Do we care enough about the role of smoking in the etiology of polycythemia?

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ABSTRACT

Aims: Smoking is associated with both primary and secondary polycythemia. In this study, we aimed to determine the role of smoking on polycythemia etiology in patients without active pulmonary pathology.

Methods: Data of the patients with polycythemia detected in Hematology clinic and referred to the Chest Diseases department for investigation of possible secondary polycythemia etiologies during the last one year were reviewed retrospectively.

Results:82 patients had been referred to Chest Diseases. In 15 patients lung diseases were found to cause secondary polycythemia. Smoking was detected in 48 patients (58.53% of all cases and 71.64% of those without pulmonary pathology). The mean hemoglobin (HGB), hematocrit (HCT), red blood cell (RBC), red cell distribution width (RDW), mean corpuscular volume (MCV) values were significantly higher in smokers (p=0.01, p=0.01, p=0.01, p=0.04 and p=0.03, respectively). Smokers had significantly higher mean carboxyhemoglobin (COHgb) ratio (p=001). In 89.58% of smokers, COHgb was found to be high. 10.42% of all smokers were found to have no COHgb elevation. There were significantly positive correlations between the COHgb ratios with the cigarette quantity (package/year), HGB, HCT, RBC, RDW and MCV values. Isolated smoking was accepted as the presumably cause of secondary polycythemia in 58.53% of all cases.

Conclusions: Smoking history should be questioned in the etiological assessment of polycythemia. While COHgb measurement may prevent many unnecessary investigations, it should be borne in mind that COHgb is not the only factor in the effect of smoking on erythropoiesis.

Introduction

Polycythemia denotes hemoglobin values greater than 16.5 g/dl in men and 16 g/dl in women and / or hematocrit values greater than 49% in men and 48% in women. Those who are related to myeloproliferative diseases are defined as primary polycythemia (polycythemia vera) whereas those secondary to other underlying diseases are called secondary polycythemia (1). Pulmonary diseases have an important place in etiology of secondary polycythemia. On the other hand, in many cases without active pulmonary pathology, the use of isolated tobacco was associated with both secondary polycythemia and myeloproliferative diseases such as myelofibrosis and polycythemia vera (2, 3).

Smoking has acute and chronic effects on hematopoiesis such as accelerated erythropoiesis, leukosis and thrombocytosis. These conditions are thought to play a triggering role with polycythemia vera, essential thrombocythemia and early period of myelofibrosis. The Janus kinase/signal transducers and activators of transcription (JAK-STAT) and nuclear factor kappa light chain enhancer of activated B cells (NF-kB) signaling pathways are activated in both smokers and myelofibrosis patients. In both clinical tables, an increase in pro-inflammatory cytokines, in vivo activation of leukocytes and platelets, endothelial dysfunction and increased systemic oxidative stress are evident. In the light of all these data, the roles of smoking in primary polycythemia including hematological malignancies and secondary polycythemia are prominent. However, considering the doubts whether the smoking leads to secondary polycythemia or primary polycythemia with different mechanisms, the effects of smoking on erythropoiesis are still controversial (2-4).

In this study, we aimed to determine the hematopoietic effects of tobacco use and amount of usage, and to determine its possible relationships with secondary polycythemia in patients without active pulmonary pathology.

Methods

Patients who were diagnosed with polycythemia in the Hematology Department and referred to the Chest Diseases Department for the purpose of investigating possible secondary polycythemia etiologies during the last one year were reviewed retrospectively. The ethical approval number is 18/182. Data

of the cases clinically examined between January 2017 and January 2018 were assessed. Primary polycythemia had been excluded by Hematology Department in all cases but possible etiology of secondary polycythemia had not been clearly demonstrated.

Clinical, laboratory, radiological findings, pulmonary function tests were investigated. Age, gender, complete blood count values including hemoglobin (HGB), hematocrit (HCT), red blood cell (RBC), red cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) were determined. The history of the patients was evaluated in terms of known lung diseases, respiratory complaints, high altitude, occupational inhalation / exposure, history of drug use. Smoking habits, cigarette usage amounts and durations were determined. The data on the presence and the amount of cigarette use in all cases were investigated. Smoking habits, cigarette usage amounts and smoking habit period of the cases were determined from their medical records. Those who actively smoke minimum 10 cigarettes per day and for at least one year were evaluated as active smokers. Package/year data of tobacco use were determined for smokers. Arterial blood gas results obtained in the room air were compiled. Partial oxygen (PaO_2) and carbon dioxide pressures ($PaCO_2$), oxygen saturation (SaO_2%) and carboxyhemoglobin (COHgb) ratios at arterial blood gas were examined.

