ORIGINAL ARTICLE

Iron Deficiency is Highly Prevalent in Patients with Pulmonary Arterial Hypertension

El déficit de hierro en pacientes con hipertensión arterial pulmonar es altamente prevalente

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ABSTRACT

Background: The aim of this study was to assess the prevalence of iron deficiency in pulmonary hypertension, to compare it with other patient populations and to establish its prognostic value.
Methods: This was a prospective, observational study. Serum iron parameters were measured in consecutive patients diagnosed with pulmonary hypertension and compared with heart failure patients and healthy controls. A correlation was sought between serum iron levels and functional class, distance walked in the 6-minute walk test and NT-proBNP.
Results: A total of 107 patients were included in the study: 60 with pulmonary hypertension, 26 with heart failure and 21 healthy controls. Iron deficiency was 78.3% in patients with pulmonary hypertension, 45.8% in those with heart failure and 23.8% in healthy controls (p <0.001). The prevalence of anemia was 25% in pulmonary hypertension, 26.9% in heart failure and 19% in healthy controls (p <0.8). In patients with functional class I-II, iron deficiency was: 78% in pulmonary hypertension vs. 43.5% in heart failure (p <0.005), and anemia was 17.1% vs. 28%, respectively (p <0.2). A significant correlation was found between serum iron and transferrin saturation with the distance walked in the 6-minute walk test (r: 0.35; p <0.01 and r: 0.34; p <0.01, respectively) and no correlation was found for transferrin and ferritin. Also, no significant correlation was found between iron deficiency and functional class or NT-proBNP.
Conclusions: Iron deficiency is highly prevalent in pulmonary hypertension, and superior to that found in heart failure patients and healthy controls. No relationship was established with anemia, which was similar in the three groups. Serum iron is clearly related with the distance walked, but not with functional class, a result which may be attributed to the limited number of patients.

Key words: Hypertension – Arterial – Pulmonary – Iron – Deficiency – Prevalence

RESUMEN

Objetivos: Evaluar la prevalencia del déficit de hierro en hipertensión pulmonar y compararlo con otras poblaciones de pacientes. Establecer su valor pronóstico.
Material y métodos: Estudio prospectivo, observacional. Se midieron parámetros de hierro sérico en pacientes consecutivos con diagnóstico de hipertensión pulmonar. Se compararon con pacientes con insuficiencia cardíaca y con controles sanos. Se buscó correlación entre los valores séricos de hierro y la clase funcional, la distancia recorrida en TC6M y el NT-proBNP.
Resultados: Participaron 107 pacientes: 60 con hipertensión pulmonar, 26 con insuficiencia cardíaca y 21 controles sanos. El déficit de hierro fue del 78,3% en los pacientes con hipertensión pulmonar; del 45,8%, en aquellos que presentaban insuficiencia cardíaca; y del 23,8% (p< 0,001) en los controles sanos. La prevalencia de anemia resultó del 25% en los pacientes con hipertensión pulmonar; del 26,9% en los que padecían insuficiencia cardíaca; y del 19% (p< 0,8) en los controles sanos. En el subgrupo de pacientes en clase funcional I-II, la prevalencia de DFe fue del 78% en los pacientes con hipertensión pulmonar vs. el 43,5% (p< 0,005) en los que tenían insuficiencia cardíaca, y la anemia resultó del 17,1% vs. el 28% (p< 0,2). Se halló correlación significativa entre ferremia y saturación de transferrina con distancia caminada en TC6M (r: 0,35; p< 0,01 y r: 0,34; p< 0,01) y no hubo correlación para ferritina y transferrina. No se encontró significancia estadística entre déficit de hierro y clase funcional o NT-proBNP.
Conclusiones: El déficit de hierro en la hipertensión arterial es altamente prevalente y superior al observado en la insuficiencia cardíaca y en los sujetos control, y no se establece relación con prevalencia de anemia, la cual fue similar en los tres grupos. El hierro sérico tiene una clara relación con la distancia caminada, no así con clase funcional, lo que, tal vez, obedezca al bajo número de pacientes.

