The Effect of Exercise on Oxygen Content in Anemic Patients With Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND: Anemia is reported in one-third of the patients with chronic obstructive pulmonary disease (COPD). Anemia, by decreasing oxygen content, can be a contributing factor for hypoxemia. We determined to find whether anemia causes more prominent hypoxia by decreasing the total oxygen content after exercise in anemic patients with COPD.

METHODS: Stable moderate-to-severe COPD patients with and without anemia were recruited. Arterial blood gas analyses were performed on room air before and after a 6-minute walking test (6MWT). Walking distance, oxygen saturation, and heart rate were recorded in each case before and after the 6MWT. Pulmonary function test measurements and other data were obtained from the chart. The mean and standard deviations were calculated for continuous variables. The independent *t*-test and Kruskal-Wallis test were performed for numerical covariate and univariate analyses. The paired *t*-test was used for the analyses of data before and after exercise.

RESULTS: A total of 24 male patients were included in the study; 12 of which were anemic. The oxygen content was decreased in the anemic group (15.22 ± 1.28 vs 15.07 ± 1.22) after exercise, but it was not significant. In the non-anemic group, no oxygen content decrease was observed after exercise (18.83 ± 1.41 vs 18.9 ± 1.37). Interestingly, the Spo_2, but not Sao_2, was significantly lower after exercise in anemic patients with COPD ($93.46\% \pm 5.06\%$ vs $88.20\% \pm 6.35\%$ before and after exercise, respectively).

CONCLUSIONS: Anemia does not cause more prominent hypoxemia after exercise in patients with COPD. However, the recorded Spo_2 levels were significantly lower after exercise in the anemic patients with COPD.

KEYWORDS: COPD, anemia, oxygen content, oxygen saturation

Introduction

Previous studies have reported that 13%–33% of patients with chronic obstructive pulmonary disease (COPD) may have anemia.[1–3] The mechanism of anemia is not clear, but it is likely related to the systemic effects of COPD.[4] Hypoxemia refers to insufficient oxygenation in blood. It can be caused by hypoventilation, a ventilation-perfusion mismatch, right-to-left shunt effects, diffusion impairment, or reduced inspired oxygen tension. Hypoxemia is most commonly due to a ventilation/perfusion (V/Q) mismatch in COPD.[5] Anemia, itself, does not cause hypoxemia. However, anemia decreases the total oxygen content in the blood. This effect can be compensated by increasing the cardiac output and oxygen extraction ratio. Therefore, until very low levels of hemoglobin are observed, hypoxemia is not a concern in anemic patients.[6]

In patients with COPD, besides a V/Q mismatch, the low oxygen content due to anemia may play a role in deterioration, and oxygenation and compensatory mechanisms may not be sufficient to overcome the effects. As a result, anemic patients with COPD may have more indications for long-term oxygen therapy (LTOT) than those without anemia. The significance of low hemoglobin (Hgb) levels in terms of LTOT indications has not been determined for patients with COPD.

Our clinical observations suggested that anemic patients with COPD were prescribed more LTOT than non-anemic patients with COPD. In a retrospective study, we found that anemic patients with COPD were more likely to be qualified for LTOT and had much lower mean oxygen saturation after exercise.[7] Because our previous study was limited being retrospective and not including arterial blood gases (ABG), we were unable to assess arterial oxygen content.

In this study, we determined to find if anemia causes more prominent hypoxia by decreasing total oxygen content after exercise in anemic patients with COPD compared to that of non-anemic patients with COPD.

Methods

This was a prospective clinical study conducted at the Captain James Lovell Federal Health Care Center (FHCC) and was approved by the Institutional Review Board. Patients with COPD who were scheduled in the outpatient pulmonary/oxygen clinic were screened using electronic charts. Inclusion criteria were moderate and severe COPD patients with and without anemia. Exclusion criteria were mild COPD patients, any patient who had a fistula or graft on a radial artery, having

bleeding diathesis, were on anticoagulant therapy, patients who were unable to walk, and any patient with a co-morbid condition such as congestive heart failure, pulmonary hypertension, malignancy, pleural disease, history of venous thromboembolism, chronic renal failure, any blood disease, any other important organ failure, or systemic disorder. Any patient who has recent acute exacerbation of COPD was also excluded from the study. We did not exclude any patient with common co-morbidities such as hypertension, diabetes, hyperlipidemia, post-traumatic stress disorder, prostate hypertrophy, and osteoarthritis.

