

BMJ Open Impact of anaemia on lung function and exercise capacity in patients with stable severe chronic obstructive pulmonary disease

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ABSTRACT

Objective: This study intended to search for potential correlations between anaemia in patients with severe chronic obstructive pulmonary disease (COPD; GOLD stage III) and pulmonary function at rest, exercise capacity as well as ventilatory efficiency, using pulmonary function test (PFT) and cardiopulmonary exercise testing (CPET).

Setting: The study was undertaken at Shanghai Pulmonary Hospital, a tertiary-level centre affiliated to Tongji University. It caters to a large population base within Shanghai and referrals from centres in other cities as well.

Participants: 157 Chinese patients with stable severe COPD were divided into 2 groups: the anaemia group (haemoglobin (Hb) <12.0 g/dL for males, and <11 g/dL for females (n=48)) and the non-anaemia group (n=109).

Primary and secondary outcome measures:

Arterial blood gas, PFT and CPET were tested in all patients.

Results: (1) Diffusing capacity for carbon monoxide (DLCO) corrected by Hb was significantly lower in the anaemia group ((15.3±1.9) mL/min/mm Hg) than in the non-anaemia group ((17.1±2.1) mL/min/mm Hg) (p<0.05). A significant difference did not exist in the level of forced expiratory volume in 1 s (FEV₁), FEV₁% pred, FEV₁/forced vital capacity (FVC), inspiratory capacity (IC), residual volume (RV), total lung capacity (TLC) and RV/TLC (p>0.05). (2) Peak Load, Peak oxygen uptake ($\dot{V}O_2$), Peak $\dot{V}O_2$ %pred, Peak $\dot{V}O_2$ /kg, Peak O₂ pulse and the ratio of $\dot{V}O_2$ increase to WR increase ($\Delta\dot{V}O_2/\Delta WR$) were significantly lower in the anaemia group (p<0.05); however, Peak minute ventilation (VE), Lowest $\dot{V}E$ /carbon dioxide output ($\dot{V}CO_2$) and Peak dead space/tidal volume ratio (VD/VT) were similar between the 2 groups (p>0.05). (3) A strong positive correlation was found between Hb concentration and Peak $\dot{V}O_2$ in patients with anaemia (r=0.702, p<0.01).

Conclusions: Anaemia has a negative impact on gas exchange and exercise tolerance during exercise in patients with severe COPD. The decrease in amplitude of Hb levels is related to the quantity of oxygen uptake.

Strengths and limitations of this study

- The results strongly indicate that oxygen carrying capacity may depend upon the level of haemoglobin for anaemic patients and oxygen delivery is crucial for the maintenance of oxidative metabolism.
- Anaemia had a negative impact on gas exchange and impaired exercise tolerance in severe chronic obstructive pulmonary disease (COPD) patients.
- A limitation of this study is that the proportion of female patients was small.
- The present data were derived from patients with severe (GOLD stage III) COPD and thus cannot be applied to the overall population of COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects various functional and structural domains of the lungs and is recognised as a systemic disease that is frequently present in addition to other diseases.¹ Polycythaemia, traditionally thought to be highly prevalent in COPD, is less frequent nowadays with a more rigorous correction of hypoxaemia.² Reversely, recent research shows that anaemia is highly prevalent in patients with COPD.^{3–4}

Anaemia, which is a well-recognised comorbidity in many chronic illnesses, occurs in 10–30% of patients with COPD.^{3–12} Anaemia has been related to increased mortality and morbidity including increased healthcare costs and hospitalisation.^{3–12} Although cardiopulmonary exercise testing (CPET) parameters have been widely used to grade the severity of exercise limitation and provide a quantitative assessment on patients' ventilator response and cardiovascular response during exercise,¹³ all of which might be impaired due to anaemia. It has seldom been used for functional assessment

of patients with COPD with anaemia. The present study is the first to investigate the impact of anaemia in patients with COPD using CPET in a Chinese population. The aims of our study were to (1) investigate the prevalence of anaemia in patients with stable severe COPD and (2) evaluate the impact of anaemia on pulmonary function at rest, ventilatory efficiency and exercise capacity in patients with COPD, using pulmonary function test (PFT) and CPET.

