International Journal of Cardiology 205 (2016) 6–12

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The impact of iron deficiency and anaemia on exercise capacity and outcomes in patients with chronic heart failure. Results from the Studies Investigating Co-morbidities Aggravating Heart Failure

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ARTICLE INFO

Article history:
Received 10 September 2015
Received in revised form 25 November 2015
Accepted 27 November 2015
Available online 2 December 2015

Keywords:
Iron deficiency
Anaemia
Heart failure
Exercise capacity

ABSTRACT

Anaemia and iron deficiency (ID) are important co-morbidities in patients with chronic heart failure (HF) and both may lead to reduced exercise capacity.

Methods: We enrolled 331 out-patients with stable chronic HF (mean age: 64 ± 11 years, 17% female, left ventricular ejection fraction [LVEF] 35 ± 13%, body mass index [BMI] 28.5 ± 5.2 kg/m^2, New York Heart Association [NYHA] class 2.2 ± 0.7, chronic kidney disease 35%, glomerular filtration rate 61.7 ± 20.1 mL/min). Anaemia was defined according to World Health Organization criteria (haemoglobin [Hb] <13 g/dL in men, <12 g/dL in women). ID was defined as serum ferritin <100 μg/L or ferritin <300 μg/L with transferrin saturation (TSAT) <20%. Exercise capacity was assessed as peak oxygen consumption (peak VO_2) by spiroergometry and 6-minute walk test (6MWT).

Results: A total of 91 (27%) patients died from any cause during a mean follow-up of 18 months. At baseline, 98 (30%) patients presented with anaemia and 149 (45%) patients presented with ID. We observed a significant reduction in exercise capacity in parallel to decreasing Hb levels ($r = 0.24$, $p < 0.001$). In patients with anaemia and ID (n = 63, 19%), exercise capacity was significantly lower than in patients with ID or anaemia only. Cox regression analysis showed that after adjusting for NYHA, age, hsCRP and creatinine anaemia is an independent predictor of mortality in patients with HF (hazard ratio [HR]: 0.56, 95% confidence interval [CI]: 0.33–0.97, $p = 0.04$).

Conclusion: The impact of anaemia on reduced exercise capacity and on mortality is stronger than that of ID. Anaemia remained an independent predictor of death after adjusting for clinically relevant variables.

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1. Introduction

Anaemia and iron deficiency (ID) are prevalent in patients with chronic heart failure (HF) and their presence may, but does not necessarily overlap. Both anaemia and ID are associated with worse symptoms and adverse clinical outcomes [1]. In the last decade, there has been an enormous interest in the subject of ID and anaemia and their management in patients with HF. Many questions with regard to the role and therapy of the two clinical entities have not been answered to date. Komajda et al. [2] showed a prevalence of anaemia of 15.9% and an incidence of 14.2% over one year. Importantly, hospitalized HF patients with anaemia showed a 43% higher risk of death than non-anaemic patients [2]. In general, anaemic patients are older, more often female and present with hypertension and chronic kidney disease [3]. In addition, it needs to be acknowledged that anaemia may be the cause of HF or may contribute to its progression and to the patients' clinical deterioration. The prevalence of ID is high – even in the absence of anaemia – in patients with chronic HF. Although ID can be easily diagnosed using two biomarkers (serum ferritin and transferrin saturation, TSAT), it remains underdiagnosed in patients with HF [4]. Thus, ID remains undertreated even though patients may benefit symptom-wise.

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http://dx.doi.org/10.1016/j.ijcard.2015.11.178
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Table 1
Baseline characteristics of patients with chronic HF expressed as mean ± standard deviation.

Characteristics	Chronic HF patients
	n = 331
Age [years]	64 ± 11
Sex [%female]	17
New York Heart Association class	2.2 ± 0.7
Left ventricular ejection fraction [%]	34.7 ± 12.7
Left atrial diameter [cm]	4.8 ± 0.7
Left atrial area [cm^2]	26.5 ± 8.7
Body mass index [kg/m^2]	28.5 ± 5.2
Cholesterol [mg/dL]	176.6 ± 47.6
Haemoglobin [g/dL]	13.6 ± 1.6
Mean corpuscular haemoglobin [pg]	30.2 ± 2.7
Mean corpuscular haemoglobin concentration [g/dL]	34.0 ± 1.4
Mean corpuscular volume [fL]	88.8 ± 6.8
Haematocrit [%]	40.1 ± 2.7
Transferrin saturation [%]	26.2 ± 11.4
Glomerular filtration rate [mL/min∗1.73 m^2]	61.7 ± 20.1
Creatinine [mg/dL]	1.19 ± 0.42
High sensitivity C-reactive Protein	4.96 ± 7.81
Peak VO_2 [mL/kg∗min]	16.5 ± 5.1
6 minute walk test [m]	447.7 ± 126.1

The aetiology of anaemia in HF is a matter of ongoing debate. Using hospital discharge codes, Ezekowitz et al. [5] showed that absolute ID was found in only 21% of patients discharged from hospital with a main diagnosis of HF. However, 58% of the remaining patients were diagnosed with anaemia of chronic disease in which iron cannot be mobilized due to an inflammatory cascade being active [5]. Most iron in the body is bound to haemoglobin (Hb), thus it is important to differentiate between ID with normal Hb and ID anaemia. The differential diagnosis of the different forms of anaemia is rather complex and ID and anaemia are important factors that limit patients' exercise capacity and can be used as predictors of unfavourable outcomes [6,7,8,9]. Therefore the influence of anaemia and ID on exercise capacity and outcomes is of outstanding interest in patients with HF.