The data obtained were evaluated statistically. Descriptive statistics were performed. Means ± standard deviations for continuous variables were obtained. Correlations between the parameters examined were evaluated. Probability (p) values less than 0.05 were considered statistically significant.

Results

A total of 82 patients with preliminary diagnosis of secondary polycythemia in Hematology Department had been referred to Chest Diseases Department for investigation of possible underlying pulmonary diseases. The patients were questioned about the history, signs and symptoms of the possible underlying pulmonary diseases. Subsequently, all patients underwent chest X-ray and pulmonary function tests. 63 patients received arterial blood gas test in the room air. In 15 patients (18.29%) who had no previous pulmonary pathology diagnosis, lung diseases were found to cause secondary polycythemia. 9 patients had chronic obstructive pulmonary disease (COPD) (10.97%), 4 patients had asthma (4.88%), 3 patients had interstitial lung disease (3.66%), 2 patients had bronchiectasis (2.44%). Tobacco use was detected in 48 of 67 patients (58.53% of all cases and 71.64% of those without pulmonary pathology) who were not diagnosed with active pulmonary pathology (Figures 1 and 2).

In females, etiologies of secondary polycythemia were affiliated to active pulmonary disease in 6 cases (20.6%) and to smoking in 19 cases (65.5%). In 4 female cases (13.8%), there was no pulmonary disease which could lead to secondary poly-

