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ORIGINAL ARTICLE

Iron Deficiency in Patients With Idiopathic Pulmonary Arterial Hypertension

Vanessa P.M. van Empel, MD, PhD[a,b*], Joy Lee, MD[c], Trevor J. Williams, MD, PhD[c], David M. Kaye, MD, PhD[a,b,d]

[a]Baker IDI Heart and Diabetes Institute, Melbourne, Australia
[b]Heart Center, Alfred Hospital, Melbourne, Australia
[c]Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Australia
[d]Department of Medicine, Monash University, Australia

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Background Iron deficiency has been reported to be highly prevalent in idiopathic pulmonary arterial hypertension (iPAH) patients, with the potential to influence cardiac performance, pulmonary artery pressures and the pulmonary vascular response to hypoxia.

Methods Iron status was evaluated in 29 iPAH patients, and was related to haemodynamic, echocardiographic and exercise parameters.

Results Iron deficiency was present in 44.8% of all iPAH patients, although anaemia was only present in 13.8%. Iron-deficient patients had similar exercise capacity (6MWD: 446 ± 141 m), compared to iron-sufficient patients (421 ± 193 m), however 46.2% of iron deficient patients had NYHA FC 3 or higher, compared to 12.5% in non-iron deficient group. Additionally iron-deficient patients showed increased mean pulmonary arterial pressure (63.3 ± 12.2 mmHg; iron deficient vs. 38.8 ± 16.7 mmHg; non-iron deficient) and reduced cardiac index (1.3 ± 0.2 L/min/m^2; iron deficient vs. 2.5 ± 0.4 L/min/m^2; non-iron deficient).

Conclusions Iron deficiency is highly prevalent in iPAH, and the extent of iron deficiency is related to haemodynamics and NYHA functional class. While the exact mechanism of iron deficiency is unknown, our study suggests that treatment of iron deficiency should be considered in iPAH patients.

Keywords Pulmonary arterial hypertension • Iron deficiency • Anaemia • Haemodynamics • Exercise capacity

Introduction

Idiopathic pulmonary arterial hypertension (iPAH) is a life-threatening disease, characterised by intimal and medial proliferation of the small pulmonary arteries, and subsequently the development of secondary fibrotic and plexiform vascular lesions. Together these lead to increased pulmonary vascular resistance and pulmonary arterial pressures. Consequently, the increase in afterload leads to RV hypertrophy and dilation. In the absence of effective therapy, persistent and increasing pulmonary vascular resistance eventually progresses to end-stage RV failure [1]. Despite recent novel therapeutic options iPAH is still associated with poor prognosis.

Recent studies reported iron deficiency to be prevalent in 43–63% of iPAH patients [2,3]. Iron deficiency has been proposed to influence exercise tolerance, assessed by 6MWD and NYHA functional class [3]. This may not be simply due to reduced oxygen carrying capacity of blood. Iron availability could affect pulmonary haemodynamics

*Corresponding author at: Heart Center, Alfred Hospital, 3rd floor, Phillip Block, Commercial Rd., Melbourne, Victoria 3004, Australia. Tel.: +61 3 9076 3195; fax: +61 3 9076 8075., Emails: vpmvanempel@hotmail.com, vanessa.van.empel@mumc.nl

and influence the vasoconstrictive response to hypoxia [4], although an earlier study did not show any relation of haemodynamic parameters with iron deficiency [3].

In heart failure due to left ventricular systolic dysfunction, iron deficiency itself is an independent predictor of outcome. Currently it is unknown whether iron deficiency is associated with poor outcome in iPAH, although it was correlated negatively with exercise capacity. Recently, we showed that the myocardial content of iron was reduced in heart failure patients, suggesting the iron deficiency in HF may have direct myocardial effects [5]. Treatment with iron supplements or with EPO improves exercise capacity and prognosis in heart failure patients [6]. Although a recent trial in elderly HFPEF patient did not show any effect of EPO therapy on LV remodelling nor on exercise tolerance or quality of life, in this specific subset of heart failure patients [7].

