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IMPAIRMENT OF ERYTHROCYTE REDOX STATUS AND HEMOGLOBIN ALTERATIONS ACROSS DISEASE SEVERITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Abstract. Systemic hypoxemia in chronic obstructive pulmonary disease (COPD) is traditionally attributed to impaired pulmonary gas exchange. However, alterations in erythrocyte redox regulation may further compromise oxygen transport. The objective of this study is to evaluate the erythrocyte electron-transport and oxygen-transport functions at different stages of COPD**.**

This single-center cross-sectional study included 150 clinically stable COPD patients (mild – $n = 54$, moderate – $n = 59$, severe – $n = 37$) and 40 healthy controls. Erythrocyte cytochrome C and cytochrome b_5 content, NADH- and NADPH-dependent reductase activities, glucose-6-phosphate dehydrogenase activity, 2,3-diphosphoglycerate levels, hemoglobin fractions, and blood gas parameters were measured. COPD patients demonstrated reduced erythrocyte cytochrome C and cytochrome b_5 content and decreased glucose-6-phosphate dehydrogenase activity, accompanied by increased reductase activities (all – $p < 0.001$). Oxyhemoglobin levels declined, while deoxyhemoglobin and methemoglobin levels increased with disease severity. Elevated 2,3-diphosphoglycerate levels suggested partial compensation. Blood gas analysis revealed progressive hypoxemia and metabolic disturbance. It has been posited that progressive impairment of erythrocyte redox status and hemoglobin alterations may contribute to impaired systemic oxygen delivery in COPD beyond pulmonary dysfunction.

Keywords: erythrocytes, oxidative stress, redox regulation, hemoglobin, oxygen transport, cytochrome systems, hypoxemia

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НАРУШЕНИЕ ОКИСЛИТЕЛЬНО-ВОССТАНОВИТЕЛЬНОГО СТАТУСА ЭРИТРОЦИТОВ И ИЗМЕНЕНИЕ ГЕМОГЛОБИНА В ЗАВИСИМОСТИ ОТ ТЯЖЕСТИ ЗАБОЛЕВАНИЯ ПРИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЁГКИХ

Аннотация. Системная гипоксия при хронической обструктивной болезни лёгких (ХОБЛ) традиционно связывается с нарушением лёгочного газообмена, однако изменения в регуляции окислительно-восстановительного статуса эритроцитов могут дополнительно ухудшать транспорт кислорода. Целью исследования явилась оценка функции электронного и кислородного транспорта эритроцитов на разных стадиях ХОБЛ.

В одноцентровое поперечное исследование включены 150 клинически стабильных пациентов с ХОБЛ (легкая форма – $n = 54$, умеренная форма – $n = 59$, тяжелая форма – $n = 37$) и 40 здоровых контрольных лиц. Определены содержание цитохрома С и цитохрома b_5 в эритроцитах, активность НАДН- и НАДФН-редуктаз, активность глюкозо-6-фосфатдегидрогеназы, уровни 2,3-дифосфоглицерата, фракции гемоглобина и параметры газового состава крови. У пациентов с ХОБЛ наблюдалось снижение содержания цитохрома С и цитохрома b_5 в эритроцитах, а также снижение активности глюкозо-6-фосфатдегидрогеназы, сопровождающееся повышением активности редуктазы (все – $p < 0{,}001$). Установлено снижение уровня оксигемоглобина, в то время как содержание дезоксигемоглобина и метгемоглобина повышалось с усугублением тяжести заболевания. Повышенный уровень 2,3-дифосфоглицерата может свидетельствовать о частичной компенсации состояния. Анализ газов крови позволил выявить прогрессирующую гипоксию и метаболические нарушения. Прогрессирующее нарушение окислительно-восстановительного статуса эритроцитов и изменения гемоглобина могут усугублять лёгочную дисфункцию за счет нарушения системной доставки кислорода при ХОБЛ.