Informed consent was obtained in the clinic from the eligible patients who agreed to participate in the study. The patients were taken inside an exam room and allowed to rest for 10 minutes in a chair. An ABG measurement in room air was taken from the radial artery. After the ABG measurement was complete, pulse oximetry was obtained by attaching the device to the patient's finger. Oxygen saturation and heart rate were recorded in room air while at rest. A research assistant walked with the patient in the corridor for 6 minutes in room air, and the heart rate and walking distance were recorded. After returning to the exam room, the patient's ABG level was immediately measured from the other radial artery, while in room air. Finally, blood samples were taken for subsequent measurements within 10 minutes of collection.

The patients' age, first forced expiratory volume (FEV_1), forced vital capacity (FVC), FEV_1/FVC, Hgb, hematocrit, body mass index (BMI), smoking history, and prior and current medications were recorded. The cause of anemia was recorded for each anemic patient. If Hgb data were older than 3 months, or if there was a suspicion for an aberrant Hgb measurement, a new Hgb level measurement was requested. Because our previous study showed a mean Hgb level of 11.7 ± 0.92 g/dL in the anemic group and 14.8 ± 0.99 g/dL in the non-anemic group, we included patients with COPD having these hemoglobin levels for each group (10.8–12.6 g/dL for anemic and 13.7–15.7 g/dL for non-anemic patients). Two-year intervals were accepted for the pulmonary function test (PFT) data.

Techniques

Arterial blood gases. A pro-vent arterial blood sampling kit with dry lithium heparin was used for arterial blood ABG measurements. Before the procedure, an Allen test was performed to ensure that both the ulnar and radial arteries were patent. Approximately 3 cm³ of arterial blood was drawn each time. A filter was placed on the tip of the syringe, and air bubbles inside the syringe were removed. After the 6-minute walking test (6MWT), the same procedure was repeated on the other radial artery. Blood samples were sent immediately to the laboratory after the second arterial blood sample was drawn. The ABG analysis was initiated using an ABL 835 Flex blood gas analyzer radiometer within 10 minutes of collection for all blood samples. After the second ABG sample was taken, the patient

was asked to remain for 30–60 minutes in the waiting area. The hands and radial pulse were re-evaluated every 5–10 minutes before the patient was allowed to leave.

6-Minute walking test. The patients walked in a 52-foot-long (15.8 m) corridor during the test. A pulse oximeter (Masimo, Irvine, CA, USA) was placed on the index finger during the test, and a research assistant walked with the patient. The total distance walked was recorded at the end of 6 minutes. The SpO_2 and heart rate were also recorded at the end of the walk.

Oxygen content was calculated using the PaO_2, SaO_2, and Hgb levels with the standard formula: (oxygen content = $PaO_2 \times 0.003 + Hgb \times SaO_2 \times 1.34$).

Statistics

The mean and standard deviation were calculated for continuous variables. The independent *t*-test and Kruskal-Wallis test were used for numerical covariate and univariate analyses. The paired t-test was used for the analyses of data before and after exercise in both groups. $P < .05$ was accepted as significance level.

Results

A total of 26 patients with COPD were enrolled in the study. Two of the patients were excluded due to technical reasons, so 24 patients were included in the study. All patients were male, and 50% were anemic. The patients' characteristics are listed in Table 1. Both groups were matched in terms of age, PFT findings, and severity of COPD. The mean age was not different between the groups, but the anemic group was slightly older. The Hgb levels and hematocrit values were significantly lower in the anemic group. There were 5 patients in non-anemic group and 4 patients in anemic group who had acute exacerbation of COPD within 1-year time period. But during the recruitment date, all patients were stable and free of sign and symptoms of exacerbations.

The PFT values (FEV_1, FVC, FEV_1/FVC, and total lung capacity [TLC]) and the severity of COPD were not different between the groups. The mean carbon monoxide diffusion capacity (DLCO) was lower in the anemic group compared with the non-anemic group, but did not reach significance. The mean walking distance was lower for the anemic group, but was not significant.

For data analyses, we compared the anemic vs non-anemic groups before and after exercise. The ABG values, heart rates, SpO_2, and oxygen content values are shown in Table 2 in both the anemic and non-anemic COPD groups before exercise. The ABG values, SpO_2, and heart rates were not different at rest. But the oxygen content was significantly lower in the anemic group (15.22 ± 1.28 vs 18.83 ± 1.41). After exercise, similar results were observed between the groups except for the SpO_2 values, which were lower in the anemic group with a marginal significance (Table 3). Further analyses of the anemic group before and after exercise showed significant increases in heart rate and a significant drop in SpO_2, but not SaO_2. All

Table 1. Patient characteristics.