The aim of this study was to assess the prevalence of iron deficiency in idiopathic pulmonary arterial hypertension (iPAH) and to determine its relationship to disease severity, assessed by indices of functional capacity and haemodynamics.

Methods

The study was conducted with the approval of the Alfred Hospital Human Research and Ethics Committee. All patients gave written informed consent.

Patient Population

In this study 29 iPAH patients attending the Alfred Hospital were evaluated between June and December 2012. All patients with iPAH were requested to participate in this study. Six patients did not want to participate, two patients were excluded because they received iron suppletion, and 32 patients were included. In three patients of those 32 patients blood data collection was not complete. iPAH was diagnosed, in all included patients, by right heart catheter as mean pulmonary artery pressure (mPAP) > 25 mmHg and pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg, with the absence of associated causes, in keeping with PAH-guidelines [1]. Patients on iron suppletion were excluded from the study.

Blood Tests

Assessments of all laboratory measurements were done on peripheral venous blood. Investigation of iron status included the measurement of serum levels of iron, transferrin saturation levels, red blood cell distribution width and soluble transferrin receptor. Transferrin saturation was calculated from iron and transferrin levels [8]. Iron deficiency was defined by raised levels of soluble transferrin receptor (sTfR), >4.4 mg/l in females, >5.0 mg/l in males. Anaemia was defined as Hb < 130 g/L for males, and <120 g/L for females. Haemoglobin, haematocrit, MCV, creatinine, high-sensitivity C-reactive protein (hs-CRP) and N-terminal-pro-B-type natriuretic peptide were measured in peripheral venous blood using standard commercial assays.

Transthoracic Echocardiography

Standard M-mode, 2D and Doppler blood flow recordings were performed using standardised instruments [9,10]. This was performed in all patients during the study period as part of normal assessment. Measurements were performed off-line. All parameters were measured in triplicate and averaged. Tissue Doppler images of the mitral annulus movement were obtained from the apical 4-chamber view. A sample volume was place at the lateral and septal annular sites. Analysis was performed for the early (e') and late (a') diastolic peak velocities. The E/e' ratio was calculated using the mean from the lateral and septal E/e'. Pulsed-wave Doppler echocardiography was used to assess peak early (E) and late (A) wave flow velocity.

Cardiac Catheterisation

Data was analysed if performed within six months of the blood test; this is reported in a subset of 11 patients. A 7-F balloon-tipped pulmonary artery catheter (Edwards Lifesciences, Irvina, CA, USA) was inserted through an introducer sheath placed in the right internal jugular or a brachial vein for measurement of right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure. The wedge position was confirmed by fluoroscopy and pressure waveform, and the mean PCWP was measured at end-expiration. Cardiac output was measured using thermodilution with measurements taken in triplicate. Pulmonary vascular resistance (PVR) was calculated as (mean PAP – mean PCWP)/cardiac output. Measurements were indexed to body surface area, as appropriate.

Statistical Analysis

Categorical data are given as counts and percentages. Continuous data are presented as mean $\pm$ SD or median (interquartile range). Groups were compared using chi-square test for categorical variables and t-test for normally distributed continuous variables. Groups were compared using Mann–Whitney U test if variables were not normally distributed. Regression analyses were used for adjusted comparisons. A p value of <0.05 was considered to be statistically significant. Analyses were performed using a commercially available software package (IBM SPSS Statistics version 20, SPSS Inc., Chicago, IL).

Results

Iron Deficiency is Prevalent iPAH

Iron deficiency as defined above was present in 44.8% (n = 13) of all iPAH patients, although anaemia was only present in 13.8% (n = 4) (Fig. 1). Iron deficient patients had a mean serum iron of 12.9 $\pm$ 7.8 µmol/L and mean transferrin saturation of 20.2 $\pm$ 14.5%, which was not significantly different from non-iron deficient patients (serum iron 14.4 $\pm$ 5.8 µmol/L p = 0.308; transferrin sat 21.6 $\pm$ 7.7%, p = 0.288). However of all non-iron deficient patients only 6.2% had low transferrin