MATERIALS AND METHODS

Study participants

The relevant population consisted of consecutive, clinically stable patients with a diagnosis of severe COPD (GOLD stage III),¹⁴ who visited the Respiratory Unit of Shanghai Pulmonary Hospital as outpatients between December 2011 and November 2013. Patients were diagnosed as clinically stable if they had had no hospital admission, exacerbation, respiratory infection or change in medication 3 months prior to entering the study. Exclusion criteria included: (1) a history of bronchiectasis, asthma or other concomitant respiratory diseases; (2) a diagnosis of malignancy; (3) inability to complete CPET according to the American Thoracic Society/American College of Chest Physicians guidelines,¹⁵ such as unstable angina, acute myocardial infarction, uncontrolled arrhythmias causing symptoms and orthopaedic impairment and (4) any disease that could affect haemoglobin (Hb) levels (thyroid disease, liver disease, chronic renal failure, chronic heart failure, history of gastrointestinal bleeding and chronic inflammatory rheumatic disease). Anaemia was defined as the presence of Hb levels <12 g/dL in males and <11 g/dL in females according to China-specific criteria.¹⁶

Study procedures

During the initial visit, all the patients with a potential or known diagnosis of COPD underwent physical examination, arterial blood gas (ABG) analysis and lung function testing. All patients with stable severe COPD (if $30\% \leq$ forced expiratory volume (FEV_1) $\leq 50\%$ predicted) underwent peripheral venous blood sampling to determine full blood count, liver transaminase, total protein (albumin and globulin), thyroid hormone, serum levels of urea and creatinine. Patients who subsequently presented with abnormal thyroid hormone values (either high or low), glomerular filtration rate below 60 mL/min¹⁷ and increased liver enzymes twice the upper limit of normal were excluded. The patients included in the study visited the outpatient clinic within 2 weeks from the initial visit and performed CPET.

ABG analysis and resting pulmonary function measurements

ABG measurements such as pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and arterial oxygen saturation (SaO_2) were

taken just after 10 min of rest. Each participant underwent resting PFT of forced vital capacity (FVC), FEV_1 , inspiratory capacity (IC), diffusing capacity for carbon monoxide (DLCO) corrected by Hb, residual volume (RV) and total lung capacity (TLC) using standard methodology 12 and equipment (Jaeger Corp, Hoechberg, Germany). All resting lung function values were reported in absolute terms and normalised to percentage of predicted (%pred). Predicted spirometry values were calculated using accepted equations for Chinese adults.¹⁹

CPET measurements

All the patients performed on a cycle ergometer using a breath-by-breath system according to the American Thoracic Society/American College of Chest Physicians Statement on CPET.¹⁵ The equipment was calibrated in accordance with the manufacturer's specifications using reference and calibration gases before each test. Standard 12 lead ECGs and pulse oximetry were continuously monitored. Arterial blood pressure was measured every 2 min with an automatic cuff. The protocol comprised 3 min of rest and 3 min of unloaded cycling at 55–65 rpm, followed by a progressively increasing work rate of 5–15 W/min for the patients with COPD and 4 min of recovery.¹⁹

Most CPET values were reported in absolute terms and normalised to %pred. Predicted values were calculated using accepted equations.¹⁹ CPET variables including oxygen uptake ($\dot{V}O_2$), minute ventilation ($\dot{V}E$), carbon dioxide output ($\dot{V}CO_2$), work rate (WR) and dead space/tidal volume ratio (VD/VT) were calculated at peak exercise. Peak $\dot{V}O_2$ was defined as the highest 30 s average of oxygen uptake in the last minute of exercise and other peak parameters were calculated at the same time. Lowest $\dot{V}E/\dot{V}CO_2$ was determined by averaging the lowest consecutive 90 s data points.²⁰

Statistical analysis

Statistical analysis was performed using SPSS (V.16, SPSS, Chicago). Parameters were expressed as mean \pm SD. Most PFT and CPET values are expressed in absolute terms and %pred. Unpaired Student t test was used to identify differences between groups, whereas χ^2 test was used to assess differences in categorical variables between groups. Correlations between CPET parameters and Hb levels were determined by Pearson's correlation test. A p value of <0.05 was considered significant.

