

Effect of therapeutic phlebotomy on blood oxygen in patients with chronic obstructive lung diseases

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ABSTRACT

Background: Secondary polycythemia could be found in chronic obstructive lung disease (COPD) with chronic hypoxemia and it may also raise the blood viscosity. This experiment evaluated acute alterations in oxygenation, hematocrit, arterial blood gas indicators and pulmonary artery systolic pressure, as well as documented the symptoms after therapeutic phlebotomy.

Methods: The study is a quasi-experimental, single-arm, pre-pretest post-test study that took place at the Pulmonology Unit of Ayub Teaching Hospital, Abbottabad between November 2025 and March 2026. Eighty-seven COPD patients, whose hematocrit exceeded 56 percent were sampled consecutively. About 200-450 mL blood was taken out depending on the hematocrit level, and clinical status. The values of SpO₂, arterial blood gas values, and chosen symptoms were measured pre-phlebotomy and around 24-48 hours post-phlebotomy. Data were compared by use of paired statistical test SPSS 21 was used to analyze the data.

Results: The mean age was 62.15 ± 4.08 years; 62 (71.3%) patients were male, 62 (71.3%) were smokers, and 56 (64.4%) had severe COPD. Mean SpO₂ increased from $73.63 \pm 3.53\%$ to $80.78 \pm 2.26\%$ ($p < 0.001$). Hematocrit decreased from $60.05 \pm 1.46\%$ to $52.25 \pm 0.99\%$ ($p < 0.001$), while PaO₂ increased from 51.11 ± 2.91 to 59.71 ± 2.24 mmHg ($p < 0.001$). PaCO₂ decreased from 45.31 ± 2.08 to 40.31 ± 2.08 mmHg, while pH increased from 7.32 ± 0.02 to 7.39 ± 0.02 (both $p < 0.001$). Pulmonary artery systolic pressure also decreased from 51.32 ± 9.23 to 44.54 ± 7.35 mmHg ($p < 0.001$).

Conclusion: Short-term patients with COPD and secondary polycythemia showed positive changes with the application of therapeutic phlebotomy. Yet, this uncontrolled before-after study is not able to determine a causal effect of treatment. There is a need to have controlled studies under standardized oxygen conditions and with extended follow-ups.

Keywords: Chronic Obstructive Pulmonary Disease, Hematocrit, Therapeutic Phlebotomy, Secondary Polycythemia

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Introduction

COPD is a prevalent chronic respiratory disease that is associated with limitations and obstruction of airflow and respiratory symptoms (1,2). It is a major cause of morbidity and mortality on a global basis and

it has a significant burden in low- and middle-income nations that are at-risk due to smoking, occupational exposures, air pollution and biomass fuel exposures (3,4).

Secondary polycythemia can be caused by chronic hypoxemia, which is an important complication of advanced COPD (5). The continuous tissue hypoxia induces erythropoietin synthesis and red blood cell output leading to a high hematocrit but this response can raise blood viscosity and can impair cardiopulmonary functioning (6,7).

Therapeutic phlebotomy is well established in polycythemia vera, but not in secondary erythrocytosis secondary to chronic hypoxic lung disease, where an extreme paradox may be the reduction of oxygen-carrying capacity by an excessive reduction of the red cell mass (8,9). As such the available advantages and threats of phlebotomy must be addressed with reference to the prominent hypoxemia as well as the clinical status of the patient (10,11).

Past research proposals have provided the idea that chosen individuals with intensive COPD and pronounced polycythemia can undergo the exercise performance shifts or cardiopulmonary assessments following hematocrit reduction. But the existing evidence is minimal and information of the area, especially the Hazara area is scarce in Pakistan.

The current research was done to evaluate the short term effects in oxygen saturation, hematocrit, paraxanthine arterial blood gases, pulmonary artery systolic pressure and registered symptoms after therapeutic phlebotomy in COPD with secondary polycythemia patients.

Methods

A quasi-experimental before and after study, single arm was carried out in the Pulmonology Unit of the Ayub Teaching Hospital, Abbottabad, between November

2025 and March 2026. All subjects were enrolled upon obtaining an ethical approval of institutional ethical review committee (Ref. RC-EA-2025/131, dated 16 May 2025) and informed consent was obtained in written form.

