Anemia of Chronic Disease in Chronic Obstructive Pulmonary Disease: A Case-Control Study of Cardiopulmonary Exercise Responses

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Key Words

Anemia of chronic disease • Cardiopulmonary exercise testing • Chronic obstructive pulmonary disease • Exercise capacity

Abstract

Background: Anemia may be present in patients with chronic obstructive pulmonary disease (COPD) and further impair their functional capacity. **Objectives:** This study investigated the prevalence of anemia of chronic disease (ACD) in COPD patients and its impact on dyspnea and exercise capacity, utilizing cardiopulmonary exercise testing (CPET). **Methods:** ACD prevalence was assessed in 283 consecutive patients with stable COPD (263 males, 60 females; age 60.31 ± 5.34 years; percent forced expiratory volume in 1 s 46.94 ± 6.12). ACD diagnosis was based on a combination of clinical and laboratory parameters [hemoglobin (Hb) <13 g/dl for males, <12 g/dl for females; ferritin >30 ng/ml; total iron-binding capacity <250 μ g/dl, and transferrin saturation rate between 15 and 50%]. Twenty-seven patients who were identified with ACD (cases) and 27 matched nonanemic patients (controls) completed maximal CPET, and data were compared between the groups. **Results:** ACD was diagnosed in 29 pa-

tients, which represents a prevalence of 10.24%; the severity of anemia was generally mild (mean Hb: 12.19 ± 0.66 g/dl). Patients with ACD had a higher Medical Research Council dyspnea score compared to controls (2.78 ± 0.44 vs. 2.07 ± 0.55 ; $p < 0.001$) and lower peak O_2 uptake (VO_2) (59.54 ± 17.17 vs. $71.26 \pm 11.85\%$ predicted; $p < 0.05$), peak work rate (54.94 ± 21.42 vs. $68.72 \pm 20.81\%$ predicted; $p < 0.05$) and peak VO_2 /heart rate (69.07 ± 17.26 vs. $82.04 \pm 18.22\%$ predicted; $p < 0.05$). There was also a trend for a lower anaerobic threshold (48.48 ± 15.16 vs. $55.42 \pm 9.99\%$ predicted; $p = 0.062$). No exercise parameter indicative of respiratory limitation differed between the groups. **Conclusions:** ACD occurs in approximately 10% of stable COPD patients and has a negative impact on dyspnea and circulatory efficiency during exercise.

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Introduction

Anemia of chronic disease (ACD) is a condition that occurs in patients with acute or chronic immune activation [1–3]. Although the pathogenesis of ACD is not fully understood, there are substantial data supporting the no-

tion that inflammatory cytokines affect iron homeostasis, hemoglobin (Hb) production and the bone marrow response to erythropoietin [2, 4]. Chronic obstructive pulmonary disease (COPD) is a disorder characterized not only by airflow limitation but also by important systemic manifestations due to the circulation of inflammatory mediators [5–7]. In light of this, COPD is a disorder that could be associated with ACD.

The prevalence of anemia in populations with COPD of various severity ranges from 7.5 to 21.0% [8, 9]. However, a combined clinical and laboratory approach has never been used to investigate the specific prevalence of ACD in COPD, while the only study that attempted to associate anemia and inflammation in COPD did not exclude patients with renal impairment [10]. Regardless of its etiology, anemia has been associated with increased morbidity [11] and mortality [9, 11, 12], higher costs of care [9], increased dyspnea [12] and reduced 6-min walk distance [12] in COPD patients. Although cardiopulmonary exercise testing (CPET) can provide a quantitative assessment of a patient's cardiovascular and ventilatory response during exercise [13], both of which can be impaired due to anemia, it has never been used for the functional evaluation of anemic COPD patients.

Based on the aforementioned data, the aims of this study were to (1) estimate the prevalence of ACD based on specific clinical and laboratory criteria in a population of consecutive patients with stable COPD and (2) investigate the impact of ACD on dyspnea and exercise capacity, utilizing CPET.

Material and Methods

Study Population

The first part of the study followed a cross-sectional design. The relevant population consisted of consecutive, clinically stable patients with COPD who visited the Respiratory Failure Unit and the Pulmonary Clinic of the 'G. Papanikolaou' Hospital (Thessaloniki, Greece) as outpatients between December 2009 and May 2010. A COPD diagnosis was confirmed, according to the American Thoracic Society criteria, by the presence of a ratio of forced expiratory volume in 1 s (FEV₁) to forced vital capacity of <0.7 measured after albuterol administration [14]. Patients were characterized as clinically stable if they had had no exacerbation, hospital admission, respiratory infection or change in medication within 3 months prior to entering the study. Subjects with a history of asthma were excluded.