RESULTS

Baseline clinical and demographic characteristics

One hundred and fifty-seven patients diagnosed with severe COPD (GOLD stage III) in outpatients were included. The vast majority (93%) of patients in the data set were males. The mean age was 61 years. The characteristics of the patients with COPD with anaemia and without anaemia are presented in table 1. Forty-eight (31%) patients from this population fulfilled laboratory

Table 1 Demographic and clinical characteristics of patients included in the study

Variable	Patients with low haemoglobin concentration (%)	Patients with normal haemoglobin concentration (%)
Number of patients (n=157) (%)	48 (31%)	109 (69%)
Sex	Men (M) 45(94%)	Men (M) 99 (91%)
Age (years)	61.32±6.03	60.82±7.13
BMI (kg/m ²)	21.72±2.93	22.18±2.15
Haemoglobin concentration (g/dL)	10.6±0.8*	12.9±1.1*
MCV (fL)	85.9±9.1	87.1±10.2
Smoking index (pack-years)	43.58±7.70	45.56±4.63
pH	7.39±0.017	7.38±0.023
PaCO ₂ (mm Hg)	44.67±1.32	44.31±1.28
PaO ₂ (mm Hg)	68.11±3.01	67.33±3.62
SaO ₂ (%)	94.44±0.94	94.77±1.13

Values represent numbers of patients or means±SD, as appropriate.

*p<0.05, patients with COPD with anaemia versus patients without anaemia using unpaired Student t test.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; MCV, mean corpuscular (erythrocyte) volume; PaCO₂, carbon dioxide partial pressure; PaO₂, oxygen partial pressure.

criteria for anaemia, and therefore the prevalence of anaemia among outpatients with stable COPD (GOLD stage III) in our study was 31%. The Hb level for patients with anaemia was 10.6±0.8 g/dL. No difference was noted in body mass index, ages, pack-years of smoking and ABG analysis parameters (pH, PaO₂, PaCO₂ or SaO₂) between patients with anemia and without anemia.

Resting pulmonary function measurements

The PFT parameters of the patients with anemia and without anemia are presented in table 2. There was no statistical significance in FEV₁, FEV₁%pred, FEV₁/FVC, IC, RV, TLC, RV/TLC between the two groups, indicating that resting pulmonary ventilation function was similar in both patient groups. However, DLCO

corrected by Hb was significantly lower among patients with anaemia compared with patients without anaemia.

Cardiopulmonary exercise testing

All individuals completed their CPET studies without incident. Nearly all patients stopped exercise because of leg fatigue and/or acute shortness of breath. All participants achieved a respiratory exchange ratio (RER) >1.10, indicating sufficient metabolic stress. Since the anaerobic threshold (AT) may not be determined by the V-slope method²¹ or the interpreter may feel that AT is

Table 2 Comparison of pulmonary function indices in patients with COPD with and without anaemia

Variable	Patients with low haemoglobin concentration (n=48)	Patients with normal haemoglobin concentration (n=109)
FEV ₁ (L)	1.33±0.27	1.41±0.13
FEV ₁ (%pred)	42.15±7.53	43.28±5.72
FEV ₁ /FVC (%)	41.32±2.19	43.36±1.38
RV (L)	3.98±1.55	4.11±1.24
TLC (L)	7.82±0.93	7.11±1.78
RV/TLC (%)	50.12±6.78	53.27±6.79
IC (L)	1.52±0.47	1.61±0.43
DLco (L)	15.31±1.94*	17.10±2.05*

Values represent numbers of patients or means±SD, as appropriate.