Ключевые слова: эритроциты, окислительный стресс, регуляция окислительно-восстановительного статуса, гемоглобин, транспорт кислорода, цитохромные системы, гипоксемия

Для цитирования: Нарушение окислительно-восстановительного статуса эритроцитов и изменение гемоглобина в зависимости от тяжести заболевания при хронической обструктивной болезни лёгких / Д. К. Муминов, Л. Т. Даминова, Н. Н. Климкович, С. У. Муминова // Весці Нацыянальнай акадэміі навук Беларусі. Серыя медыцынскіх навук. – 2026. – Т. 23, № 3. – С. 223–228. https://doi.org/10.29235/1814-6023-2026-23-3-223-228

Introduction. Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity and mortality worldwide, responsible for more than 3.5 million deaths annually and affecting over 200 million individuals globally[1]. Beyond the scope of progressive airflow limitation, COPD is characterized by systemic consequences driven in part by chronic hypoxemia and oxidative stress [1]. Hypoxemia plays a central role in the disease progression and the extrapulmonary manifestations of COPD; however, the systemic mechanisms contributing to impaired oxygen delivery remain incompletely understood. While pulmonary gas exchange abnormalities are the primary determinant of arterial hypoxemia, increasing evidence suggests that alterations in erythrocyte metabolism and redox homeostasis may further compromise oxygen transport capacity [2, 3]. Previous studies have reported changes in the hemoglobin–oxygen affinity as well as disturbances in intracellular adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG) levels, which may influence oxygen unloading in peripheral tissues [4, 5]. Under physiological conditions, hemoglobin exists in a dynamic equilibrium between oxyhemoglobin, deoxyhemoglobin, and methemoglobin, maintained by erythrocyte enzymatic redox systems that preserve hemoglobin in its functional ferrous state [6, 7]. Glucose-6-phosphate dehydrogenase (G6PD) plays a pivotal role in maintaining intracellular antioxidant capacity by generating nicotinamide adenine dinucleotide phosphate(NADPH) through the pentose phosphate pathway, and reduced G6PD activity predisposes erythrocytes to oxidative injury and methemoglobinemia [8]. Disruption of erythrocyte redox regulation under chronic hypoxic and inflammatory conditions may therefore impair effective oxygen transport in COPD. Despite these observations, the contribution of erythrocyte redox enzyme systems and hemoglobin redox balance to oxygen transport dysfunction across the various stages of COPD has not been systematically characterized. We hypothesized that COPD severity is associated with progressive alterations in erythrocyte redox regulation, hemoglobin fractions, and oxygen transport capacity.

Purpose: to evaluate erythrocyte electron-transport and oxygen-transport functions across the various stages of chronic obstructive pulmonary disease.

Material and methods. *Study design and setting.* This was a single-center, observational, cross-sectional study conducted at the Republican Specialized Scientific and Practical Medical Center of Therapy and Medical Rehabilitation (Tashkent, Republic of Uzbekistan) between January 2023 and December 2024. The study protocol was reviewed and approved by the Local Ethics Committee of the Republic of Uzbekistan, operating in accordance with national ethical regulations and the principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

Study population. The study included 150 patients with chronic obstructive pulmonary disease (COPD) of varying severity and disease duration ranging from 3 to 15 years. The median age of the COPD patients was 52 years (IQR 44–56). The control group consisted of 40 apparently healthy age-matched individuals with a median age of 46 years (IQR 42–50). There were no statistically significant differences in age between the groups ($p > 0.05$). Among the COPD patients, 109 (72.7 %) were male and 41 (27.3 %) were female. Patients were stratified according to disease severity into mild (COPD I, $n = 54$), moderate (COPD II, $n = 59$), and severe (COPD III, $n = 37$) subgroups. The diagnosis of COPD and severity classification were established based on standardized clinical assessment and post-bronchodilator spirometry ($FEV_1/FVC < 0.70$) in accordance with GOLD recommendations. All patients were in a clinically stable condition, devoid of acute exacerbation, for at least six weeks prior to evaluation. The control subjects had no history of chronic pulmonary, cardiovascular, metabolic, renal, or systemic inflammatory diseases.

Inclusion and exclusion criteria. Eligible participants were adults aged ≥40 years, able to undergo spirometry and blood sampling procedures, and provided written informed consent. For the COPD group, eligibility required a confirmed diagnosis based on post-bronchodilator spirometry ($FEV_1/FVC < 0.70$) and clinical stability without respiratory infection or exacerbation within the preceding 6 weeks. The control subjects were age-matched individuals with normal spirometry and no chronic respiratory symptoms or systemic disease.