Palabras clave: Hipertensión - Arterial - Pulmonar - Hierro - Ferropenia - Déficit - Prevalencia

Rev Argent Cardiol 2019;87:182-186. http://dx.doi.org/10.7775/rac.v87.i3.14845

SEE RELATED ARTICLE: Rev Argent Cardiol 2019;87:177-178. http://dx.doi.org/10.7775/rac.v87.i3.15414

Received: 10/24/2018 – *Accepted:* 12/18/2018

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Abbreviations

IC	Control subjects	**SI**	Serum iron
Ft	Ferritin	**6MWT**	6-minute walk test
HF	Heart failure	**Tf**	Transferrin
ID	Iron deficiency	**TfS**	Transferrin saturation
PH	Pulmonary hypertension		

INTRODUCTION

Iron is an essential element for the human body. It plays a vital role in numerous biological activities related with oxygen transport, mitochondrial respiration, intermediary metabolism and regulation of DNA synthesis. Iron deficiency (ID) is a systemic disorder affecting the homeostasis of several organs. (1) Even in the absence of anemia, ID is a powerful substrate for dyspnea and exercise intolerance. (2, 3) Almost a third of the world's population suffers from ID and it is particularly common in persons with certain chronic diseases as heart failure (HF), renal failure or inflammatory diseases. (4) In the last years, a growing number of studies have been focused on evaluating the iron level in patients with pulmonary arterial hypertension (PH). Ruiter et al. found that the prevalence of ID in patients with idiopathic PH was 43%. (5) Other studies showed a correlation between ID and lower exercise capacity. (6)

To date, there are no available studies evaluating the prevalence of ID in patients with PH in Latin America. The aim of this study was to assess the prevalence of ID in this population comparing it with left ventricular HF patients and healthy controls and to establish the correlation between ID and clinical and laboratory parameters and the 6-minute walk test (6MWT).

METHODS

This was a prospective, observational, single-center study, conducted at Hospital Juan A. Fernández, of the Autonomous City of Buenos Aires. Patients >18 years with PH, (Groups 1 and 4, diagnosed according to international criteria by means of right heart catheterization) attending our hospital between July 2015 and July 2017, were consecutively included in the study. Patients with left ventricular HF [followed up in the HF outpatient clinic and with left ventricular ejection fraction (LVEF) <35%] and control healthy subjects (C, with no history of cardiovascular or chronic diseases) were also included in the study. An informed consent was obtained from all participants and recorded in the clinical history.

Iron parameters [serum iron (SI), ferritin (Ft), transferrin (Tf), transferrin saturation (TfS)] and complete blood count (hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, white cell count and platelet count) were measured in the three groups. Functional class (FC), NT-proBNP and the 6MWT were assessed in patients with PH.

A value of Ft <100 ng/ml or between 100 and 300 ng/ml with TfS <20% was considered for the diagnosis of ID in the PH and HF groups, taking as reference the cutoff values recommended for patients with chronic diseases and with HF. (7-10) In healthy controls, the cutoff value to consider ID was Ft <30 ng/mL or TfS <16%. (7, 8)

Statistical analysis

Continuous variables are expressed as mean ± SD or median and interquartile range, according to their distribution. The chi-square test for discrete variables and ANOVA or the Kruskal Wallis test for continuous variables were used to compare between groups according to their distribution. Spearman's coefficient was used to analyze the correlation between variables.

Ethical considerations

No approval by the institutional Research or Ethics Committees was necessary since the study did not involve any invasive procedure or unusual study. An informed consent was requested, for each patient included in the study, and recorded in the personal clinical history of the patient.

RESULTS

A total of 107 patients (PH: 60, HF: 26, C: 21) were included in the study. None referred abnormal blood loss.

Table 1 shows the characteristics of each group. The HF group was older and with greater incidence of male gender. Patients with PH had worse FC than those presenting with HF.