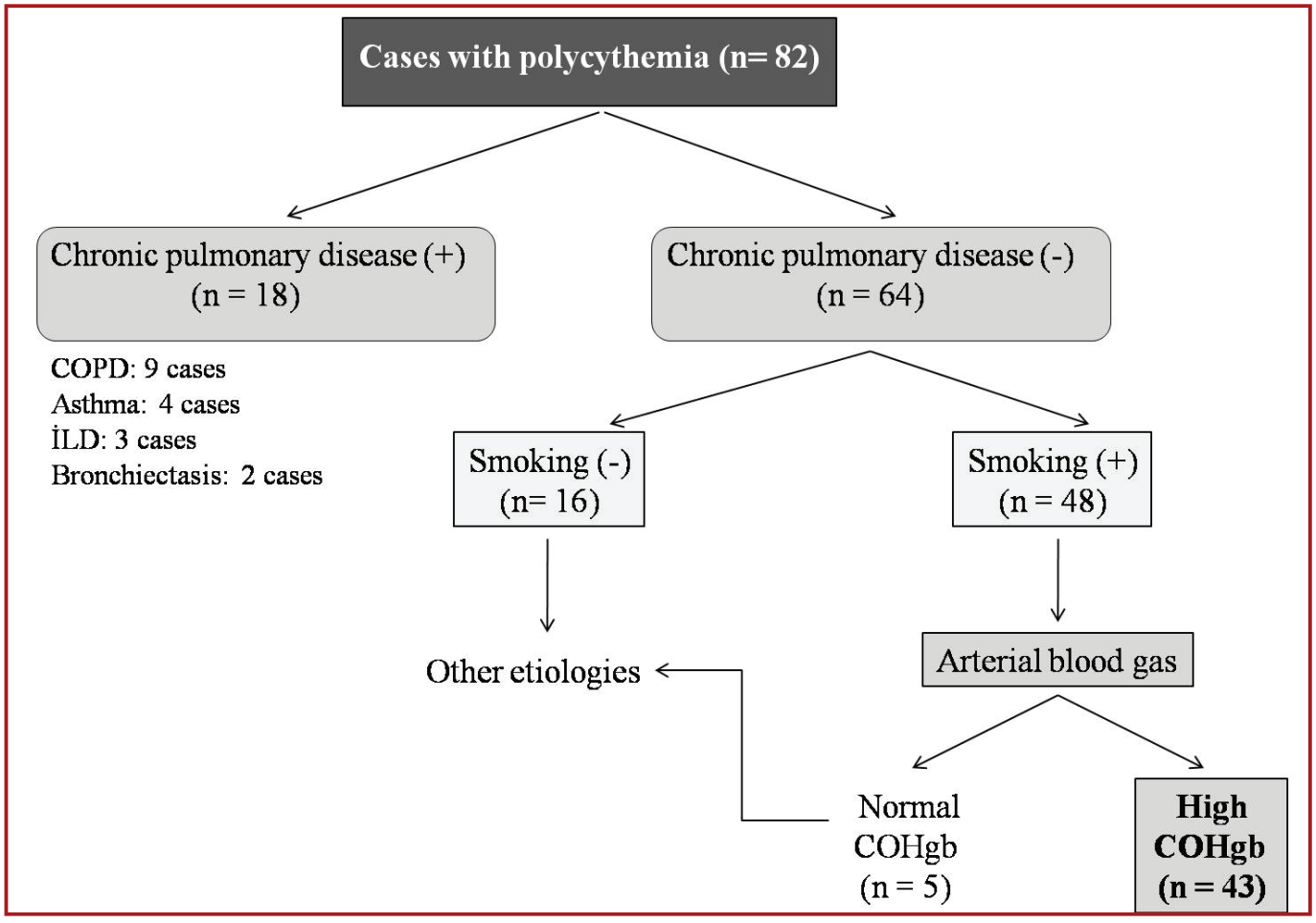

Figure 1. The results of pulmonary evaluation in the etiology of secondary polycythemia.
COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, COHgb: carboxyhemoglobin.