Exclusion criteria for all participants included acute infection or COPD exacerbation within 6 weeks; known hematologic disorders (including hemoglobinopathies or glucose-6-phosphate dehydrogenase deficiency); moderate-to-severe anemia (hemoglobin <100 g/L); chronic kidney disease stage ≥3; uncontrolled diabetes mellitus; active malignancy or chronic inflammatory disease; chronic liver disease; recent

[1] World Health Organization. Chronic obstructive pulmonary disease (COPD). Fact sheet. Geneva: WHO; 2024. Available at: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) (accessed 16.01.2026).

blood transfusion (within 3 months); long-term oxygen therapy; pregnancy or breastfeeding; current investigational drug use; and inability to comply with study procedures.

Blood sampling and laboratory measurements. Venous blood samples were collected for biochemical analyses. The erythrocytes were isolated by means of centrifugation and hemolyzed to assess erythrocyte redox enzyme activity. The content of cytochrome b_5 and cytochrome C-related heme protein was measured spectrophotometrically. The activities of NADH-cytochrome b_5 reductase and NADPH-cytochrome C reductase in erythrocyte hemolysates were determined using standardized biochemical assays and expressed as nmol/min per gram of hemoglobin. G6PD activity was quantified using a kinetic enzymatic method. The intracellular concentrations of 2,3-DPG were measured using a commercial enzymatic kit and normalized to hemoglobin content (μmol/g Hb).

Arterialized capillary blood samples obtained from the fingertip or earlobe were used to assess gas exchange and acid-base status. The partial pressures of oxygen (pO_2) and carbon dioxide (pCO_2), blood pH, and base excess were measured using a blood gas analyzer. Corresponding venous blood samples were analyzed for pH, pO_2, and pCO_2. Hemoglobin derivatives (oxyhemoglobin [HbO_2], deoxyhemoglobin [DHb], and methemoglobin [MetHb]) were quantified by co-oximetry. Intracellular erythrocyte pH was determined in cell lysates using a microelectrode-based pH sensor.

Statistical analysis. Statistical analyses were performed using SPSS software (version 26.0, IBM Corp.). The normality of the data distribution was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation. For comparisons between two groups, Student's *t*-test was used for normally distributed variables, while the Mann–Whitney *U* test was applied for non-normally distributed data. Comparisons among multiple groups (COPD severity subgroups) were performed using one-way ANOVA for normally distributed variables or the Kruskal–Wallis test for non-parametric data with post-hoc pairwise comparisons. Categorical variables were analyzed using the χ^2 test. A two-sided p-value < 0.05 was considered statistically significant.

Results. *Erythrocyte redox enzyme activity.* Patients diagnosed with COPD demonstrated significant alterations in the activity of erythrocyte redox enzymes when compared with healthy controls (Table 1). Even in mild COPD, erythrocyte cytochrome C-related heme protein content and cytochrome b_5 levels were approximately 25–30 % lower than in controls ($p < 0.001$), with progressively greater reductions observed in moderate and severe disease cases. In the severe COPD group, the mean cytochrome C content was found to be 4.20 ± 0.14 nmol/Hb, in comparison to 6.41 ± 0.21 nmol/Hb in controls ($p < 0.001$). The content of cytochrome b_5 was significantly reduced in mild and moderate COPD cases (both $p < 0.001$ vs. control), whereas in severe COPD cases the value remained numerically lower (0.33 ± 0.01 vs. 0.47 ± 0.02 nmol/Hb) but did not reach statistical significance (Table 1). G6PD activity was significantly lower in severe COPD cases (53.38 ± 1.53 vs. 69.12 ± 2.04 nmol/min/Hb; $p < 0.001$). In contrast, the activities of NADH-cytochrome b_5 reductase and NADPH-cytochrome C reductase were significantly increased in all COPD groups compared with controls (all $p < 0.001$). In severe COPD cases, NADH-cytochrome b_5 reductase activity reached 79.09 ± 2.59 nmol/min/Hb compared with 63.21 ± 1.97 nmol/min/Hb in controls ($p < 0.001$), while NADPH-cytochrome C reductase increased to 67.92 ± 1.89, compared with 49.51 ± 1.64 nmol/min/Hb ($p < 0.001$). Plasma cytochrome C concentration increased progressively with disease severity, rising from 0.21 ± 0.007 nmol/Hb in controls to 0.33 ± 0.009 nmol/Hb in severe the COPD group ($p < 0.001$). Erythrocyte 2,3-diphosphoglycerate levels were significantly elevated in all COPD groups relative to controls (all $p < 0.001$).