	NON-ANEMIC	ANEMIC	*P* VALUE
N	12	12	
Age (y)	70.58 ± 7.8	74.20 ± 7.3	.25
Hgb (g/dL)	14.53 ± 1.6	11.79 ± 0.8	<.001
Htc	43.10 ± 2.9	36.60 ± 2.8	.00
$FEV_1\%$	54.92 ± 15.8	58.36 ± 19.0	.66
FVC%	90.25 ± 18.3	81.91 ± 18	.23
FEV_1/FVC	45.50 ± 10.6	51.10 ± 14.6	.18
TLC%	96.83 ± 31.3	82.08 ± 18.3	.16
DLCO%	54.50 ± 18	52.33 ± 23.41	.80
Walking distance (m)	276.40 ± 40.3	251.80 ± 75.7	.16

Abbreviations: DLCO, diffusion capacity; FEV_1, first forced expiratory volume; FVC, forced vital capacity; Hgb, hemoglobin; Htc, hematocrit; TLC, total lung capacity.

Table 2. Comparison of anemic and non-anemic patients with COPD before exercise.

	NON-ANEMIC	ANEMIC	*P* VALUE
Pao_2	72.54 ± 8.15	71.30 ± 16.32	.90
$Paco_2$	39.12 ± 2.97	40.90 ± 5.46	.34
pH	7.41 ± 0.02	7.42 ± 0.02	.75
Sao_2	95.60 ± 1.4	94.05 ± 4.93	.81
Spo_2	94.00 ± 1.8	93.36 ± 5.3	.90
Heart rate	85.10 ± 4.9	84 ± 16.34	.90
O_2 content	18.83 ± 1.41	15.22 ± 1.3	<.01

Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 3. Comparison of anemic and non-anemic patients with COPD after exercise.

	NON-ANEMIC	ANEMIC	*P* VALUE
Pao_2	76.87 ± 9.72	70.27 ± 14.91	.21
$Paco_2$	40.18 ± 3.05	40.92 ± 4.94	.66
pH	7.40 ± 0.03	7.41 ± 0.03	.93
Sao_2	95.92 ± 1.37	94.49 ± 5.05	.17
Spo_2	92.42 ± 4.31	88.36 ± 6.64	.07
Heart rate	104.7 ± 15.14	102.6 ± 20.7	.75
O_2 content	18.90 ± 1.37	15.14 ± 1.26	<.001

Abbreviation: COPD, chronic obstructive pulmonary disease.

other parameters, including the oxygen content, did not show a difference (Table 4). In the non-anemic group after exercise, the Pao_2, $Paco_2$, and heart rates showed significant increases, but the Spo_2 and oxygen content did not show any differences (Table 5). Oxygen content and Spo_2 changes before and after exercise in both groups are shown in Figures 1 and 2.

Discussion

We hypothesized that total oxygen content in the arterial blood of anemic patients with COPD would be significantly lower after exercise. During exercise, compared to rest, oxygen release to the tissues would be higher in anemic patients as a compensatory mechanism. Patients with COPD already have a tendency for hypoxemia, mostly due to a V/Q mismatch. As a result, the mean mixed venous blood oxygen saturation would be lower. Also, the increased oxygen demand during exercise would increase cardiac output due to a rising heart rate. Therefore, the circulation time would be shorter for the red blood cells in the pulmonary vasculature for oxygenation.[6,8,9] If the blood returning to the lungs (mixed venous blood) has a lower Po_2 than normal, it takes longer time for equilibration with the alveolar Po_2 to occur in the lung. Therefore, it is expected that total arterial oxygen content would be much lower after exercise in anemic patients with COPD.

We have found 2 important but unexpected findings in this study. First, total oxygen content was not different before and after exercise in anemic patients with COPD contrary to our hypothesis (Table 4 and Figure 1). Second, we found significant decrease in Spo_2 but not Sao_2 in anemic group after exercise (Table 4 and Figure 2). In non-anemic patients with COPD, as expected, the oxygen content and Spo_2 did not show a significant decrease. The reason for the first finding

Table 4. Comparison of anemic patients with COPD before and after exercise.