In patients with PH, time from symptom onset since diagnosis was 34.7±41 months; the 6MWT was 398.5±118.8 m; NT-proBNP was 311 (119-1049) pg/ml; and FC distribution was: FC I: 44.2%, FC II: 22.9%, FC III: 24.6% and FC IV: 6.5%. Hemodynamic parameters were: mean pulmonary artery pressure (PAPm): 54±17.5 mmHg, pulmonary vascular resistance (PVR): 797.1±324.3 din.cm-5 and cardiac index (CI): 2.68±0.85 l/min/m2. The HF group presented the following echocardiographic parameters: LVEF: 31.6±6.3%, left ventricular diastolic diameter (LVDD): 69.4±6.1 mm, systolic pulmonary artery pressure (sPAP): 43.9±21.5 mmHg and 96.2% were in FC I-II.

Iron deficiency was found in 78.3% of patients of the PH group, 45.8% of the HF group and 23.8% of the C group (p <0.001 for the three groups). No significant difference in the prevalence of anemia was found among the three groups. In the subgroup of patients in FC I-II, the prevalence of ID was 78% in the PH group and 43.5% in the HF group (p <0.005) without a significant difference in the prevalence of anemia (17.1% in PH and 28% in HF; p <0.2) (Figure 1).

No differences among groups were found for hematocrit, hemoglobin, platelets or leukocytes.

In the PH group, SI and TfS were positively corre-

Table 1. Patient characteristics

	PH n=60	HF n=26	C n=21	p value
Clinical parameters				
Age (years±SD)	42.7±16.5 *	57.4±15.8 **	41.3±17.2	<0.01
Female gender (%)	80 *	42.3 **	77,7	<0.05
Functional class I/II (%)	68.3 *	96,2	NA	<0.01
Laboratory parameters				
Hematocrit (%±SD)	43±8.4	40.5±4.9	41.2±3.9	NS
Hemoglobin (g/dl ± SD)	13.8±2.5	13.2±1.7	13.4±1.2	NS
Serum iron (mg/dl±SD)	71.5±32.5 *	82.8±26.5 **	101.3±29.3	<0.01
Ferritin (ng/ml±SD)	88.3±115.1 #	166.4±107.7 **	76.8±58.8	<0.01
Transferrin (mg/ml±SD)	292.2±75.4	251.2±66.8	278.9±67.1	NS
Transferrin saturation (%±SD)	20.5±16.8	25.6±8.7	26.9±8.7	NS
Leukocytes (count/ml±SD)	7,914±5,390	7,959±2,372	6,729±1,594	NS
Platelets (count/ml±SD)	20,2245±67,354	347,434±550,822	241,950±56,285	NS
Iron deficiency (%)	78,3	45,8	23,8	0.001
Anemia (%)	25	26,9	19	0,8

* p <0.05 PH vs. HF, # p <0.05 PH vs. C, ** p <0.05 HF vs. C

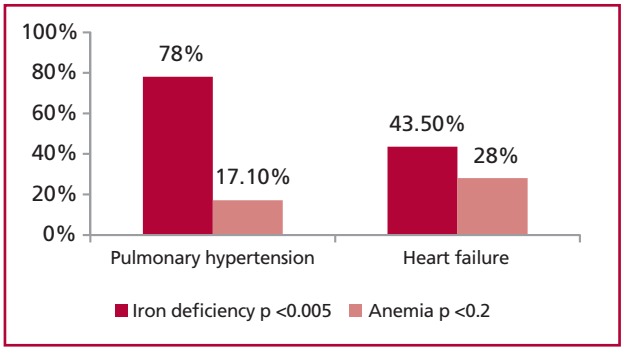

Fig. 1. Anemia and iron deficiency in pulmonary hypertension and heart failure in the subgroup with FC I-II

lated with the distance walked in the 6MWT (r: 0.35; p <0.01 and r: 0.34; p <0.01) (Figure 2). No significant correlation was observed between Ft or Tf and the 6MWT. Neither were significant differences found in high or low FC, distance walked in the 6MWT and NT-proBNP between patients with and without iron deficiency (Table 2).