Table 1. **Activity of erythrocyte electron-transport system enzymes in patients with COPD**

Parameter	Control ($n = 40$)	COPD I (mild, $n = 54$)	COPD II (moderate, $n = 59$)	COPD III (severe, $n = 37$)
Cytochrome C (plasma), nmol/Hb	0.21 ± 0.007	0.26 ± 0.007***	0.31 ± 0.008***	0.33 ± 0.009$^{***\wedge\wedge\wedge}$
Cytochrome C (RBC), nmol/Hb	6.41 ± 0.21	4.53 ± 0.11***	4.48 ± 0.11***	4.20 ± 0.14$^{***\wedge}$
Cytochrome b_5 (RBC), nmol/Hb	0.47 ± 0.02	0.33 ± 0.01***	0.34 ± 0.01***	0.33 ± 0.01
NADH-cyt b_5 reductase, nmol/min/Hb	63.21 ± 1.97	76.18 ± 2.10***	78.96 ± 2.12***	79.09 ± 2.59***
NADPH-cyt c reductase, nmol/min/Hb	49.51 ± 1.64	62.12 ± 1.74***	65.63 ± 1.61***	67.92 ± 1.89$^{***\wedge}$
G6PD (RBC), nmol/min/Hb	69.12 ± 2.04	55.77 ± 1.47***	54.75 ± 1.46***	53.38 ± 1.53***
2,3-DPG (RBC), μmol/Hb	2.47 ± 0.08	3.20 ± 0.11***	3.02 ± 0.07***	3.39 ± 0.10***

Note. For Tables 1–3: stars indicate significance vs. control (* – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$); carets indicate significance vs. COPD I (mild) ($^{\wedge}$ – $p < 0.05$, $^{\wedge\wedge}$ – $p < 0.01$, $^{\wedge\wedge\wedge}$ – $p < 0.001$).

Hemoglobin fractions and total hemoglobin. The distribution of hemoglobin fractions was shifted toward reduced oxyhemoglobin and increased deoxyhemoglobin and methemoglobin in COPD patients (Table 2). In severe COPD cases, oxyhemoglobin concentration was found to be 57.51 ± 1.95 g/L compared with 75.65 ± 2.45 g/L in controls ($p < 0.001$). The levels of deoxyhemoglobin increased to 15.66 ± 0.58 g/L, in comparison with 11.30 ± 0.39 g/L in controls ($p < 0.001$), while the levels of methemoglobin rose to 1.411 ± 0.043 g/L compared with 0.901 ± 0.026 g/L in controls ($p < 0.001$). Analogous yet less pronounced changes were observed in mild and moderate COPD (all $p < 0.001$ vs. controls). The total hemoglobin concentration did not differ significantly between controls and patients with mild COPD, but was significantly reduced in the moderate and severe disease groups. The mean values were 109.24 ± 6.75 g/L in the severe COPD group and 129.34 ± 5.87 g/L in the control group ($p < 0.001$).

Table 2. **Hemoglobin fractions in the blood of COPD patients**

Parameter	Control ($n = 40$)	COPD I (mild, $n = 54$)	COPD II (moderate, $n = 59$)	COPD III (severe, $n = 37$)
Hemoglobin (Hb), g/L	129.34 ± 5.87	127.27 ± 5.05	119.76 ± 4.38$^{***\wedge\wedge\wedge}$	109.24 ± 6.75$^{***\wedge\wedge\wedge}$
Oxyhemoglobin (HbO_2), g/L	75.65 ± 2.45	70.51 ± 1.54***	68.14 ± 1.55***	57.51 ± 1.95***
Deoxyhemoglobin (DHb), g/L	11.30 ± 0.39	13.45 ± 0.35***	14.59 ± 0.41***	15.66 ± 0.58***
Methemoglobin (MetHb), g/L	0.901 ± 0.026	1.241 ± 0.037***	1.310 ± 0.035***	1.411 ± 0.043$^{***\wedge\wedge}$

Blood gas and acid–base parameters. Blood gas analysis demonstrated lower capillary oxygen tension (pO_2) in COPD patients compared with controls, with a progressive decline across disease severity (Table 3).

