

Smoker's Polycythemia: Is It a Cardiovascular Risk?

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ABSTRACT

Increase red blood cell mass and decrease plasma volume can elevate blood viscosity, which can impair blood flow, making individuals susceptible to vaso-occlusive events. Smoking that results in secondary polycythemia and erythrocytosis can cause additional harms in smokers. It can be defined by an expansion of red cell mass with elevated haemoglobin and hematocrit as a physiologic response to increased erythropoietin production secondary to generalized tissue hypoxia. Hypoxia in smoker's polycythemia is present with normal or falsely elevated oxygen saturation value. This article stressing the importance of being aware of cardiovascular risk in patients with polycythemia as a result of chronic smoking exposure.

Keywords

Smoker's Polycythemia, Erythrocytosis, Hematocrit.

Introduction

Smoking is a well-known risk factor in promoting cardiovascular disease. Secondary polycythemia most often develops as a response to chronic hypoxemia, which triggers the increased production of erythropoietin by the kidneys. Secondary polycythemia has a wide range of possible aetiologies, among which smoker's polycythemia has been discovered a long time ago [1]. Smoking deprives the bone marrow of oxygen that pushes its production of red blood cells (RBCs), the carriers of oxygen. Elevated hematocrit (HCT) resulting from excessive erythrocytosis can increase RBC mass, increase blood viscosity, reduce blood return through the venous system (sluggish of blood flow), and increase platelet adhesion. Clot formation occurred as a result of this increase in blood viscosity and platelet activation at the vessel wall [2]. Secondary polycythemia would more accurately be called secondary erythrocytosis or erythrocythemia, as those terms specifically denote increased red blood cells above the sex-specific normal range but polycythemia as a term is used in myeloproliferative disorder called polycythemia vera where all three blood cells—RBCs, white blood cells, and platelets, are elevated [3]. In this mini-review, we focus on the strong association between smoking and erythrocythemia as a cause of cardiovascular disease.

Definition of Smoker's Polycythemia

Smokers' polycythemia (erythrocythemia) is a 'mixture' of relative polycythemia, a high plasma red blood cell (RBC) concentration due to erythrocytosis (increased RBC count) and decreased plasma volume (hemoconcentration), combined with secondary polycythemia, a disorder of increased haemoglobin or hematocrit (increased RBC mass), most often resulting from systemic hypoxia that attributed to states of carbon monoxide (CO) inhalation from chronic tobacco smoke [4].

Carbon Monoxide in the Pathogenesis of Polycythemia and Thrombosis

In smokers, carbon monoxide (CO) taking over the binding sites on haemoglobin forming carboxyhemoglobin that causes at least four harmful effects (Figure 1). First, Carboxyhemoglobin has a strong affinity for oxygen and reduces the oxygen content of circulating blood at any given P_{O_2} and increases the affinity for oxygen of the remaining haem sites, causing a left-shift of the carboxyhemoglobin dissociation curve, leading in turn to hypoxemia [5]. Therefore, carboxyhemoglobin from chronic tobacco smoking causes tissue hypoxia with a normal or falsely elevated oxygen saturation value (PO_2). Second, CO causes local mitochondrial dysfunction which, combined with hypoxemia, leads to local tissue hypoxia. Third, the blood is not only carrying less oxygen, but it is also more reluctant to release that oxygen to the tissues leading to reduced oxygen delivery to the renal oxygen