The second part of this project was a case-control study. The first 29 patients with stable COPD and ACD from the initial population were the 'cases' and another 29 COPD patients without ACD, matched for sex, age, height, FEV₁ and current smoking status, represented the controls. ACD was defined by the presence of a low Hb

concentration (Hb <13 g/dl for males and <12 g/dl for females) among patients in whom any other potential cause of anemia had been excluded based on medical history and laboratory results and was confirmed by the coexistence of a normal or high serum ferritin concentration (>30 ng/ml), a low transferrin saturation rate (>15 and <50%), low total iron-binding capacity (TIBC; <250 µg/dl) and normal folate levels [2, 15–17]. Since low B₁₂ levels occur in about 10–15% of the elderly but cause anemia only in 1–2%, those patients with low B₁₂ levels were excluded only when they presented macrocytosis [18]. Patients with a history of a malignancy or hematologic disorders, inflammatory bowel disease, acute or chronic infections, systematic or autoimmune disorders, thyroid disease, liver cirrhosis, heart failure (ejection fraction <55%), renal impairment (glomerular filtration rate <60 ml/min/1.73 m²) [19], gastrointestinal or other hemorrhage, blood transfusion within the last 3 months or mental impairment were excluded. Patients with medical conditions which are contraindications to exercise testing according to the American Thoracic Society/American College of Chest Physicians guidelines [20], such as acute myocardial infarction, unstable angina, uncontrolled arrhythmias causing symptoms, orthopedic impairment limiting exercise capacity and room air desaturation <85% at rest, were also excluded.

Study Procedures

During the initial (baseline) visit, all patients with a known or potential COPD diagnosis gave a detailed medical history and underwent physical examination and lung function testing 15 min after albuterol administration. All stable COPD patients underwent peripheral venous blood sampling to determine full blood count, serum levels of urea, creatinine, liver transaminases, total protein (albumin and globulin), vitamin B₁₂, folate, iron, ferritin and TIBC. In approximately 12% of patients, serum levels of thyroid hormones were also tested due to clinical suspicion of thyroid disease. Transferrin saturation was calculated using the following equation: (serum iron/TIBC) × 100 [15]. Patients who were found to have ACD visited the outpatient clinic within 2 weeks from the baseline visit and performed a physician-supervised maximum CPET on a cycle ergometer; controls underwent the same protocol within a month. The institution's bioethics committee approved the protocol, and all participants gave their informed consent.

Measurements

Spirometry

Complete lung function testing, including measures of lung volume, inspiratory capacity, diffusion capacity and expiratory flow, was performed using standard spirometric techniques (MasterScreen PFT, Jaeger) [21]. All studies were conducted at an altitude of 500 m.

Exercise Testing

Maximum CPET was performed under continuous monitoring of pulse oximetry, heart rate (HR), arterial pressure and a 12-lead electrocardiogram [22]. After 3 min of rest, patients performed 3 min of unloaded pedaling at 60 rpm, followed by a ramp protocol with the work rate (WR) increasing by 10–15 W/min until the subject reached his or her symptom-limited maximum [23]. The ramp protocol was personalized for each patient with the aim of reaching maximum exercise in about 10–12 min. All studies were conducted in room air.

Fig. 1. Study flowchart.

Exercise parameters and gas exchange values were collected breath-by-breath and averaged over 10-second intervals [23] using the cardiopulmonary metabolic cart software from Medical Graphics. Minute ventilation (V_E), tidal volume (V_T), respiratory rate, oxygen uptake (VO_2) and end-tidal carbon dioxide were measured directly, while the anaerobic threshold (AT), ventilatory equivalent for carbon dioxide at the AT and oxygen pulse (VO_2/HR) were calculated using previously described techniques [23, 24]. Maximum voluntary ventilation was calculated as $FEV_1 \times 40$, and breathing reserve as $FEV_1 \times 40$ minus maximum V_E [23].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 17 for Windows XP. The normal predicted values for pulmonary function testing (PFT) and CPET parameters were derived from standard equations [20, 23, 25]. PFT and CPET parameters are presented as means $\pm$ standard deviation (SD) or as mean percent predicted $\pm$ SD.