*p<0.05, patients with COPD with anaemia versus patients without anaemia using unpaired t test.

COPD, chronic obstructive pulmonary disease; DLco, carbon monoxide diffusion capacity corrected for haemoglobin concentration; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity.

Table 3 Comparison of cardiopulmonary exercise testing parameters in patients with COPD with and without anaemia

Variable	Patients with low haemoglobin concentration	Patients with normal haemoglobin concentration
Peak Load (W)	66.36±16.62*	69.46±28.18*
Peak $\dot{V}O_2$ (mL/min)	866.28±274.32**	1180.42±319.18**
Peak $\dot{V}O_2$ (%pred)	56.21±14.79**	69.11±18.72**
Peak $\dot{V}O_2$ /kg (mL/min/kg)	14.88±3.92*	18.72±3.86*
Peak $\dot{V}E$ (L/min)	37.89±6.33	36.71±5.42
$\Delta O_2/\Delta WR$ slope (mL/min/W)	8.02±1.03*	9.20±1.42*
Peak O ₂ pulse (mL/beat)	7.88±2.63*	11.3±2.19*
Lowest $\dot{V}E/\dot{V}CO_2$	32.15±1.28	31.28±2.90
Peak VD/VT (%)	33.2±7.2	34.9±6.1

Values represent numbers of patients or means±SD, as appropriate.

*p<0.05, **p<0.01, patients with COPD with anaemia versus patients without anaemia using unpaired Student t test.

$\Delta O_2/\Delta WR$ slope, the ratio of $\dot{V}O_2$ increase to WR increase; %pred, percentage of predicted; COPD, chronic obstructive pulmonary disease; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, Peak oxygen uptake; VD/VT, dead space/tidal volume ratio.

unreliable after reviewing an exercise test in a substantial number of patients with severe COPD, CPET variables including $\dot{V}O_2$, $\dot{V}E$, $\dot{V}CO_2$, workload and VD/VT were calculated at peak exercise without AT. Exercise responses of all the patients with COPD at peak are presented in table 3. Overall, there was a negative impact of anaemia on exercise capacity. Peak Load, Peak $\dot{V}O_2$, Peak $\dot{V}O_2/kg$, Peak $\dot{V}O_2$ pulse and the ratio of $\dot{V}O_2$ increase to WR increase ($\Delta\dot{V}O_2/\Delta WR$ slope) were significantly lower among patients with anaemia compared with patients without anaemia. None of the exercise parameters indicative of respiratory limitation and ventilatory efficiency (Peak $\dot{V}E$, Lowest $\dot{V}E/\dot{V}CO_2$, Peak VD/VT) differed between the two groups.

Correlations

Peak $\dot{V}O_2$ is frequently used as the most reliable measure of overall exercise capacity, so we choose Peak $\dot{V}O_2$ as the typical CPET parameters to investigate for potential associations between Hb levels and exercise capacity. The correlations between Hb concentration and Peak $\dot{V}O_2$ for the patients with COPD with anemia and without anemia are shown in figure 1. A strong positive correlation was found between Hb concentration and Peak $\dot{V}O_2$ in patients with anaemia ($r=0.702$, $p<0.01$) (figure 1A), but no statistical significant correlation was found with patients without anaemia ($r=0.055$, $p>0.05$) (figure 1B).

DISCUSSIONS

In this study, anaemia was present in 31% of patients with severe COPD. The prevalence of anaemia was higher than in patients from previous studies,^{3–12} possibly because the study population comprised patients with more severe COPD. The result confirms that anaemia is a common phenomenon in patients with severe COPD. The main aim of this study was to search for potential correlations between patients with anaemia with severe COPD and resting pulmonary function and

exercise capacity, as well as ventilatory efficiency based on PFT and CPET.