The aim of this study was to examine the impact of anaemia and ID on exercise capacity as assessed by spiroergometry testing and by the six minute walk test using data from the Studies Investigating Comorbidities Aggravating Heart Failure (SICA-HF). SICA-HF is a multinational, pathophysiological observation study into HF and its comorbidities [10]. Using these data, we also assessed the prevalence of anaemia and ID in patients with HF along with their influence on mortality.

2. Methods

We analysed data of subjects enrolled into SICA-HF between February 2010 and March 2014 at participating center in Berlin (Charité Medical School, Campus Virchow-Klinikum) and Wroclaw (Laboratory for Applied Research on Cardiovascular System, Medical University Wroclaw). We included 331 patients who were followed until death or until April 2014 when the follow-up was censored. All subjects provided written informed consent at enrolment, and the local ethics committees approved the protocol. The study was funded by the European Commission's 7th Framework programme (FP7/2007–2013) under grant agreement number 241558 and fulfils all principles of the Declaration of Helsinki.

The inclusion and exclusion criteria together with the study's rationale and design have been published previously [10]. In brief, all patients were diagnosed according to guidelines issued by the European Society of Cardiology [11]. All patients had a history of chronic HF of at least 3 month duration and were in stable condition on medication for at least 4 weeks before entering the study. Patients taking non-steroidal anti-inflammatory drugs (except low dose aspirin) or other immunomodulatory agents were excluded. Subjects with clinical signs of infection, severe neuro-muscular disease, rheumatoid arthritis, significant renal dysfunction (serum creatinine >250 μmol/L), or cancer were also excluded, as were subjects younger than 18 years of age and those with a history of unstable angina, myocardial infarction, or stroke within three months prior to the study. All participants had standard blood tests performed including kidney function, liver function tests, uric acid, and nutritional status (lipoproteins, albumin). In addition, we analysed parameters of iron homeostasis and a full blood count. Hb (g/dL) was measured and anaemia was defined according to World Health Organization (WHO) criteria as Hb <13 g/dL in men and <12 g/dL in women. Microcytic anaemia was defined as mean corpuscular volume (MCV) ≤80 fL, normocytic anaemia as MCV between 81 and 95 fL and macrocytic anaemia as MCV ≥96 fL. Markers of iron metabolism were measured including serum concentrations of ferritin (mg/L), iron (mg/dL), and total iron-binding capacity (TIBC, mg/dL). TSAT was calculated as the ratio of serum iron (mg/dL) and TIBC (mg/dL) multiplied by 100 and expressed as a percentage. Serum ferritin was measured and ID was defined as in previous studies as ferritin <100 μg/L or ferritin <300 μg/L TSAT <20% [12]. Estimated glomerular filtration rate (eGFR, mL/min∗1.73 m^2) was calculated using the Modification of Diet in Renal Disease equation [13]. Chronic kidney disease was defined as GFR ≤60 mL/min∗1.73 m^2. General clinical status and physical examination including a resting ECG and a 24 h ECG

Table 2
Baseline characteristics and medication expressed as patient count and percent.

	Patient at baseline n = 331	%
Heart failure with reduced ejection fraction	253	76
Chronic kidney disease	116	35
Iron deficiency	149	45
Anaemia and iron deficiency	63	19
Anaemia	98	30
Angiotensin converting enzyme-inhibitor or angiotensin receptor blocker	307	93
Beta-blocker	307	93
Statin	223	67
Diuretic	236	71
Oral anticoagulant	117	35
Aspirin	142	43

Table 3
Characteristics of patients with vs without anaemia. Data expressed as mean ± standard deviation.

	Chronic HF without anaemia n = 233	Chronic HF with anaemia n = 98	p-Value
Age [years]	62.6 ± 11.5	67.8 ± 9.6	<**0.0001**
New York Heart Association class	2.1 ± 0.7	2.5 ± 0.6	<**0.0001**
Left ventricular ejection fraction [%]	34.7 ± 12.8	34.6 ± 12.3	0.94
Body mass index [kg/m^2]	29.0 ± 5.2	27.2 ± 5.0	**0.003**
Cholesterol [mg/dL]	181.8 ± 47.0	164.5 ± 47.0	**0.003**
Transferrin saturation [%]	28.5 ± 10.7	20.6 ± 11.1	<**0.0001**
Haemoglobin [g/dL]	14.7 ± 1.1	11.7 ± 0.9	<**0.0001**
Haematocrit [%]	42.1 ± 4.5	35.3 ± 2.8	<**0.0001**
Mean corpuscular haemoglobin [pg]	30.6 ± 2.4	29.2 ± 3.2	<**0.0001**
Mean corpuscular haemoglobin concentration [g/dL]	34.3 ± 1.2	33.2 ± 1.7	<**0.0001**
Mean corpuscular volume [fL]	89.2 ± 6.7	87.6 ± 6.8	0.051
Left atrial diameter [cm]	47.3 ± 5.8	49.4 ± 8.4	**0.042**
Left atrial area [cm^2]	25.5 ± 5.8	28.7.6 ± 12.6	**0.017**
Peak VO_2 [mL/kg∗min]	17.3 ± 5.0	14.4 ± 4.8	<**0.0001**
6 min walk test [m]	473.7 ± 113.6	385.6 ± 128.8	<**0.0001**
High sensitivity C-reactive Protein [mg/dL]	4.51 ± 7.96	6.04 ± 7.36	**0.0093**
Creatinine [mg/dL]	1.1 ± 0.4	1.3 ± 0.5	<**0.0001**
Glomerular filtration rate [mL/min∗1.73 m^2]	65.4 ± 18.8	53.9 ± 20.6	<**0.0001**

Bold values indicate significance at p > 0.05.

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