The sample size of the case-control study was calculated with peak VO_2 as the primary variable. The study was designed to have 80% power to detect a difference in peak VO_2 of 2.2 ml/kg·min between the two groups, and group size was calculated as $n = 30$. Data distribution was assessed using the Kolmogorov-Smirnov test of normality. Between-group comparisons were performed with either Student's *t* test for independent samples or the Mann-Whitney *U* test, depending on the normality or not of the distribution of each variable. Pearson's correlation coefficient *r* and Spearman's rho were used to investigate correlations between Hb, CPET parameters and Medical Research Council (MRC) dyspnea scale score, depending on the normality of their distribution. A level of $p < 0.05$ was considered statistically significant.

Results

The study flowchart is presented in figure 1. From the initial cohort of 1,171 subjects who visited the outpatient clinics, we originally identified 315 COPD patients with stable disease, 283 of whom provided consent and formed the original population (223 males, 60 females; mean age 60.31 ± 5.34 years; FEV_1 $46.94 \pm 6.12\%$ predicted). Twenty-nine patients from this population fulfilled both laboratory and clinical criteria for ACD; therefore, the prevalence of ACD among stable COPD outpatients was 10.24%. The characteristics of the anemic and nonanemic COPD patients are presented in table 1. Patients with ACD were older, had lower FEV_1 and presented with more severe disease, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [26], compared to the patients without ACD. Moreover, the proportion of males was significantly higher in the group of ACD patients. No difference was noted in weight, body mass index, smoking status, pack-years of smoking, arterial oxygen partial pressure or the proportion of patients who received long-term oxygen treatment between anemic and nonanemic patients. The Hb level for anemic patients was 12.19 ± 0.66 g/dl, and according to anemia severity classification systems [27, 28], all patients had mild anemia, i.e. Hb concentration >10 g/dl. Anemia was normocytic and normochromic in 27 patients (25 males, 2 females), while the remaining 2 (males) had microcytic

Table 1. Demographic and clinical characteristics of COPD patients with and without ACD

	ACD patients (n = 29)	Non-ACD patients (n = 254)	p
Sex			
Male	27 (93.10%)	196 (77.17%)	<0.001
Female	2 (6.90%)	58 (22.83%)	
Age, years	64.63 ± 8.27	60.29 ± 5.46	0.031
Height, cm	167.89 ± 1.23	166.12 ± 2.47	0.713
Weight, kg	71.37 ± 14.48	73.29 ± 5.18	0.645
Body mass index, kg/m ²	25.01 ± 3.79	26.53 ± 4.12	0.296
Hb, g/dl	12.19 ± 0.66	14.71 ± 1.2	<0.001
FEV ₁			
liters	1.19 ± 0.38	1.41 ± 0.24	0.002
% predicted	42.26 ± 9.76	50.74 ± 6.12	
COPD severity according to GOLD [26]			
Moderate (stage II)	7 (24.14%)	76 (29.92%)	0.023
Severe (stage III)	13 (44.83%)	119 (46.85%)	
Very severe (stage IV)	9 (31.03%)	59 (23.23%)	
Smoking status			
Never smoked	2 (6.89%)	18 (7.09%)	0.842
Current smokers	6 (20.70%)	55 (21.65%)	
Ex-smokers	21 (72.41%)	181 (71.26%)	
Pack-years	64.21 ± 29.83	68.70 ± 33.98	0.912
LTOT			
Yes	10 (34.48%)	82 (32.28%)	0.334
No	19 (65.52%)	172 (67.72%)	
PO ₂ , mm Hg	65.95 ± 7.90	67.95 ± 8.13	0.514

Values represent numbers of patients or means ± SD, as appropriate. LTOT = Long-term oxygen treatment; PO₂ = oxygen partial pressure.

and hypochromic anemia. The 2 female patients had a mean Hb concentration of 11.65 ± 0.07 g/dl. Due to the small proportion of females, there was no separate analysis of the patient characteristics by gender.