Non-probability consecutive sampling was used to select a total of 87 patients. Statulator software was used to calculate the required sample size to use a single mean with a 95% confidence interval, absolute precision of 1.5 and standard deviation of 7, on which the estimated sample size was calculated to be 87 patients. The inclusion criteria consisted of both male and female patients aged 20 years to 85 years, having COPD, and a hematocrit $\geq 56\%$. On the parameter of post-bronchodilator FEV1/FVC = 0.70, COPD was diagnosed. Congenital heart disease, polycythemia vera, pregnancy, severe hypoxemia, necessitating ambulatory oxygen or non-invasive ventilation, renal diseases, hepatocellular carcinoma, severe mental illness, and obstruction of the upper airway were excluded.

A comprehensive history and physical exam were conducted on the enrollment day. Age, sex, residence, occupation, socioeconomic status, smoking status, pack-years, COPD severity and prior exacerbations were taken on a structured proforma. The hematocrit and complete blood count were done using the laboratory of the hospital. After eliminating other pertinent alternative causes of erythrocytosis, patients with hematocrit $\geq 56\%$ were evaluated with a view to administer therapeutic phlebotomy.

The levels of oxygen before and after phlebotomy were measured using pulse oximetry. Preoperative and postoperative measurements of the arterial blood gases were recorded to measure the PaO₂, P_fCO₂, and PH. The measurements were taken 2-4 hours

post phlebotomy. The measurements were either on the room air or where in case of clinical need receive oxygen using a nasal cannula. Echocardiographic parameters, the right ventricular overload and the pulmonary artery systolic pressure were also documented where available. Clinical effects were observed as improvement reported after phlebotomy, such as dyspnea, exercise tolerance, headache, and chest discomfort. The dataset did not have separate pre- and post-procedure symptom scores.

Meta phlebotomy was done using an aseptic method by trained medical personnel. 200 mL or 450 mL of blood was taken out based on the level of hematocrit, the target hematocrit and the clinical state. The treating clinician said it was 50 percent or 52 percent, the target of the hematocrit. A majority of the patients had been involved in a single session, with two patients receiving additional session. When indicated clinically, intravenous saline was used. Adverse events during the procedure and post procedure were tracked such as dizziness, syncope, hematoma or complications.

All the data were typed and compared with the SPSS 21. The variables that were categorical (i.e., continuous and categorical) were summarized using frequencies and percentages whereas the variables that were continuous were treated using mean and standard deviation. The Shapiro-Wilk test was used to assess normality. Normally distributed paired measurements (paired t-test), and non-normally distributed paired measurements (Wilcoxon signed-rank test) were performed. Calculation of mean changes in saturation of oxygen, hematocrit, PaO₂, and pulmonary artery systolic pressure that were paired with a 95% confidence interval was done. In the case of PaCO₂ and pH, the change observed was fixed among the participants

and thus, the exact paired change and Wilcoxon signed-rank p-value were reported, compared to a t-based confidence interval, which was undefined. A p-value <0.05 was considered statistically significant.

Results

Eighty-seven COPD patients with secondary polycythemia had been covered. The mean age was 62.15 ± 4.08 years. There were 62 (71.3%) male and 25 (28.7%) female patients. 61 (70.1%) patients were from rural areas and 26 (29.9%) were from urban areas. 62 (71.3%) were smokers. 31 (35.6%) patients had moderate COPD and 56 (64.4%) had severe COPD. GOLD grade 3 was present in 49 (56.3%), grade 2 in 25 (28.7%), and grade 4 in 13 (14.9%). The diagnosis technique was spirometry, which was documented in 71 (81.6%) patients, whereas 16 (18.4%) patients had the combination of spirometry and HRCT.

Table 1 presents baselines features.

Variable	Value
Age, years	62.15 ± 4.08
Male	62 (71.3%)
Female	25 (28.7%)
Rural residence	61 (70.1%)
Urban residence	26 (29.9%)
Smoker	62 (71.3%)
Non-smoker	25 (28.7%)
Moderate COPD	31 (35.6%)
Severe COPD	56 (64.4%)
GOLD grade 2	25 (28.7%)
GOLD grade 3	49 (56.3%)
GOLD grade 4	13 (14.9%)
Spirometry	71 (81.6%)
Spirometry + HRCT	16 (18.4%)

