), which is used clinically to distinguish iron deficient anemias. In otherwise healthy older persons, RDW predicts cardiovascular mortality, and its prognostic value in chf has been linked to iron shortage and inefficient erythropoiesis. In multivariable models, RDW outperformed more recognized markers such as N-terminal pro-brain natriuretic peptide and blood urea nitrogen readings in individuals with pulmonary hypertension.

Genetic factors are thought to play a significant role in iron status variation. Indeed, genome-wide association studies have discovered common gene variations linked to haemoglobin levels and blood cell features that indicate erythropoiesis and iron regulation problems. SNPs in the TMPRSS6 and TRF2 genes, which encode the serine protease matriptase-2 and transferrin receptor type-2, respectively, have been linked to variations in iron and haemoglobin levels as well as RDW. Furthermore, a recent study connected the TMPRSS6 genotype to hepcidin production, suggesting that some variations are more prone to iron homeostasis imbalances. More research is needed to see if genetic differences have a role in the disruption of iron homeostasis in pulmonary hypertension.

Patients with group 3 PH were identified using the Minnesota Pulmonary Hypertension Repository and classified using the World Health Organization classification criteria. Only patients with group 3 PH who had serum Soluble Transferrin Receptor (sTfR) levels at any time previous to right cardiac catheterization (n = 142) were included. Because sTfR is unaffected by inflammation and has been used to define ID in prior articles on cardiac disease, ID was defined as sTfR >4.4 mg/L.

In group 3 PH, we looked at the relationship between ID and pulmonary vascular disease severity (mPAP, PAC, and PVR from baseline right heart catheterization), right ventricular function (tricuspid annular plane systolic excursion, fractional area change, myocardial systolic excursion velocity, Right Atrial Pressure (RAP), and cardiac index), and exercise capacity (baseline 6-minute walk distance [6MWD]).

ID was found in 53% of individuals with group 3 PH who took part in our research. This summarizes the demographics, comorbidities, iron studies, spirometry, and echocardiographic data. The age and sex distributions of the ID and non-ID groups were similar. Interstitial lung disease, COPD, combined pulmonary fibrosis and emphysema, OSA, and alveolar hypoventilation disorders were the most common causes of PH in Group 3, with COPD, combined pulmonary fibrosis and emphysema, OSA, and alveolar hypoventilation disorders accounting for the majority of the cohort. There were no differences in lung function as determined by FVC or carbon monoxide corrected diffusion capacity. Except for a larger prevalence of heart failure with intact ejection fraction in patients with ID, cardiac comorbidities were comparable. The Pulmonary Capillary Wedge Pressure (PCWP) did not differ between the groups.

Patients with ID had lower free iron levels, higher total iron binding capacity, and lower transferrin saturation, and they were more likely to be anemic, as expected. The percentage of patients on supplemental oxygen and oxygen saturation at rest were not different. The majority of patients in both groups had sTfR obtained within 3 months of their baseline right cardiac catheterization. Patients with ID had significantly higher C-reactive protein levels (29.2 64.3 vs 15.7 40.4 mg/L; P=.027).

ID is prevalent in group 3 PH and is related with increased mPAP and lower PAC, according to our findings. Patients with ID had a higher PVR, a shorter 6MWD, and a lower survival rate, although none of these factors were statistically significant. Nonetheless, these findings are in line with previous research that has demonstrated the role of iron in maintaining adequate pulmonary vascular function and hypoxic vasoconstriction. HIF, a transcription factor important for cellular adaptability to changes in oxygen supply, could be a molecular mediator of our findings. HIF activity is iron-sensitive, as HIF is degraded by the von Hippel-Lindau tumor suppressor protein, which requires iron. As a result, patients with group 3 PH may be particularly vulnerable due to the combination of ID and hypoxia, two triggers that lead to HIF signaling.

In Group 3 PH, iron deficiency is linked to worsening pulmonary vascular disease. This shows that iron deficiency may have a role in pulmonary vascular disease in Group 3 PH, and more research is needed to see if iron replacement medication could be used to treat this lethal form of the disease. However, among patients with group 3 PH, the link between ID and PH severity could just be a result of their overall condition. More severe PH could lead to gut malabsorption, low food intake, or a reduction in reticuloendothelial system iron release, all of which could contribute to ID. We recognize that our study has significant flaws, such as missing data and a single-center design. Furthermore, we limited our research to patients having sTfR levels, which could have resulted in selection bias. As a result, more research into our findings is needed, and if confirmed, these findings could pave the way for a future clinical trial examining the effects of IV iron on exercise capacity and hemodynamics in patients with ID and group 3 PH.

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