Two of the 29 COPD patients with ACD were not included in the case-control study because in these patients CPET was prematurely terminated due to a hypertensive crisis (1 male patient) and uncontrolled arrhythmia (1 male patient). Therefore, in the second part of this study, the final population consisted of 27 cases (COPD patients with ACD) and 27 matched controls (COPD patients without ACD), all of whom completed the maximal CPET. The demographic and clinical characteristics and the PFT parameters of the cases and the controls are presented in tables 2 and 3, respectively. The controls were selected to have similar gender, age, height, FEV₁ and smoking status to the 27 cases. No difference was found in the remaining PFT parameters, COPD severity according to the GOLD classification [26], pack-years of smoking, the proportion of patients who received long-term oxygen treatment and

arterial blood gas analysis parameters between the two groups. However, the controls had significantly higher weight and body mass index compared to the cases.

Exercise capacity parameters for the two groups are presented in table 4. Five patients (3 anemic and 2 non-anemic) completed maximal CPET without reaching the AT. Overall, there was a negative impact of anemia on exercise capacity. Peak VO₂, peak WR, WR at the AT, peak VO₂/HR and VO₂/HR at the AT were significantly lower among cases compared to controls. There was also a trend for a lower absolute peak VO₂ value ($p = 0.072$) and a lower AT ($p = 0.062$) in the cases. None of the exercise parameters indicative of respiratory limitation (breathing reserve, peak respiratory rate, maximum V_E, maximum V_T, ratio of V_T at peak exercise to inspiratory capacity and ratio of V_E at peak exercise to maximum voluntary ventilation) differed between the two groups.

Furthermore, a negative effect of low Hb levels on breathlessness was noted. Although Hb concentration was not correlated to the MRC dyspnea score, the cases

Table 2. Demographic and clinical characteristics of cases and controls

	Cases (n = 27)	Controls (n = 27)	p
Sex			
Male	25 (92.59%)	25 (92.59%)	1.0
Female	2 (7.41%)	2 (7.41%)	
Age, years	64.82 ± 8.01	65.33 ± 7.24	0.741
Height, cm	167.21 ± 2.13	168.89 ± 5.57	0.537
Weight, kg	72.16 ± 14.02	83.33 ± 14.18	0.003
Body mass index, kg/m ²	25.32 ± 4.72	29.19 ± 4.18	0.003
Hb, g/dl	12.15 ± 0.72	14.57 ± 0.75	<0.001
MCV, fl	87.01 ± 8.06	89.98 ± 4.13	0.071
MCH, pg/cell	28.04 ± 2.98	29.77 ± 1.63	0.101
MCHC, g/dl	32.18 ± 1.66	32.99 ± 0.84	0.099
COPD severity according to GOLD [26]			
Moderate (stage II)	6 (22.22%)	7 (25.92%)	0.632
Severe (stage III)	12 (44.45%)	11 (40.75%)	
Very severe (stage IV)	9 (33.33%)	9 (33.33%)	
Smoking status			
Never smoked	2 (7.41%)	2 (7.41%)	0.711
Current smokers	6 (22.22%)	5 (18.52%)	
Ex-smokers	19 (70.37%)	20 (74.07%)	
Pack-years	62.98 ± 27.33	65.34 ± 25.41	0.695
LTOT			
Yes	8 (29.63%)	6 (22.22%)	0.101
No	19 (70.37%)	21 (77.78%)	
PO ₂ , mm Hg	66.82 ± 7.20	68.76 ± 6.95	0.252
PCO ₂ , mm Hg	40.12 ± 5.01	41.95 ± 3.97	0.107
pH	7.41 ± 0.03	7.41 ± 0.02	0.500

Values represent numbers of patients or means ± SD, as appropriate. MCV = Mean corpuscular (erythrocyte) volume; MCH = mean corpuscular Hb; MCHC = mean corpuscular Hb concentration; LTOT = long-term oxygen treatment; PO₂ = oxygen partial pressure; PCO₂ = carbon dioxide partial pressure.

had a significantly higher dyspnea scale score than the controls (2.78 ± 0.44 vs. 2.07 ± 0.55 ; $p < 0.001$).

Investigating for potential associations between Hb levels and CPET parameters, we noted intermediate correlations between Hb concentration and WR at the AT ($r = 0.432$, $p = 0.002$), peak VO₂/HR ($r = 0.412$, $p = 0.003$), VO₂/HR at the AT ($r = 0.431$, $p = 0.004$) and peak VO₂ ($r = 0.436$, $p = 0.001$). In contrast, no correlation was evident between Hb values and any of the exercise parameters which reflect respiratory limitation.