	BEFORE	AFTER	*P* VALUE
Pao_2	71.27 ± 15.56	70.27 ± 5.06	.74
Pco_2	40.83 ± 5.46	40.92 ± 4.94	.84
pH	7.42 ± 0.02	7.41 ± 0.03	.19
Sao_2	94.30 ± 4.78	94.62 ± 4.84	.82
Spo_2	93.46 ± 5.06	88.20 ± 6.35	<.008
Heart rate	84.33 ± 16.25	102.33 ± 20.6	<.01
O_2 content	15.22 ± 1.28	15.07 ± 1.22	.59

Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 5. Comparisons of non-anemic patients with COPD before and after exercise.

	BEFORE	AFTER	*P* VALUE
Pao_2	72.54 ± 8.15	76.87 ± 9.73	.03
Pco_2	39.12 ± 2.97	40.18 ± 3.05	.049
pH	7.42 ± 0.02	7.41 ± 0.03	.47
Sao_2	95.60 ± 1.41	95.92 ± 1.34	.39
Spo_2	94.08 ± 1.83	92.42 ± 4.32	.16
Heart rate	85.08 ± 14.91	104.67 ± 15.14	.001
O_2 content	18.83 ± 1.41	18.90 ± 1.37	.34

Abbreviation: COPD, chronic obstructive pulmonary disease.

Figure 1. Oxygen content before and after exercise in anemic and non-anemic patients with COPD.
Oxygen content was significantly lower in the anemic group both before and after exercise compared to the non-anemic group. However, there were no differences in oxygen content before and after exercise in both the anemic and non-anemic groups. COPD indicates chronic obstructive pulmonary disease.

Figure 2. Spo_2 changes before and after exercise in anemic and non-anemic patients with COPD.
Mean Spo_2 levels significantly decreased in the anemic group after exercise. In non-anemic group, there was a slight decrease, which was not significant. COPD indicates chronic obstructive pulmonary disease.

may be explained by the severity of anemia and length of the walking distance. The mean hemoglobin level was 11.79 g/dL in the anemic group. This level of anemia was not severe. Some compensatory mechanisms were possibly effective enough to keep the oxygen content close to resting levels. Also, we limited the walking distance with the 6-minute walking distance (6MWD). We do not know if a longer distance or more strenuous effort would result in a lower oxygen content. In an interesting and similar study, Boutou et al[10] investigated impact of anemia on dyspnea and exercise capacity by utilizing cardiopulmonary exercise test (CPET) in patients with COPD. They found higher dyspnea score and lower peak oxygen uptake (Vo_2), lower work rate, and peak Vo_2/heart rate in anemic COPD patients compared with non-anemic COPD patients. They also noticed a trend for a lower anaerobic threshold in anemic patients with COPD. These results are compatible with insufficient oxygen supply due to anemia. Their findings may suggest that if we used more intense exercise, oxygen content might be lower in anemic patients with COPD. Compared to 6MWT, CPET needs high intense exercise activity. We also did not check
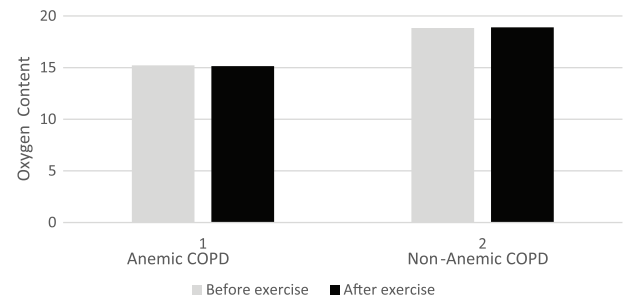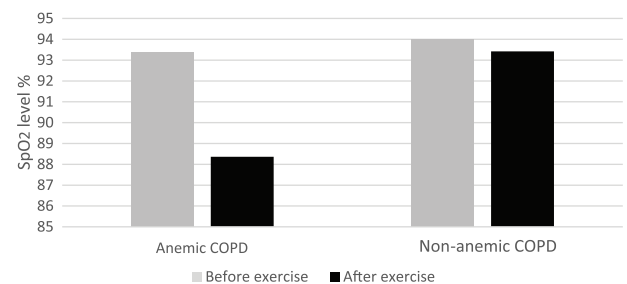
lactic acid level considering our patients would not reach anaerobic threshold with low-intensity walking test.