The usual PFT parameters like FEV_1 , $FEV_1\%pred$, FEV_1/FVC , IC, RV, TLC and RV/TLC of the two groups were similar to each other except for DLCO corrected by Hb. A severe obstructive pattern characterised the population studied. The finding that patients in the anaemia group had significantly lower DLCO values (corrected by Hb) ($p<0.05$) indicates that the decreased level of Hb may affect the rate of oxygen uptake across the alveolocapillary bed and reduce the diffusing capacity of the lungs, without having an obvious influence on the pulmonary ventilation function. Studies examining the effect of just anaemia or anaemia combined with disorder of the alveolocapillary membrane consistently mention that anaemia does affect the diffusion capacity, but the defect of the respiratory membrane on diffusing capacity is greater.^{22–23} In this study, we have patients with COPD and anaemia who commonly also have defect with the respiratory membrane, both contributing to the reduced DLco as noted. We think that the initial poor correlation with blood gases in this study is because the compensatory mechanisms are not yet fully dysfunctional and the anaemia not severe. Also, all patients in the study were clinically stable and under adequate medication.

Although anaemia has been associated with dyspnoea and reduced exercise tolerance in patients with chronic kidney disease, heart failure and cancer,^{24–26} few studies have been published concerning the effect of anaemia on exercise capacity in patients with COPD. Cote *et al*²⁷ studied patients with stable COPD, observed that the presence of anaemia affects the general feeling of dyspnoea measured in the Medical Research Council (MRC) scale and concluded that anaemia decreases exercise tolerance measured in 6 min walk test (6MWT). However, this study is the first to investigate the impact of anaemia on the exercise capacity and ventilatory efficiency of patients with severe COPD using CPET in the Chinese population.

On the one hand, this study showed that patients with anaemia with severe COPD had lower Peak Load, Peak $\dot{V}O_2$ (%pred), Peak $\dot{V}O_2/kg$, $\Delta O_2/\Delta WR$ slope and Peak oxygen pulse (O_2 pulse) compared with those without anaemia, demonstrating the negative effect of anaemia on exercise capacity. Peak $\dot{V}O_2$ is frequently used as the most reliable measure of overall exercise capacity. By Fick's principle,^{20–28–30} $\dot{V}O_2 = \text{cardiac output} \times \text{arteriovenous } O_2 \text{ difference}$, the arteriovenous O_2 difference is dependent on the availability of Hb, blood oxygenation in the lung, and extraction of oxygen in the periphery. For a given increase in cardiac output, the patient with anaemia, who has a decreased level of Hb and arterial O_2 concentration, will have a lower Peak $\dot{V}O_2$. The O_2 pulse is the quotient of the $\dot{V}O_2$ and heart rate. The $\Delta\dot{V}O_2/\Delta WR$ slope is an important measurement to evaluate exercise capacity in patients with heart disease. The decreased $\Delta\dot{V}O_2/\Delta WR$ slope is a marker of

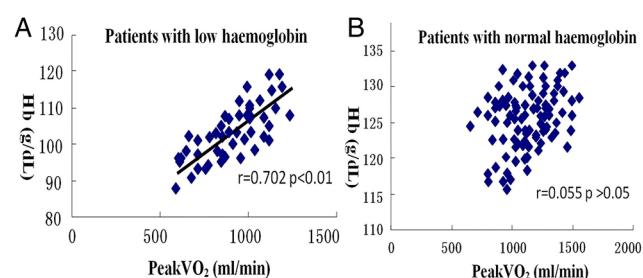


Figure 1 (A and B) Showing the correlation between Peak $\dot{V}O_2$ and haemoglobin (Hb) concentration in patients with COPD with and without anaemia, respectively. Significant positive correlation was found between Hb concentration and Peak $\dot{V}O_2$ in patients with anaemia ($r=0.702$, $p<0.01$) (A), but no statistical significant correlation was found with patients without anaemia ($r=0.055$, $p>0.05$) (B).