Discussion

The present study is the first to examine the prevalence of ACD in a population of stable COPD patients using a combination of clinical and laboratory criteria. Ap-

proximately 1 out of 10 stable COPD patients had ACD. This study is also the first to investigate the impact of ACD on exercise capacity, utilizing CPET. Exercise capacity was significantly lower and the MRC dyspnea score was significantly higher in ACD patients compared to controls.

At the time of this writing, a few studies had evaluated the prevalence of anemia among COPD outpatients, but their results vary significantly. The highest frequency of anemia was noted in a study by Halpern et al. [9], where 21% of elderly COPD outpatients presented with low Hb levels (<13 g/dl for males and <12 g/dl for females); however, all patients were over 65 years of age, and significant causes of anemia, such as infectious diseases and connective tissue disorders, were not excluded. Cote et al. [12] estimated the prevalence of anemia among stable COPD patients to be 17%, but this percentage referred to anemia

Table 3. PFT parameters among cases and controls

	Cases (n = 27)	Controls (n = 27)	p
FEV ₁			
liters	1.18 ± 0.32	1.21 ± 0.41	0.881
% predicted	42.30 ± 9.98	42.76 ± 12.83	0.827
FVC			
liters	2.34 ± 0.74	2.73 ± 0.97	0.108
% predicted	67.88 ± 18.08	71.63 ± 19.61	0.137
FEV ₁ /FVC	48.94 ± 6.04	47.93 ± 13.53	0.726
FEF ₂₅			
liters	1.31 ± 0.51	1.58 ± 1.07	0.252
% predicted	19.31 ± 7.63	21.19 ± 12.98	0.326
FEF ₅₀			
liters	0.58 ± 0.28	0.56 ± 0.23	0.729
% predicted	14.62 ± 6.96	13.20 ± 5.07	0.400
FEF ₇₅			
liters	0.22 ± 0.09	0.23 ± 0.12	0.832
% predicted	16.49 ± 7.34	15.37 ± 8.43	0.606
PEF			
liters	3.27 ± 1.26	3.04 ± 1.87	0.605
% predicted	42.74 ± 14.89	40.39 ± 21.32	0.641
TLC			
liters	6.05 ± 1.54	6.63 ± 1.12	0.261
% predicted	96.09 ± 23.97	102.45 ± 13.53	0.258
FRC			
liters	4.22 ± 1.23	4.19 ± 0.98	0.665
% predicted	122.79 ± 35.64	119.98 ± 27.28	0.597
VC			
liters	2.60 ± 0.80	2.96 ± 0.97	0.159
% predicted	71.02 ± 19.99	76.47 ± 19.56	0.245
IC			
liters	2.20 ± 0.59	2.15 ± 0.81	0.131
% predicted	75.13 ± 23.75	73.51 ± 22.42	0.101
RV			
liters	3.35 ± 1.11	3.62 ± 0.75	0.332
% predicted	143.22 ± 47.50	149.72 ± 32.40	0.583
T _{LCO}			
mmol·min ⁻¹ ·kPa ⁻¹	2.10 ± 0.67	2.41 ± 1.04	0.222
% predicted	63.78 ± 21.69	70.54 ± 15.29	0.131
T _{LCOc}			
mmol·min ⁻¹ ·kPa ⁻¹	2.77 ± 1.13	2.28 ± 0.63	0.337
% predicted	72.18 ± 15.22	64.69 ± 13.24	0.192
K _{CO}			
mmol·min ⁻¹ ·kPa ⁻¹ ·l ⁻¹	0.52 ± 0.33	0.56 ± 0.27	0.214
% predicted	57.14 ± 34.79	58.57 ± 17.49	0.881
K _{COc}			
mmol·min ⁻¹ ·kPa ⁻¹ ·l ⁻¹	0.60 ± 0.26	0.52 ± 0.23	0.331
% predicted	61.54 ± 19.16	55.07 ± 22.04	0.231
V _A , liters	4.28 ± 1.28	4.38 ± 0.85	0.634

FVC = Forced vital capacity; FEF = forced expiratory flow; PEF = peak expiratory flow; TLC = total lung capacity; FRC = functional residual capacity; VC = vital capacity; IC = inspiratory capacity; RV = residual volume; T_{LCO} = carbon monoxide transfer factor; T_{LCOc} = carbon monoxide transfer factor corrected for Hb concentration; K_{CO} = carbon monoxide transfer coefficient; K_{COc} = carbon monoxide transfer coefficient corrected for Hb concentration; V_A = alveolar ventilation.

of all causes. In the only previous study that attempted to make a pathophysiologic connection between COPD, anemia and inflammation [10], the prevalence of anemia was 13%; however, apart from Hb concentration, no other laboratory parameter was used to diagnose ACD, and the renal function of the patients was not determined. The present study is the only one which uses a combination of clinical and laboratory parameters to indicate that ACD occurs frequently in COPD and could be present in approximately 10% of stable COPD patients.