The treatment of phlebotomy therapy showed a positive short-term improvement in the regulation of oxygen and hematology. Mean SpO₂ increased from $73.63 \pm 3.53\%$ to $80.78 \pm 2.26\%$, while hematocrit decreased from $60.05 \pm 1.46\%$ to $52.25 \pm 0.99\%$. Mean PaO₂ increased from 51.11 ± 2.91 mmHg to 59.71 ± 2.24 mmHg. PaCO₂ decreased from 45.31 ± 2.08 mmHg to 40.31 ± 2.08 mmHg, and pH

increased from 7.317 ± 0.021 to 7.387 ± 0.021 . PASP decreased from 51.32 ± 9.23 mmHg to 44.54 ± 7.35 mmHg. The paired comparisons were all statistically significant ($p < 0.001$). The

obtained results are displayed as the paired measurements and the means changes and 95% confidence interval as in Table 2.

Table: paired measurements and mean changes of Therapeutic Phlebotomy

Parameter	Before	After	Mean change	95% CI	P-value
SpO ₂ (%)	73.63 ± 3.53	80.78 ± 2.26	+7.15	6.87 to 7.43	<0.001
Hematocrit (%)	60.05 ± 1.46	52.25 ± 0.99	-7.80	-7.91 to -7.70	<0.001
PaO ₂ (mmHg)	51.11 ± 2.91	59.71 ± 2.24	+8.60	8.43 to 8.76	<0.001
PaCO ₂ (mmHg)	45.31 ± 2.08	40.31 ± 2.08	-5.00	-5.00 (constant change)	<0.001 (Wilcoxon)
pH	7.32 ± 0.02	7.39 ± 0.02	+0.07	+0.070 (constant change)	<0.001 (Wilcoxon)
PASP (mmHg)	51.32 ± 9.23	44.54 ± 7.35	-6.78	-7.19 to -6.37	<0.001

Measures were taken 2-4 hours after the phlebotomy. 71 (81.6) patients were evaluated on room air, and 16 (18.4) with oxygen supplied by nasal cannula use. In the group of patients with oxygen, 14 were administered 2 L/min of oxygen, and 2 were given 3 L/min. A volume of 450 mL was removed in 62 (71.3%) patients and 200 mL in 25 (28.7%). A session was done in 85 (97.7) patients and two sessions in 2 (2.3). Forty-five (51.7%) patients received saline. The target hematocrit was 52% in 61 (70.1%) and 50% in 26 (29.9%).

In dyspnea, exercise tolerance, headache and chest discomfort were reported to have improved after the procedure in 87 (100.0) patients, 82 (94.3) patients, 62 (71.3) patients respectively. Table 3 shows these values. Since the dataset reflected improvement as opposed to distinct pre- and post-procedure symptom scores, these percentages can be viewed as reported post-procedure improvement, but not measured changes in symptom scores.

Table 3: Percentage of symptom improved with phlebotomy

Symptom	Improved, n (%)
Dyspnea	87 (100.0%)

Exercise tolerance	82 (94.3%)
Headache	62 (71.3%)
Chest discomfort	63 (72.4%)

Right ventricular overload was documented in 45 (51.7%) patients. No adverse event was recorded in 0 (0.0%) patients. Syncope occurred in 2 (2.3%), while dizziness and hematoma were each recorded in 1 (1.1%) and 1 (1.1%), respectively.

Discussion

The current paper presents short-term effects of therapeutic phlebotomy in patients who have COPD and significant secondary polycythemia. Hematocrit has decreased about 7.8 percentage points and the SpO₂ and PaO₂ have recommended an improvement during the short post procedure observation duration. PaCO₂ and pH, as well as, PASP, was also altered. Interpretation of these findings should be interpreted as pre and post procedure changes as opposed to evidence that the changes were as a result of phlebotomy alone.

The decrease in PASP post phlebotomy in the present study is of interest but it cannot be viewed as a reflection of the effect on pulmonary hypertension due to the absence of

a control group and other factors might have altered the measurements.

In polycythemia vera, therapeutic phlebotomy is established, but in case secondary erythrocytosis, the underlying cause remains to be considered. (11) There is a published case report of the use of phlebotomy in secondary polycythemia, which is related to chronic hypoxic respiratory disease, but case-level evidence cannot prove its effectiveness. (12)

Earlier physiological work in polycythemic patients with COPD suggested that reducing hematocrit may influence exercise performance in selected patients. (13) The present findings of reduced hematocrit and reported improvement in exercise tolerance are compatible with this physiological concept, although the current study did not use a validated exercise test and therefore cannot establish an objective improvement in exercise capacity.

