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Prevalence of iron deficiency in different subtypes of pulmonary hypertension

Xue Yu, MD, Qin Luo, MD, Zhihong Liu, MD, PhD *, Zhihui Zhao, MD, Qing Zhao, MD, Chenhong An, RN, Zhiwei Huang, MD, Qi Jin, MD, Liu Gao, MD, Lu Yan, MD

Center for Pulmonary Vascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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ABSTRACT

Objectives: Iron deficiency (ID) prevalence in Chinese patients suffering from pulmonary hypertension (PH) is unclear so far. This study aimed to investigate ID prevalence in different subtypes of PH and its relevant factors.

Methods: Hospitalized patients diagnosed with PH from September 2015 to March 2017 were retrospectively enrolled. Patients were grouped based on etiology. Logistic regression analysis was performed to determine factors associated with ID.

Results: ID was found in 38.25% of 251 PH patients; with the highest prevalence in connective tissue disease associated pulmonary arterial hypertension (CTD-PAH). Univariate logistic regression analysis showed that female sex, age, CTD-PAH diagnosis and high sensitive C reactive protein (hs-CRP) were associated with ID. After adjusting for age, sex and hs-CRP, the diagnosis of CTD-PAH was still associated with ID (OR = 3.01, 95%CI 1.02–8.90, $P < 0.05$).

Conclusions: ID is common in PH in China. CTD-PAH is independently associated with ID, after adjustment for age, sex, and hs-CRP.

Introduction

Pulmonary hypertension (PH) is a pathophysiological syndrome, characterized by elevated pulmonary artery pressure and pulmonary vascular resistance (PVR) due to endothelial dysfunction and structural remodeling of pulmonary arterioles. Without appropriate treatment, it will finally progress into advanced right heart failure and death.[1] According to the fifth World Symposium on Pulmonary Hypertension, PH is divided into five groups: group 1, pulmonary arterial hypertension (PAH); group 2, PH due to left heart disease; group 3, PH due to lung disease and/or hypoxia; group 4, chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions; group 5, PH with unclear and/or multifactorial mechanisms.[2] Of note, group 1 PH (PAH) can be subdivided into idiopathic arterial pulmonary hypertension (IPAH), heritable PAH, drug and toxin induced PAH, and PAH associated with pathological conditions like connective tissue disease (CTD-PAH) and congenital heart disease (CHD-PAH).

Iron is an essential element of the human body. Iron-containing proteins play a vital role in various biological activities involving oxygen transport, mitochondria respiration, intermediary metabolism, and regulation of DNA synthesis. In this regard, iron deficiency (ID) is a systemic disorder affecting the homeostasis of multiple organs.[3] Even without anemia, ID is a potent substrate for dyspnea and exercise intolerance.[4,5] Up to one-third of the world's population suffer from ID, and it is particularly common in those with certain chronic diseases.[6] Heart failure, chronic renal insufficiency and inflammatory diseases are often accompanied by ID.[7,8] In recent years, an increasing number of studies have focused on iron status in PAH. Ruiter and his colleagues first reported that ID existed in

Abbreviations: PH, Pulmonary hypertension; PVR, pulmonary vascular resistance; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic arterial pulmonary hypertension; CTD-PAH, connective tissue disease related pulmonary arterial hypertension; CHD-PAH, congenital heart disease related pulmonary arterial hypertension; ID, iron deficiency; mPAP, mean pulmonary artery pressure; RHC, right heart catheterization; TSAT, transferrin saturation; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; RDW, red blood cell width; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-CRP, high sensitive C reactive protein; mRAP, mean right atrial pressure; CI, cardiac index; NYHA, New York Heart Association; BMI, body mass index; 6MWD, six minutes walking distance.

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* Corresponding author. Fax: +86 010 88396589.
E-mail address: zhihongliufuwai@163.com (Z. Liu).

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43% of 70 patients with IPAH. In addition, a relationship between ID and lower exercise capacity was found in their research.[9] Since then, substantial evidence has shown that ID is highly prevalent in PAH patients and may be a predictor of poor clinical outcome.[10] In this context, clinical trials on safety and efficacy of intravenous iron replacement in PAH are ongoing.[11] The concept of iron supplementation in PAH patients with ID was first proposed in the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PAH.[12]

However, data are still lacking about the prevalence of ID in PH in China. Hence, we aimed to investigate ID prevalence in PAH (including IPAH, CHD-PAH and CTD-PAH) and CTEPH, and to explore whether there is a difference between them. Besides, we intended to identify potential factors associated with ID.

Materials and methods

This single-center study was conducted in Fuwai Hospital, National Center for Cardiovascular Diseases in Beijing, China. The study was performed with the approval of the Fuwai Hospital Ethics Committee. Written informed consent of all participants was obtained.

Study sample

We retrospectively reviewed the data of hospitalized patients suspected of PH between September 2015 and March 2017. Patients confirmed with PH were included. The golden standard of PH is defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest measured by right heart catheterization (RHC).[12] PH patients were then divided into four study groups including IPAH, CHD-PAH, CTD-PAH and CTEPH according to etiology. All patients were over eighteen years old. Patients having one of the following conditions were excluded[13]: 1) pathological bleeding, 2) major operation within one year, 3) hematological malignancy, 4) oral iron treatment, or 5) chronic liver and/ or kidney failure.