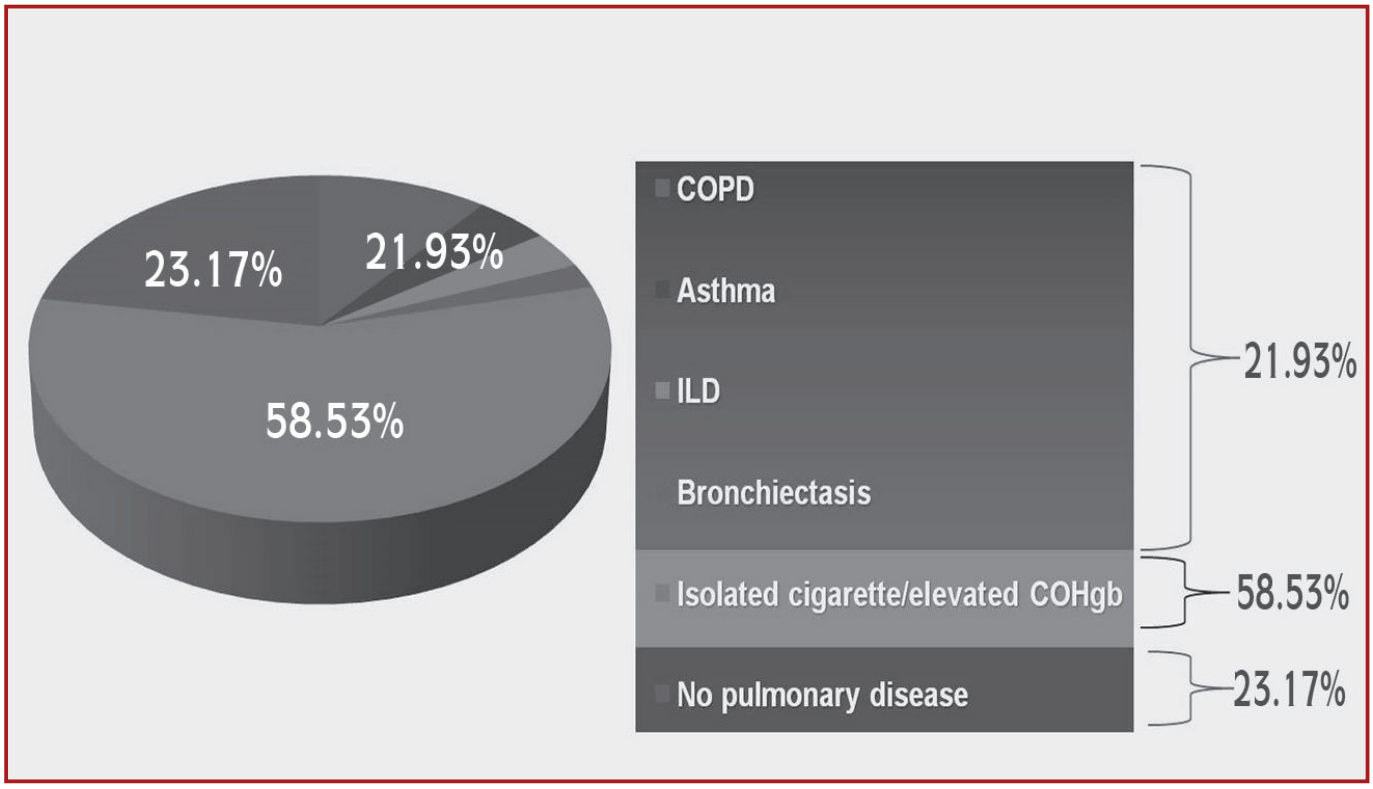

Figure 2: Distribution of pulmonary causes in the etiology of secondary polycythemia.
COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, COHgb: carboxyhemoglobin.

cythemia. In males, etiologies were affiliated to active pulmonary disease in 12 cases (22.6%) and to smoking in 29 cases (54.7%). Additionally, in 12 male cases (22.6%), there was no pulmonary disease which could lead to secondary polycythemia (Table 1).

After the 18 patients with active pulmonary disease were excluded, the data of the remaining 64 cases were compared. The mean age was significantly lower in nonsmokers (p=0.001). The mean hemoglobin, hematocrit, RBC, RDW, MCV values were significantly higher in smokers (p=0.01, p=0.01, p=0.01, p=0.04 and p=0.03, respectively) (Table 1).

The arterial blood gas analysis was performed in 98.4% of the cases without a diagnosis of active pulmonary disease. While the mean COHgb ratio was 1.3 ± 0.4% in nonsmokers, smokers had a significantly higher mean COHgb ratio (5.2 ± 2.7%) (p=001). In 89.58% of smokers, COHgb was found to be high in arterial blood gas. 10.42% of all smokers were found to have no COHgb elevation.There were significantly positive correlations between the COHgb ratios with the cigarette quantity (package/year), HGB, HCT, RBC, RDW and MCV values. Cig-

Table 1: The characteristics of the patients who were evaluated for pulmonary disease in order to investigate the etiology of polycythemia.

		All cases (n=82)	Pulmonary disease exist(n=18)	Pulmonary disease absent(n=64)		
				Non-smoker (n=16)	Smoker (n=48)	p
Gender	Female (n,%)	29 (35.4%)	6 (20.6%)	4 (13.8%)	19 (65.5%)	-
	Male (n,%)	53 (64.6%)	12 (22.6%)	12 (22.6%)	29 (54.7%)	-
Age (year)		43.7±12.4	51.2±6.5	35.8±12.7	43.5±8.2	0.001
Mean Hgb (gr/dL)		18.3±2.1	18.1±2.3	17.1±0.9	18.8±1.9	0.01
Mean Hct (%)		56.2±3.7	56.3±3.1	53.3±3.9	57.1±2.3	0.01
Mean RBC (10^6/mm^3)		6.8±1.2	6.7±0.9	6.1±1.0	7.1±1.1	0.01
Mean RDW (%)		15.1±2.3	15.1±2.1	14.5±2.2	15.3±1.8	0.04
Mean MCV (fL)		92.6±5.6	86.7±5.6	86.9±5.9	96.7±4.9	0.01
Mean MCH (pg)		28.3±3.1	29.2±2.9	29.3±3.3	27.6±3.4	NS
Mean MCHC (%)		33.4±2.7	34.1±2.8	35.6±3.1	32.4±2.9	NS

Hgb: hemoglobin, Hct: hematocrit, RBC: red blood cell, RDW: red cell distribution width, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, NS: not significant.