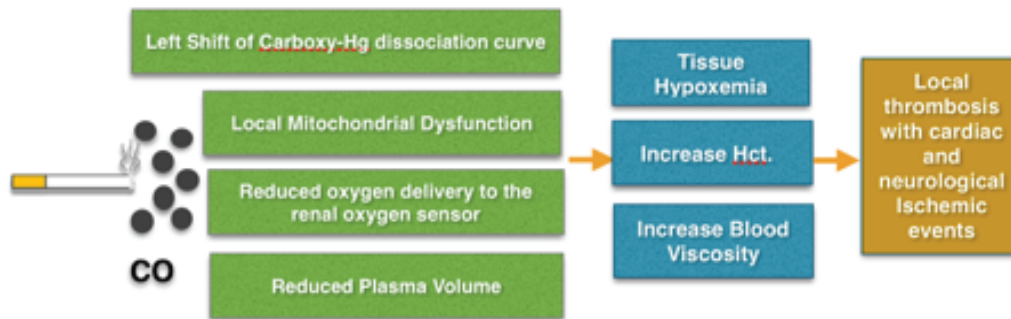


Figure 1: Harmful effects of carbon monoxide (CO) that bind to the binding sites of O₂ to hemoglobin (Carboxyhemoglobin) in smokers.

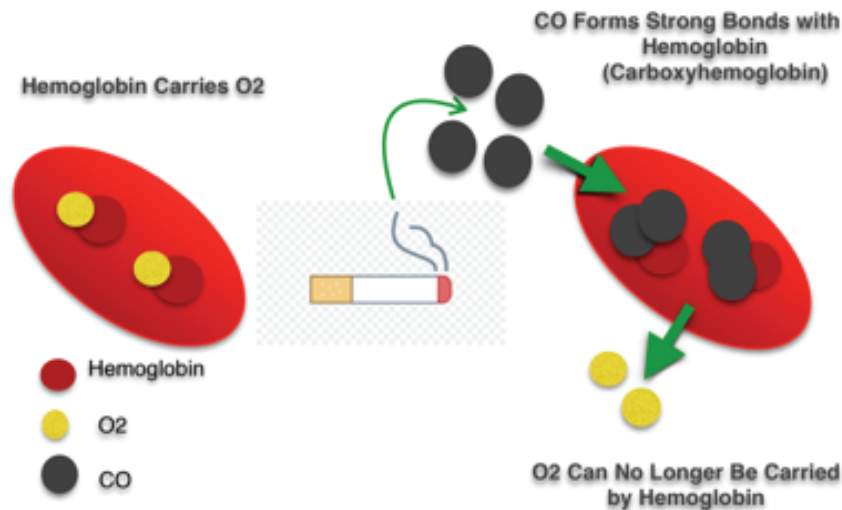


Figure (2): In smokers, carbon monoxide (CO) from chronic tobacco smoking has a strong affinity for oxygen and form strong bonds with hemoglobin (Carboxyhemoglobin). Carboxyhemoglobin reduces the oxygen content of circulating blood at any given P_{O2}.

sensor responsible for erythropoietin release [6]. This hypoxemia serves as a signal that activates a compensatory increase in RBC production, further increasing the hematocrit and inducing absolute polycythemia [7]. Fourth, a reduced plasma volume is found in many smokers with a raised haematocrit. CO exposure leads to decreased plasma volume but the underlying mechanism of this effect is not known with certainty. There is some evidence to suggest that it may occur via CO causing leakage of albumin in renal glomeruli, decreasing plasma volume and increasing haematocrit, leading to a relative polycythemia [8]. Therefore, blood viscosity increases with hematocrit, ultimately placing the patient at risk for local thrombosis and the incidence of cardiac and cerebrovascular hypoxic-ischemic events.

The Relationship between Blood Viscosity and Haematocrit Value

The relationship between blood viscosity and haematocrit is non-linear, such that at higher haematocrit values, a further small increase results in a disproportionately large jump in blood viscosity [8]. This results in rapid increase in the risk of vaso-occlusive events. An early small retrospective study found that the incidence of thrombosis increased linearly in patients with an HCT that was > 45% (range, 46–52%) and recommended to maintain the haematocrit in patients with polycythemia vera <45% in males and <42% in females, largely by using phlebotomy [9,10].