The subgroup analysis according to the etiology of PH showed no significant differences in the prevalence of ID (idiopathic: 76.5%; associated with connective tissue disease: 66.7%; Eisenmenger: 88.9%; chronic thromboembolic pulmonary hypertension (CTEPH): 77.8%; and human immunodeficiency virus (HIV): 83.3%; p=0.72). The prevalence of anemia in these subgroups was: idiopathic: 29.4%, connective tissue disease: 33.3%; Eisenmenger: 5.6%; CTEPH: 33.3%; and HIV: 33.3%. Significance was only encountered in the Eisenmanger group (p <0.02) (Figure 3).

DISCUSSION

Iron is essential for the normal function of multiple organ systems. Normally, iron homeostasis in the body is maintained through its circulation, transport and storage. (11) The imbalance between offer and demand of body iron and iron homeostasis dysregulation lead to ID, with effects on development, immune function and exercise tolerance. (12) Numerous factors may contribute to ID in PH. Right ventricular pressure overload precede right-sided heart dysfunction. Moreover, gastrointestinal edema reduces iron reabsorption in the intestine and appetite loss leads to insufficient iron intake with the diet. As the disease progresses, patients with PH present hypoxemia, which increases iron utilization due to polycythemia. (13) In addition, many patients with PH receive anticoagulant therapy, which may contribute to ID due to blood loss. This agrees with the investigation of Looker et al., (14) who reported that the prevalence of ID was much higher for premenopausal than postmenopausal women and the general population. Finally, another mechanism leading to ID involves a protein with a fundamental role in iron homeostasis: hepcidin. Hepatocytes generate hepcidin in conditions of excess iron and inflammatory stimuli, while the expression of hepcidin is inhibited by hypoxia, anemia and erythropoietic activity. Hepcidin decreases the iron level through the degradation and internalization of ferroportin, the protein in charge of iron absorption in the

	Iron deficiency	Without iron deficiency	p
FC I or II (%)	78	22	
FC III or IV (%)	78.9	21.1	
6MWT (meters ± SD)	385.45 ± 114.18	453.30 ± 128.64	0.1
NTproBNP (pg/ml ± SD)	813.54 ± 1,142.50	1,032.81 ± 1,288.66	0.58

Table 2. Comparison of usual control parameters in patients with pulmonary hypertension with and without iron deficiency