Table 2: The correlations between the cigarette quantity and carbon monoxide levels in arterial blood gas with erythrocytosis parameters (p<0.05).

		p	Correlation coefficient
Cigarette quantity package / year	Hemoglobin	0.02	+0,174
Cigarette quantity package / year	Hematocrit	0.02	+0,163
Cigarette quantity package / year	RBC	0.03	+0,120
Cigarette quantity package / year	RDW	0.02	+0,165
Cigarette quantity package / year	MCV	0.03	+0,168
Cigarette quantity package / year	COHgb	0.005	+0,220
COHgb	Hemoglobin	0.01	+0,187
COHgb	Hematocrit	0.01	+0,185
COHgb	RBC	0.02	+0,164
COHgb	RDW	0.01	+0,192
COHgb	MCV	0.01	+0,187

RBC: red blood cell, RDW: red cell distribution width, MCV: mean corpuscular volume, COHgb: carboxyhemoglobin.

arette quantity (package/year) also positively correlated with COHgb, HGB, HCT, RBC, RDW and MCV values (Table 2).

In 58.53% of all cases, isolated smoking, and in 52.44% of all cases isolated COHgb elevation was accepted as the presumably cause of secondary polycythemia. However, even if COHgb elevation in arterial blood gas is not detected in smokers, it was suggested that smoking should be considered as etiologic cause if no additional pathological condition was found.

Discussion

It has long been known that pulmonary diseases have an important role in the etiology of secondary polycythemia and erythrocytosis caused by hypoxia (2-4). Firstly, in 1919 Aldred Scott Warthin published an autopsy report entitled “A case of Ayerza’s disease: chronic cyanosis, dyspnea, and erythremia, associated with syphilitic arteriosclerosis of the pulmonary artery” (5). In the following years this subject was investigated in more detail and the association of pulmonary diseases with erythropoiesis came to the fore (3). In this regard, the investigation of pulmonary diseases in patients with erythropoiesis or polycythemia has become an agreeable approach. In our hospital, the patients with suspected secondary polycythemia are also routinely consulted to Chest Diseases Department. A total of 82 cases from with suspected secondary polycythemia were examined in the in the last year. In 18 of them (21.95%), chronic pulmonary diseases have been found to play a role in the etiology in accordance with available information given in the literature. On the other hand, smoking was detected in 48 patients (58.53% of all cases and 71.64% of those without pulmonary pathology) who were not diagnosed with active pulmonary pathology.

Questioning smoking in polycythemia patients with no chronic pulmonary disease is a suggested interrogation style. Although there are data on the relationship between smoking and polycythemia in many older studies, “Smoker’s polycythemia” was first identified by Smith and Landaw in 1978 (6). There are more recent studies in the literature about high HGB, HCT and RBC levels in smokers. In the study of Lakshmi et al. the HGB, HCT and RBC levels were significantly higher in smokers (7). Whitehead et al. reported that HGB and HCT levels were significantly increased in those smoking more than 10 cigarettes per day (8). In the study of Malenica et al., the hematological effects of smoking were similarly observed (9). Concordant to the current literature, the mean HGB, HCT, RBC values were observed significantly higher in smokers in our study (p=0.01, p=0.01 and p=0.01 respectively).

RDW is a ubiquitously reported laboratory data. RDW is a measure of the range of variation of red blood cell volume that is readily available from complete blood count results. RDW increase is seen in anisocytosis in which RBCs are not equal in size (10). This increase was shown to be in relationship between smoking which is explained by some pathophysiological mechanisms. One of these mechanisms is thought to be oxidative stress due to smoking. An association between smoking and higher oxidative stress has been established previously. It has been demonstrated that oxidized RBCs lose their flexibility owing to a loss of lipid asymmetry, causing them to be more rigid. This cytoskeleton rearrangement results in anisocytosis in RBCs. Another accused mechanism about the role of smoking in anisocytosis is effect of adrenergic activation caused by smoking on bone marrow (11, 12). In their study about the relationship of RDW with polycythemia and its effect on survival, Galea and Davidson stated that, disordered overproduction of RBC under the stress of chronic hypoxia leads to higher RDW. They emphasized that considering the level of hypoxia and the dyserythropoiesis might not be obvious to the clinicians, observing the trend of RDW could be very helpful in these situations (13). In Grant et al.’s large study including 1616 cases, the relation between lung function and RDW was investigated. They found a direct relation between RDW and the number of package/year of smoking and tobacco usage habits (14). In a study conducted in our country the mean RDW values were found higher in smokers than in nonsmokers, and also significant positive correlations between RDW and number of cigarettes smoked per day and between RDW and duration of smoking were identified. They concluded that elevated RDW is associated with cigarette smoking and may be a useful indicator of inflammatory activity in smokers (15). In accordance with the current literature, RDW was observed in association with smoking in our study results also. We observed that the

mean RDW values were significantly higher in smokers and there were significantly positive correlations between RDW with COHgb and the cigarette quantity (package/year).