Anemia has been repeatedly associated with reduced exercise capacity in patients with chronic kidney disease [29, 30], chronic heart failure [31, 32] and cancer [33, 34]. Although the underlying pathophysiologic mechanisms are complex, the role of compromised oxygen delivery to the mitochondria seems crucial. The oxygen-carrying capacity of the blood depends directly on the level of Hb [12], and in normal individuals, 15 g/dl of Hb carry approximately 21 ml of oxygen per 100 ml of blood [35]. In these subjects, a 3 g/dl decrease in Hb levels would result in a reduction of the total oxygen-carrying capacity by 4/100 ml; this effect may be more intense in patients with respiratory disorders, since the saturation of Hb is usually abnormal. Peak oxygen uptake equals cardiac output × arteriovenous O₂ difference [31], so it has been suggested that for a given increase in cardiac output, the anemic patient, who has a decreased arterial O₂ concentration, will have a lower peak VO₂. Furthermore, when the arterial oxygen content is low, the diffusion gradient of oxygen from the blood to the mitochondria decreases more rapidly, leading to early anaerobic metabolism [23].

The present study confirms the above hypotheses. Anemic patients had lower peak VO₂ and lower VO₂/HR (both at the AT and at peak exercise) and achieved lower WR compared to the nonanemic controls, while there was also a trend for a lower AT. In the only previous study that evaluated the impact of anemia on exercise capacity, low Hb levels were a predictor of reduced 6-min walk distance among COPD patients [12]; the present study confirms these results and demonstrates the negative effect of ACD on numerous exercise parameters.

Breathlessness is a common symptom among patients with anemia. In the study of Cote et al. [12], anemic COPD patients had a significantly higher MRC dyspnea score and anemia was an independent predictor of increased dyspnea. The present study showed that the severity of dyspnea differed significantly between COPD patients with and without ACD. It has been suggested that the early onset of the AT, resulting in lactate production and metabolic acidosis, could be a cause of high ven-

Table 4. CPET parameters in cases and controls, separately and combined

	Total population (n = 54)	Cases (n = 27)	Controls (n = 27)	p
Peak VO ₂ , ml/kg·min	16.77 ± 4.10	16.03 ± 3.87	17.82 ± 3.98	0.078
Peak VO ₂ , % predicted	65.40 ± 15.76	59.54 ± 17.17	71.26 ± 11.85	0.005
AT, ml/kg·min	13.30 ± 3.20	12.94 ± 2.72	13.61 ± 3.58	NS
AT, % predicted	52.16 ± 13.02	48.48 ± 15.16	55.42 ± 9.99	0.062
Peak WR, W	76.75 ± 28.68	67.04 ± 24.86	86.11 ± 29.42	0.014
Peak WR, % predicted	62.10 ± 22.02	54.94 ± 21.42	68.72 ± 20.81	0.023
WR at AT, W	58.06 ± 22.40	49.81 ± 18.12	64.73 ± 23.62	0.021
Peak VO ₂ /HR, ml/beat	9.60 ± 2.60	8.81 ± 1.98	10.42 ± 2.94	0.023
Peak VO ₂ /HR, % predicted	75.43 ± 18.74	69.07 ± 17.26	82.04 ± 18.22	0.010
VO ₂ /HR at AT, ml/beat	8.74 ± 2.33	7.95 ± 1.65	9.39 ± 2.62	0.044
Peak HR, % predicted	85.50 ± 10.69	85.14 ± 10.42	85.87 ± 11.14	NS
PETCO ₂ at AT	36.64 ± 5.49	35.41 ± 6.27	37.72 ± 4.56	NS
VE/VCO ₂ at AT	35.23 ± 6.70	36.82 ± 7.74	33.84 ± 5.36	NS
V _E max, liters	43.19 ± 13.61	41.34 ± 13.33	44.94 ± 13.74	NS
V _T max, liters	1.28 ± 0.36	1.24 ± 0.06	1.31 ± 0.07	NS
V _T max/IC	0.78 ± 0.62	0.82 ± 0.26	0.74 ± 0.85	NS
V _E max/MVV	0.91 ± 0.15	0.89 ± 0.12	0.92 ± 0.03	NS
BR, liters	4.49 ± 6.84	5.37 ± 0.95	3.64 ± 1.60	NS
Peak RR, breaths/min	35.53 ± 6.67	35.74 ± 1.45	35.31 ± 1.13	NS
Resting SaO ₂ , %	95.06 ± 2.42	94.88 ± 2.57	95.30 ± 2.06	NS
Peak SaO ₂ , %	91.29 ± 5.62	90.88 ± 5.95	91.74 ± 5.34	NS