decreased aerobic exercise capacity caused by decreased oxygen transport.³¹ In our study, we found that patients with COPD with anaemia had a lower $\Delta\dot{V}O_2/\Delta WR$ slope than those without anaemia. This result confirms that patients with anaemia may have a more serious limitation in exercise capacity than patients without anaemia, corroborating with the study by Boutou *et al.*³² Further still, unlike those including other groups as well, we just included participants with GOLD stage III. This study also differs in the fact that we have a larger sample size and the anaemia cut-off values were pertinent to the Chinese population rather than the WHO defined general cut-off values for anaemia. Unlike in our study, Rutten *et al.*³³ reported that the 6 min walk distance (6MWD) and the BODE (Body mass index, airflow Obstruction, Dyspnoea, and Exercise capacity) score were not different among the patients with and without anaemia. However, the patient profiles in our study are fundamentally different from those of Rutten *et al.* as we have taken a lower Hb cut-off value to define anaemia. Nevertheless, the patients in our study have much lower Hb levels on average, indicating that the degree of anaemia was more severe. On the other hand, there were no differences in CPET parameters as Peak $\dot{V}E$, Lowest $\dot{V}E/\dot{V}CO_2$ and Peak VD/VT (%) between the two groups. Both Peak VD/VT and Lowest $\dot{V}E/\dot{V}CO_2$ indicate the ventilatory efficiency of oxygen uptake and carbon dioxide elimination in patients, mainly due to the limitation of blood flow perfusion, that is, perfusion/ventilation (Q/VA) mismatch. Therefore, anaemia may have a negative effect on the exercise capacity of patients with severe COPD, while its influence on ventilatory efficiency is little.

Apart from that, a strong positive correlation was found between Hb concentration and Peak $\dot{V}O_2$ in patients with anaemia ($r=0.702$, $p<0.01$), but no statistically significant correlation was found with patients without anaemia. All these results strongly indicate that the oxygen carrying capacity may depend on the level of Hb of the patients with anaemia and oxygen delivery is crucial for the maintenance of oxidative metabolism. A previous study showed that in normal individuals, 15 g/dL of Hb carries approximately 21 mL of oxygen per 100 mL of blood and a 3 g/dL decrease in Hb levels would result in a reduction of the total oxygen-carrying capacity by 4/100 mL.³⁴ Moreover, anaemia may result in limited oxygen supply with the consequent increase in ventilatory drive. Among patients with COPD whose ventilatory reserves were decreased, the accompanying increased ventilatory demand may result in dyspnoea.

Our study is not free of limitations. The proportion of female patients was small. The significantly lower prevalence of COPD in females is a possible explanation for this phenomenon. Moreover, the present data were derived from patients with severe COPD (GOLD stage III) and thus cannot be applied to the overall population of patients with COPD. The reason why we chose

patients with severe COPD (GOLD stage III) as our object of study is that patients with anaemia had a tendency to have more severe COPD,^{32 35} while patients with very severe COPD may not manage to complete CPET. Efforts should be made to further assess the prevalence of anaemia in other stages of COPD.

Conclusions

Our study demonstrated that COPD can be accompanied by anaemia and implied the potential correlations between anaemia in patients with COPD and respiratory physiology using PFT and CPET. The results indicated that both the function of gas exchange and exercise capacity decreased in the patients with severe COPD with anaemia compared with the patients without anaemia, while the influence of anaemia on pulmonary ventilation function and ventilatory efficiency was little. Future studies are needed in order to evaluate the possible therapeutic approaches in patients with COPD with anaemia.

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Contributors JL, XSu, JG and CZ conceived and designed the experiments. JG, CZ, QX and WY performed the experiments. JL, JG, CZ, QX, SG and QZ analysed the data. JH contributed to tools, in this case the exercise machine; LW contributed to materials; JG, JL and XSh contributed to the analysis. JL, JG, CZ and QX wrote the manuscript.

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