Mean corpuscular volume (MCV) is a measure of the average volume of RBCs. The detection of an elevated MCV is termed macrocytosis which often prompts an extensive investigation for an underlying cause. Mostly recognized determinants of macrocytosis are vitamin B12 and folate deficiency, alcohol use, hypothyroidism, coeliac disease, drug use, hemolysis and hematological conditions such as aplastic anemia, myelodysplasia, and myeloma (16). On the other hand, an association between smoking and macrocytosis has been reported from a number of studies since the 1970s. Potential mechanisms of this association, which was first reported by Helman in 1973, are thought to include the direct toxic effect of acetaldehyde on erythrocytes in smoking and the response to reduced oxygen-carrying capacity (17). O'Reilly et al.'s cohort study, conducted in 2,047 Irish patients aged 50-69 years, is one of the prominent studies on this subject. According to their results, authors reported that smoking should be considered as an important cause of macrocytosis and daily life habits of patients should be questioned in these patients (18). In the study of Takahashi et al. the relationship between idiopathic macrocytosis and smoking was emphasized and this situation was held responsible as the potential trigger of myelodysplastic syndrome in smokers (19). Malenica et al. also reported similar results about the relationship between smoking and macrocytosis (9). In accordance with these studies, our results supported the idea that smoking is a possible factor for macrocytosis.

If we review the role of smoking in the etiopathogenesis of secondary polycythemia, hypoxemia-associated polycythemia should be re-considered. It is well known that hypoxemia-associated polycythemia due to increased erythropoietin (EPO) in response to hypoxia has several possible reasons. Elevated EPO as a cause of polycythemia is most commonly due to residence at high altitude or cardiopulmonary diseases such as chronic pulmonary diseases, obstructive sleep apnea, and cyanotic heart diseases as mentioned previously (3, 4, 20). Additionally, functional tissue hypoxia can result from decreased release of oxygen to peripheral tissues from high oxygen affinity hemoglobin as observed in carbon monoxide (CO) intoxication and methemoglobinemia (20, 21). In smokers, polycythemia is often multifactorial, including tissue hypoxia, CO exposure, smoking-related cardiopulmonary diseases, and plasma volume contraction. Smoking increases the blood levels of CO which binds to hemoglobin to form carboxyhemoglobin (COHgb), which is unable to bind oxygen. As the COHgb level in the blood increases, the binding of oxygen to hemoglobin decreases, tissue hypoxia rises and functional anemia develops. Due to this relationship, the role of COHgb in secondary polycythemia is an expected finding (4, 22). In many studies, the association between increased COHgb levels and erythrocytosis in smokers was shown (22-24). Our results also support these knowledge. We observed that in 89.58% of smokers, COHgb was high in arterial blood gas. There were significantly positive correlations between the COHgb with the cigarette quantity (package/year), HGB, HCT, RBC, RDW and MCV values. However, 10.42% of all smokers were found to have no COHgb elevation. At this point, it is prominent that smoking stimulates erythropoiesis through other multiple mechanisms except for triggering tissue hypoxia by increasing COHgb. Since COHgb increase may vary according to the amount and time of cigarette consumption, the erythropoiesis effect of smoking should not be evaluated only with COHgb measurement. In other words, even if COHgb is not found high in peripheral blood in smokers, other pathways of smoker's polycythemia may induce erythropoiesis.

In conclusion, smoking history and the amount of cigarette consumption should be questioned in the etiological assessment of polycythemia. In the light of our results, it is observed that by the amount of cigarette consumption increases and erythropoiesis is triggered. Obtaining arterial blood gas and COHgb measurement may prevent many unnecessary investigations during etiological searches for secondary polycythemia. However, it should be borne in mind that COHgb is not the only factor in the effect of smoking on erythropoiesis. We think that our results can be further elucidated by larger, prospective studies.

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Conflict of Interest

The authors declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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