Laboratory tests

After admission, iron parameters including serum iron, transferrin saturation (TSAT), ferritin, transferrin, hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV) and red blood cell width (RDW) were measured using peripheral venous blood samples. Meanwhile, N-terminal pro-brain natriuretic peptide (NT-proBNP), uric acid, creatinine and high sensitive C reactive protein (hs-CRP) were also routinely measured. ID was defined as TSAT < 20% in males and TSAT < 25% in females, which was a more precise and reliable marker for iron status than serum iron and ferritin.[14,15] The diagnosis of ID was independent of coexistent anemia (Hb < 115 g/L in females and < 130 g/L in males).[16]

Transthoracic echocardiography and right heart catheterization

Transthoracic echocardiography was routinely performed to assess severity of disease on the day of admission. Patients' ventricular parameters were measured and systolic pulmonary arterial pressure was estimated by tricuspid regurgitation velocity and right atrium pressure.[17] As the gold standard for diagnosing PH, RHC was conducted by experienced pulmonary vascular physicians during hospitalization. Time interval between echocardiography and RHC was less than seven days. All patients included in the present study were diagnosed as PH, and their hemodynamic data including mPAP, mean right atrial pressure (mRAP), cardiac index (CI), and PVR were obtained by catheterization.

Statistical analysis

Continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are given as counts or percentages. In order to compare baseline parameters among IPAH, CHD-PAH, CTD-PAH, and CTEPH, ANOVA was used for normally distributed continuous variables and a nonparametric Kruskal-Wallis test was used for non-normally distributed continuous variables. Categorical variables were compared using the χ^2 test. To identify factors correlated with ID, univariate logistic regression analysis was performed with subsequent correction for confounding effects. Data analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). P value <0.05 was considered to be statistically significant.

Results

There were 251 patients diagnosed with PH, including IPAH, CHD-PAH, CTD-PAH, and CTEPH. None of the patients had abnormal blood loss. Patients diagnosed with other subtypes of PH were excluded because the sample was too small to be analyzed. Enrollment and exclusion of participants are detailed in Figure 1.

Demographic materials and baseline characteristics of patients

As shown in Table 1, patients with CTD-PAH and CTEPH were older than patients with the other two subtypes (P < 0.001). Except for patients with CTEPH, others were mainly female (P < 0.001). CTD-PAH patients were females and none were smokers (P < 0.001). There were also significant statistical differences in body mass index (BMI) and New York Heart Association (NYHA) functional class among the four study groups (P < 0.001 and P = 0.011). Compared to the other study groups, CHD-PAH patients were mainly in the NYHA class II. In addition, CHD-PAH patients had the highest mPAP (60.6 ± 18.0 mmHg, P < 0.001) and CI (3.7 ± 1.8 L•min-1•m^{-2}, P = 0.001) but the lowest PVR (934.2 ± 635.1 dyn•s•cm^{-5}, P = 0.006) and NT-proBNP (442.1 pg•ml^{-1}, IQR: 147.2 to 1111.0 pg•ml^{-1}, P < 0.001). Except for patients with CHD-PAH, other patients were mainly in the NYHA class II-III. The NT-proBNP level was highest in patients with CTD-PAH (1546.0 pg•ml^{-1}, IQR: 774.1 to 2732.0 pg•ml^{-1}, P < 0.001). Iron parameters of the different study groups were compared, and the highest ferritin (132.6 mg•L^{-1}, IQR: 52.3 to 201.2 mg•L^{-1}, P = 0.01) was demonstrated in the CTEPH patients. MCV (90.7 ± 5.3 fL, P = 0.015) and RDW (15.4 ± 3.7 %, P = 0.014), which were closely associated with iron-deficiency anemia, were highest in CTD-PAH patients. However, Hb and Ht did not show statistical differences. The normal range of relevant iron parameters in males and females is shown in Table 2. Creatinine was significantly different among the four study groups as well (P = 0.01). As an inflammatory marker, the hs-CRP level (2.5 mg•L^{-1}, IQR: 1.3 to 6.6 mg•L^{-1}, P = 0.001) was highest in CTD-PAH patients. In terms of echocardiographic parameters, 43.48% of CTD-PAH patients presented pericardial effusion (P = 0.009). Among many co-morbidities, only diabetes mellitus showed a statistical difference (P = 0.041). Most patients received anticoagulation therapy and targeting medications. Both were statistically different among the four study groups (P < 0.001 and P = 0.001).

Prevalence of ID in different subtypes of PH

In 251 patients with PH, 96 (38.25%) patients were iron deficient, while only 16 patients (6.4%) suffered from anemia according to the above-mentioned diagnostic criteria. Table 3 reveals that ID was prevalent in all four study groups, and was highest in CTD-PAH at 69.6% and lowest in CTEPH at 19.6%.