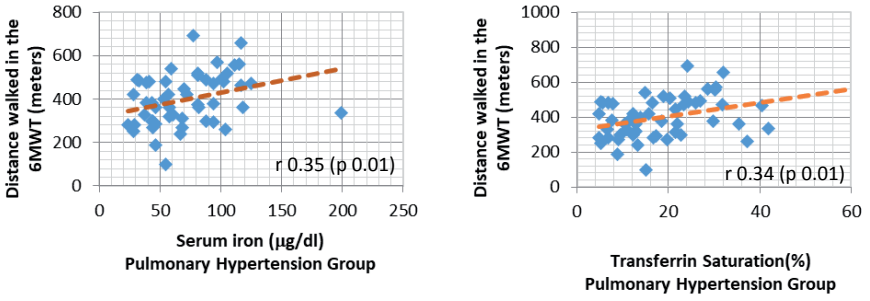

Fig. 2. Correlation of iron parameters with the 6MWT

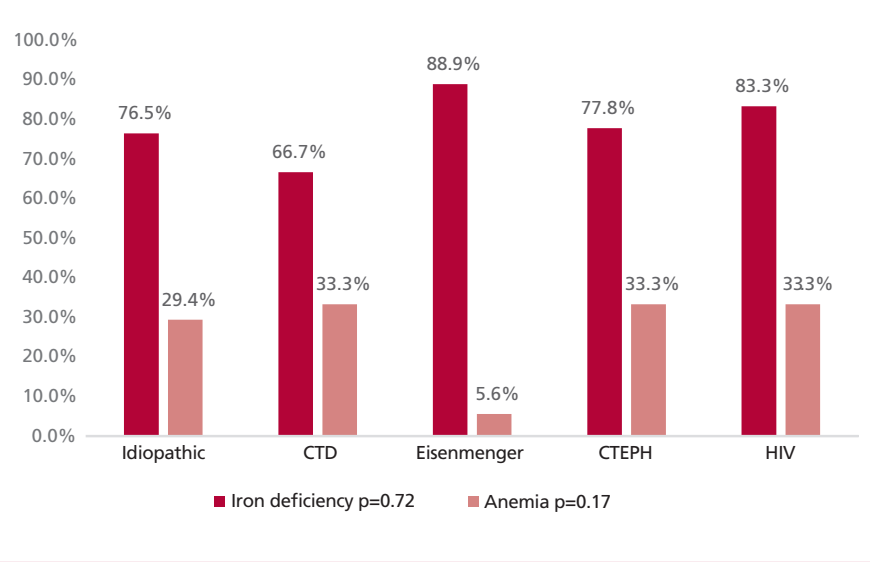

Fig. 3. Anemia and iron deficiency per etiology of pulmonary hypertension. CTD: Connective tissue disease. CTEPH: Chronic thromboembolic pulmonary hypertension. HIV: Human immunodeficiency virus.

intestine and the release of macrophage iron stores. (15) In PH, the levels of hepcidin are increased due to chronic inflammation. (16)

In agreement with previous studies, (5, 6) we found high prevalence of ID in patients with PH and significant correlation between the iron profile and the distance walked in 6 minutes. (6) It should be pointed out that, to the best of our knowledge, this is the first study of ID in patients with PH in Latin America. Compared with studies from Europe and China (6, 17, 18) where the prevalence of ID was 38% to 50%, we found a higher level in our setting, reaching almost 80% of patients. Neither are there previous studies comparing ID between patients with PH and patients with HF, in whom it is known that the deficiency is frequent. Interestingly, we found that ID is 60% more prevalent in patients with PH than in those with HF. This finding should be corroborated by larger studies to find out the cause of this phenomenon.

According to the definition of ID used and the accepted cutoff value, the prevalence of ID may vary in patients with or without PH. Sonnweber et al. (19) used four different definitions of ID to evaluate patients with PH: soluble transferrin receptor >2.07 mg/l (an uncommon assessment, but which is not affected by inflammation); Ft <30 µg/l and TfS <15%; Ft <100 µg/l and TfS <20%; or Ft index (TfS/log Ft) elevation. In this work, according to the definition adopted, the prevalence of ID varied between 9.9% and 38.9%, and ID correlated with the 6MWT, NT-proBNP and hemodynamic parameters when ID was defined according to the second criterion, but nor if the third criterion was used.

In 2014, Viethen et al. reported improved quality

of life and 6MWT parameters with ID treatment in PH. (20) Ruiter et al., in 2015, found an association between treatment with iron and improved tolerance to exercise in the cardiopulmonary test, but no relationship was obtained with right ventricular function parameters or the 6MWT. (21) Currently, the first clinical trial of parenteral iron versus placebo is underway in patients with PH (SIPHON) with the purpose of evaluating changes in PVR, the 6MWT, cardiac magnetic resonance imaging, cardiopulmonary test and NT-proBNP. (22) The 2015 European guidelines assign a IIb recommendation to ID monitoring and eventual treatment. (23)

Limitations

Some limitations of our study should be mentioned. First, since Ft and TfS can be modified by proinflammatory states, which generally occurs in these patients, a different cutoff value between healthy controls and patients was adopted, as in other studies. (7-10) An option to avoid this bias is the assessment of the soluble transferrin receptor, but this is not easily available, and therefore it would not be an alternative in the usual clinical practice. Another possibility is to look for a correlation between the values found and C-reactive protein or interleukin 6. Second, as PH has very low prevalence, the low number of patients in the sample might explain the lack of correlation of ID with NT-proBNP or FC.

The number of patients comprised in the HF group, though scarce, represents the typical patient treated in any HF clinic.

Finally, it would be interesting to perform a multi-center and more comprehensive study to put in evidence whether this deficiency is local or extends throughout the country.

CONCLUSIONS

In our study, ID is highly prevalent in patients with PH and correlates with poor prognosis parameters. It seems that in our setting it is even more frequent than in other reports. It was also found that ID is more elevated in patients with PH compared with a population without PH and with left ventricular HF.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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