The procedure itself requires careful selection of blood volume and monitoring. Practical guidance describes therapeutic phlebotomy as a procedure in which the volume removed should be individualized and patients monitored for adverse effects. (14) Reviews have emphasized that the clinical indication, underlying disorder, and patient's tolerance should be considered rather than applying a single phlebotomy strategy to all patients. (15) In a prospective series of therapeutic phlebotomy procedures, adverse effects were documented, supporting the need for monitoring during and after venesection. (16) In the present dataset, adverse events were uncommon, with syncope, dizziness, and hematoma recorded in a small number of patients.

The increase in oxygen saturation and PaO_2 observed after phlebotomy needs cautious interpretation. Chronic respiratory disease

can alter oxygen transport, and the relationship between oxygen content, hemoglobin concentration, and tissue oxygen delivery is not determined by oxygen saturation alone. (17) Reducing hematocrit may lower blood viscosity, but excessive reduction in red cell mass could potentially reduce oxygen-carrying capacity. For this reason, phlebotomy should not be viewed as a replacement for treatment of chronic hypoxemia.

Long-term oxygen therapy has an established role in appropriately selected patients with severe chronic hypoxemia and COPD. (18,19) Contemporary COPD management also emphasizes treatment of the underlying disease and associated risk factors rather than relying on a single supportive procedure. (20) The present study therefore supports considering phlebotomy only as a selective supportive intervention in patients with marked secondary polycythemia and relevant clinical features, while assessment and management of chronic hypoxemia remain central.

Clinical experience reported in therapeutic phlebotomy series also suggests that the procedure can be performed in different clinical settings when patients are appropriately selected and monitored. (21,22) However, these reports do not provide evidence that short-term changes after venesection translate into better long-term outcomes in COPD.

It has to be especially vigilant about the findings of the symptoms. Improvement recorded in dyspnea was recorded in all patients but in most improvement in exercise tolerance, headache and chest discomfort also. Nevertheless, there were no validated pre- and post-treatment symptom scores in the dataset. These results must thus be considered as reported post-procedure improvement as

opposed to quantified change in symptom severity. Symptoms and burden of exacerbation of COPD can change as time goes on and efficient assessment of symptoms should preferably rely on standardized tools. The findings should be interpreted based on the limitations of the current study. This research was carried out in one tertiary care hospital and it involved 87 patients. It employed a one arm before and after design and did not have a control group observed concurrently; thus, the changes observed cannot be characterized as being due to therapeutic phlebotomy only. Oxygen is used in some of the patients during the period and the changes could also have been due to other factors of COPD management. These post-procedure outcomes were measured at about 2-4 hours and hence, the time the effects being measured is not certain. Moreover, symptom scores were not assessed based on validated scales, iron state, recurring polycythemia, the necessity of oxygen on a long-term basis, hospitalization, thrombotic incidents, or mortality. The study is also unable to identify that repeated phlebotomy has long-term clinical benefit or impacts survivability or pulmonary hypertension over the long term. To further examine the role of therapeutic phlebotomy in the secondary polycythemia of COPD, future prospective multicentric studies with bigger sample sizes and prolonged follow-up are required. Stronger evidence on the clinical usefulness of phlebotomy would come with controlled studies whereby well-chosen patients under the phlebotomy treatment would be compared to those under regular medical management. Standardized oxygen environments, symptom and exercise measurement scales, serial hematocrit and iron indices, evaluation of prolonged clinical

studies should also be appraised in future studies.

Conclusion

Selective supportive intervention by therapeutic phlebotomy can be used as a secondary intervention in patients with COPD that is characterized by both secondary polycythemia and symptoms of clinical importance, but the primary goal remains on the treatment of underlying hypoxemia and COPD. The results fail to determine that phlebotomy lowers chances of thrombosis, enhances long-term disease outcome, or clinical benefit is long term.

Future recommendations:

To know the longer-term advantages and safety of therapeutic phlebotomy in this group, prospective controlled trials using standardized oxygen levels, validated symptom and exercise scales, serial hematocrit and iron measures and increased follow-ups are required.

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Conflict of Interest:

The authors declare no conflict of interest regarding the publication of this study.

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All the authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed.	