PETCO₂ = End-tidal carbon dioxide; VE/VCO₂ = ventilatory equivalent for carbon dioxide; IC = inspiratory capacity; MVV = maximum voluntary ventilation; BR = breathing reserve; RR = respiratory rate; SaO₂ = oxygen saturation; NS = not significant.

tilatory drive and increased dyspnea [12, 23] due to the stimulation of peripheral chemoreceptors [36]. This hypothesis needs to be investigated further.

While the presence of anemia is associated with adverse outcomes, its correction has proven beneficial in several chronic disease states. Correction of anemia has been associated with improved renal function, exercise tolerance and New York Heart Association class in heart failure patients and with better quality of life, exercise capacity and cognitive function in chronic renal failure patients [37–40]. The correction of anemia with blood transfusion in COPD patients resulted in the reduction of V_E and work of breathing [41], while in another study, 5 COPD patients were successfully weaned from mechanical ventilation after their anemia was treated [42]. Although investigating the impact of anemia correction was not the aim of this study, the results imply that hematocrit normalization may be beneficial for COPD patients. However, the therapeutic approach to ACD remains controversial [2], and prospective, large-scale clinical trials are necessary in order to identify which patients

will benefit from the use of blood transfusions, iron supplementation, erythropoietin or anti-inflammatory agents.

In the current study, special attention was paid to matching COPD cases and controls with regard to most of the known parameters that could affect their exercise performance. In a previous, cross-sectional study, the anemic COPD patients were older and had a higher disease burden than the nonanemic ones, and these characteristics had probably affected their functional capacity [8]. By controlling for these confounders, the impact of low Hb on exercise capacity became more evident in our study. However, there are also limitations to our study. The proportion of female patients was small, as also seen in previous studies of anemia among COPD patients [10, 12]. The significantly lower prevalence of COPD in females in Greece [43, 44] and the lower frequency of anemia in women >65 years old compared to men of the same age [45] are possible explanations for this phenomenon. However, previous studies that investigated the impact of anemia on elderly females in non-COPD settings

had similar results, so the possibility that the results may not be generalized to both genders is remote [46, 47]. Further, this COPD population which was followed up at a major urban hospital had more severe disease than patients in a primary care setting [48], so ACD might not be as frequent in the general COPD population.

In conclusion, this is the first study to establish that COPD can be accompanied by ACD, by utilizing a combination of clinical and laboratory parameters. The careful case-control comparison has shown that there is a negative impact of ACD on both exercise capacity and the

severity of the dyspnea score. Future studies are needed in order to investigate the potential role of inflammatory mediators on the suppression of erythropoiesis in patients with COPD and to evaluate the possible therapeutic approaches in this population.

Financial Disclosure and Conflicts of Interest

None to declare for any of the authors.

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Erratum

The authors of the article 'Anemia of Chronic Disease in Chronic Obstructive Pulmonary Disease: A Case-Control Study of Cardiopulmonary Exercise Responses', published in *Respiration* 2011;82:237–245, wish to correct the following error on page 238, in the Material and Methods section, first paragraph of Study Population, in the 5th line: the phrase 'December 2009' should be replaced by 'June 2009'.

The correct sentence should read as follows:

'The relevant population consisted of consecutive, clinically stable patients with COPD who visited the Respiratory Failure Unit and the Pulmonary Clinic of the 'G. Papanikolaou' Hospital (Thessaloniki, Greece) as outpatients between June 2009 and May 2010.'