The reason for the second finding is not clear. However, we suggest that while Sao_2 is a direct measurement of saturation of hemoglobin in the arterial blood, Spo_2 is an indirect measurement of saturation of hemoglobin in capillary blood. Pulse oximetry also is not a complete measure of circulatory sufficiency. If there were insufficient blood flow or insufficient hemoglobin (anemia), tissues could become hypoxic despite sufficient oxygen saturation in the blood. Additionally, Sao_2 is a one-time measurement, while Spo_2 provides continuous multiple readings. Nonetheless, the Spo_2 data showed a significant drop after exercise in the anemic group. Most of the oxygen evaluations were performed based on pulse oximetry and 6MWD. As a result, the anemic patients with COPD are more likely to be prescribed long-term oxygen treatment. Chambellan et al[11] reported on 2524 patients with severe COPD, and low hematocrit levels were common in patients with COPD with LTOT. We also observed low Spo_2 levels in anemic patients in our previous study.[7]

We also observed increases, but not decreases, of Spo_2 and Pao_2 during exercise in some patients. However, this phenomenon was more prominent in the non-anemic group. We also noticed significant heart rate increases in both groups after exercise, which reflected an increased cardiac output to meet the oxygen demands of the body. Unexpectedly, in the non-anemic group, the mean Pao_2 was significantly elevated, but it was not reflected in the mean oxygen content (Table 5). Indeed, the mean

Sao_2 and mean oxygen contents increased slightly but they were not significant. The reason for this elevation may be an increased circulation with activity and improvement of atelectatic areas in the lung with deeper breathing during exercise. Another finding was significant increases of $Paco_2$ in the non-anemic group after exercise (Table 5). But the *P* value was marginal, and the mean $Paco_2$ was within normal range both before and after exercise.

Guo et al performed a study on patients with COPD to evaluate the impact of anemia on PFT at rest and ventilator efficiency and exercise capacity using CPETs. They found no differences in the PFT at rest except for a lower DLCO in the anemic group. In our study, the PFT results were similar. The mean DLCO was lower in the anemic group, but no difference was found compared with that of non-anemic group. However, the mean hemoglobin level in the study of Guo et al was lower than those of our patients (11.79 g/dL vs 10.6 ± 0.8 g/dL). Additionally, our study had a smaller number of patients. They also reported a lower peak Vo_2 and Vo_2/WR in the anemic group, but they did not measure the ABG or oxygen content differences before and after exercise.[12]

The 6MWD values were lower in the anemic group, but it was not significant compared with that of non-anemic group. Rutten et al[13] reported 6MWD and Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) scores that were the same as patients with and without anemia. These results support our findings.

Cote et al[3] found that in patients with stable COPD the presence of anemia affected feelings of dyspnea and decreased exercise tolerance in the 6MWD. We did not check for dyspnea in our patients. However, the exercise tolerance based on the 6MWD was lower in the anemic group, but did not reach a significance level.

Strengths and limitations

The study was a prospective study with a control group. However, there were some limitations in our study. First, the patient number was small in the groups and we did not randomize for practical reasons. We used the ABGs before and after exercise. It would have been better if we had measured the mixed venous oxygen levels. However, we did not use mixed venous oxygen due to its invasive nature, risk, and cost. The Spo_2 accuracy was another potential limitation. To prevent erroneously low readings, we checked each patient's hands for hypo-perfusion, coldness, skin thickness, nail polish, and keeping the hands still during walk. Another concern was the time difference for the ABG sampling to the analyzer. Samples taken 6–8 minutes apart were then sent to the analyzer. But the total time was around 10 minutes. As per The American Association for Respiratory Care (AARC) guidelines, ABGs should be analyzed within 30 minutes after sampling with a plastic syringe.[14] Therefore, we think the time difference did not affect the results. We included patients with PFT measurements up to 2 years. There is no specific recommendation for frequency of PFT follow-up in patients with COPD. Therefore, we arbitrarily picked up 2-year time period. The walking course for the 6MWT was recommended to be 30 m (100 ft) in length to prevent frequent turns, which may decrease the walking distance.[15] We used a 52-foot-long corridor. However, a recent multicenter study reported no significant effects in the length of a straight course ranging from 50 to 164 ft.[15] We also used the same corridor for all patients; therefore, we do not think that the walking course length affected our results.

In conclusion, anemia does not cause more prominent hypoxemia after exercise in patients with COPD. However, the recorded Spo_2 level was significantly lower compared to Sao_2 after exercise in anemic patients with COPD. More studies need to clarify the effect of Spo_2 usage on LTOT treatment on anemic patients with COPD.

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Author Contributions
Conception and design: ASC. Acquisition of data: ASC, HD, LW and KH. Analysis and interpretation: ASC and ZC. Drafting the article for important intellectual content: ASC, AF, NA, ZC. All authors contributed to the intellectual content of the manuscript and were consulted for final approval of the submitted version.

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