Table 3. **Blood gas and acid-base parameters in COPD patients**

Parameter	Control ($n = 40$)	COPD I (mild, $n = 54$)	COPD II (moderate, $n = 59$)	COPD III (severe, $n = 37$)
Blood pH (capillary)	7.39 ± 0.24	7.39 ± 0.20	7.42 ± 0.23	7.43 ± 0.29
pO_2 (capillary, mmHg)	80.07 ± 3.26	78.60 ± 2.40	72.38 ± 2.03$^{\wedge}$	71.0 ± 2.73$^{*\wedge}$
pCO_2 (capillary, mmHg)	39.98 ± 1.19	38.01 ± 0.86	36.01 ± 0.67**	32.49 ± 0.94$^{***\wedge\wedge\wedge}$
Base excess (mmol/L)	+1.28 ± 0.04	–2.4 ± 0.06	–3.08 ± 0.07$^{***\wedge\wedge\wedge}$	–3.19 ± 0.11$^{***\wedge\wedge\wedge}$
RBC pH (hemolysate)	7.08 ± 0.24	7.06 ± 0.22	6.99 ± 0.18	6.97 ± 0.18
Blood pH (venous)	7.30 ± 0.01	7.33 ± 0.01	7.32 ± 0.05	7.34 ± 0.08
pO_2 (venous, mmHg)	41.7 ± 0.25	40.3 ± 1.2	37.6 ± 1.1	36.8 ± 0.51
pCO_2 (venous, mmHg)	43.3 ± 0.96	42.0 ± 1.7	40.1 ± 1.8	39.6 ± 0.54

In severe COPD cases, the mean capillary pO_2 level averaged 71.0 ± 2.73 mmHg, compared with 80.1 ± 3.3 mmHg in controls ($p < 0.05$). In patients diagnosed with mild COPD, pO_2 values were found to be within the normal range (78.6 ± 2.4 mmHg), while those with moderate COPD demonstrated an intermediate reduction (72.4 ± 2.0 mmHg). The arteriovenous oxygen gradient decreased with the increasing disease severity, from approximately 38 mmHg in control and mild COPD groups to approximately 34 mmHg in the severe COPD group, indicating reduced peripheral oxygen extraction. Additionally, the pCO_2 levels were found to be significantly lower in moderate and severe COPD cases, consistent with hyperventilation. Severe COPD patients demonstrated a pCO_2 of 32.5 ± 0.94 mmHg, compared with 40.0 ± 1.19 mmHg in controls ($p < 0.001$). Base excess values were significantly reduced in moderate and severe COPD, reflecting metabolic acid load (–3.19 ± 0.11 mmol/L in severe COPD vs. +1.28 ± 0.04 mmol/L in controls; $p < 0.001$). Despite these changes, the pH levels of capillary blood remained within the physiological range across all groups. Intracellular erythrocyte pH demonstrated a nonsignificant trend toward lower values in patients with COPD (6.97 ± 0.18 in severe COPD vs. 7.08 ± 0.24 in the control group). Venous blood gas parameters showed similar directional changes, including mildly reduced venous pO_2 and pCO_2 in COPD patients.

Discussion. The present study demonstrates that chronic obstructive pulmonary disease is associated with substantial alterations in erythrocyte redox regulation and hemoglobin composition, which may contribute to impaired systemic oxygen transport beyond pulmonary gas exchange abnormalities. Reduced cytochrome C-related heme protein content and a stage-dependent tendency toward lower cytochrome b_5 levels suggest compromised erythrocyte redox capacity, potentially reflecting impaired metabolic support and antioxidant defense. Decreased G6PD activity further supports diminished availability of NADPH and weakened intracellular redox buffering. Together, these changes indicate

increased vulnerability of erythrocytes to oxidative stress and impaired maintenance of hemoglobin in its functional reduced state. Similar redox disturbances in erythrocytes under oxidative stress conditions have been described previously [9]. In parallel, increased activities of NADH-cytochrome b_5 reductase and NADPH-cytochrome C reductase likely represent compensatory activation in response to oxidative challenge. Despite this upregulation, plasma cytochrome C levels were elevated, suggesting membrane injury and enhanced erythrocyte turnover, consistent with eryptotic processes [10]. These findings indicate that compensatory enzymatic responses may be insufficient to fully preserve intracellular redox balance in advanced COPD.

The increase in NADH-cytochrome b_5 reductase activity may reflect an adaptive mechanism aimed at maintaining hemoglobin in its functional ferrous state, as this enzyme participates in the reduction of methemoglobin to oxyhemoglobin [11]. Nevertheless, methemoglobin levels remained significantly elevated in our cohort, indicating that reductive capacity was likely overwhelmed by oxidative burden and/or limited substrate availability. A reduction in G6PD activity has been demonstrated to further compromise glutathione recycling and antioxidant defense, thereby predisposing erythrocytes to oxidative injury and methemoglobinemia [12]. These mechanisms together may contribute to a reduction in effective oxygen-carrying capacity.

Alterations in hemoglobin fractions provide additional evidence of impaired oxygen transport in cases of COPD. Progressive reductions in oxyhemoglobin, accompanied by increases in deoxyhemoglobin and methemoglobin, were observed with increasing disease severity. A similar hemoglobin redox imbalance has been linked to impaired oxygen delivery under hypoxic stress [13]. Elevation of erythrocyte 2,3-diphosphoglycerate represents a classical compensatory response, facilitating oxygen unloading; however, this adaptation may be insufficient to normalize oxygen delivery when oxidative hemoglobin modification and gas exchange impairment persist. Notably, early functional changes in erythrocytes were also evident in patients with mild COPD, suggesting that blood-based oxygen transport abnormalities may develop at an early stage of the disease.

Blood gas analysis demonstrated systemic hypoxemia, with partial respiratory compensation of the metabolic disturbance. Lower capillary pO_2 values and reduced pCO_2 levels in moderate and severe disease are consistent with the hyperventilatory responses commonly observed in COPD [14]. Negative base excess values suggest metabolic acid load, potentially related to impaired oxidative metabolism and lactate accumulation. Maintenance of near-normal blood pH reflects effective respiratory compensation. Modest intracellular erythrocyte acidification may influence hemoglobin-oxygen affinity via the Bohr effect, although the magnitude observed is unlikely to represent the primary determinant of oxygen transport impairment [14].

Collectively, these findings suggest that impaired systemic oxygen delivery in COPD is not solely attributable to pulmonary gas exchange limitation, but may be compounded by intrinsic abnormalities in erythrocyte redox regulation and hemoglobin homeostasis. Disruption of erythrocyte antioxidant capacity, accumulation of oxidized hemoglobin species, and altered hemoglobin composition may jointly reduce effective oxygen transport and contribute to extrapulmonary manifestations of COPD. The recognition of erythrocyte dysfunction as a contributory component of COPD pathophysiology may open perspectives for therapeutic strategies targeting oxidative balance and red blood cell function. This study provides a systematic clinical characterization of remodeling of erythrocyte redox enzyme systems and hemoglobin redox balance across different stages of COPD severity [15].

Conclusion. In patients with chronic obstructive pulmonary disease, higher disease severity is associated with increasing abnormalities in red blood cell redox balance and hemoglobin composition, which may impair systemic oxygen delivery in addition to lung dysfunction. Declines in antioxidant capacity within erythrocytes, alongside the presence of incomplete compensatory activation of reductase enzymes, are indicative of elevated oxidative stress. Decreased oxyhemoglobin, increased deoxyhemoglobin and methemoglobin, and elevated 2,3-diphosphoglycerate levels suggest reduced efficiency of oxygen transport. These changes coexist with systemic hypoxemia and may further worsen tissue oxygenation in patients with COPD. Targeting red blood cell oxidative balance may provide a complementary therapeutic approach.

Conflict of interest. The authors declare no conflict of interest.

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