The “Target” Haematocrit in Secondary Smokers’ Polycythemia

The ‘target’ haematocrit in symptomatic secondary smoker’s erythrocythemia is less clear. On theoretical grounds, erythrocytosis in response to tissue hypoxia represents to a certain extent an ‘appropriate’ physiological response and probably beneficial to many patients. The red blood cell mass that are expanded, may compensate for the lack of oxygen delivery and result in tissue oxygenation to its normal level. Therefore, the ideal haematocrit value in cases of smokers’ erythrocythemia is likely to be higher than that in cases of primary polycythemia but still no consensus exists regarding target haematocrit levels in smokers’ erythrocythemia [8]. A prospective clinical trial failed to demonstrate that an increased risk of thrombotic events with haematocrit values up to 55%, leaving the optimal haematocrit target in doubt [11]. Tromsø study stated that elevated HCT was significantly associated with an increased risk of venous thromboembolism in the general population [2].

Symptoms of Secondary Smoker’s Polycythemia

Patients with a high red blood cell mass usually have a plethora or a ruddy complexion. The symptoms are hugely variable and nonspecific. Most patients experiencing no symptoms at all, or may have symptoms resulting from increased blood viscosity

and decreases tissue perfusion in multiple organs. With impaired circulation to the central nervous system, patients may present with decreased mentation (mental sluggishness), fatigue, generalized weakness, ringing in ears (tinnitus), headaches, blurred vision, compromised exercise tolerance, lethargy, burning or “pins and needles” sensation in hands, arms, legs, or feet and confusion or more serious presentations, such as thrombosis, strokes, myocardial infarction, and deep venous thrombosis [12]. These symptoms should resolve with phlebotomy.

Cerebral Thrombosis and Smoker’s Polycythemia

Cerebral Stroke

One of the critical complications of a hyper-viscous state is ischemic stroke. Smoking as a cause of hyperviscosity leading to acute thromboembolic cerebral ischemia is much less well known [13]. Chronic CO exposure is hypothesized to cause cerebral infarction via a combination of increased blood viscosity (due to increased RBC volume and decreased plasma volume), hypoxemia, decrease cerebral blood flow, and local tissue hypoxia, causing vaso-occlusive events. Increased blood viscosity that increases with haematocrit, ultimately placing the patient at risk for local thrombosis and resulting hypoxic-ischemic stroke [8].

Cerebral Venous Thrombosis:

Cerebral sinus thrombosis (CVT), including venous sinus thrombosis and cortical vein thrombosis, is rare but is considered a life-threatening condition [14]. There are various risk factors causing CVT, these include acquired and congenital diseases, one of them is polycythemia [15]. Smoking-associated erythrocythemia can be added to the risk factors for CVT, but there are limited data regarding the actual proportion of patients affected. A review of the literature revealed few cases with initial presentation in smokers.

Acute Coronary Syndrome and Smoker’s Polycythemia

Acute coronary syndrome (ACS) presentations in young adults mostly not related to atherosclerosis and are commonly due to drug use, hypercoagulable states, or vascular abnormalities such as fibromuscular dysplasia. Polycythemia (primary or secondary) can be added to the list of non-atherosclerotic causes for ACS but it is still a rare cause for ACS. Smoker’s erythrocythemia can cause systemic thrombosis and acute arterial thrombotic occlusion, which in turn, provokes acute myocardial infarction. The presence of traditional cardiac risk factors further increases the risk of thrombosis [16].

Smoking Induced Polycythemia is Not Only Cigarette or Cigar Smoking

All over the world, smoking is usually understood as cigarette or cigar smoking. However, water pipe smoking and Electronic cigarette has increasing user rates in many countries [17].

Water-pipe (Shisha or Hookah)- induced Polycythemia

Water-pipe use (also known as Shisha or Hookah) has increased dramatically mostly as a safer option than cigarettes. The water-pipe was intended to reduce the harm of conventional tobacco smoking (since the smoke initially passes through a receptacle

of water), a belief that is still rampant amongst water-pipe users today. However, different studies indicate that water-pipe use is as, or even more, harmful than cigarettes. Water-pipe tobacco has deleterious constituents similar to that found in cigarettes but at greater amounts. These constituents are known to induce oxidative stress and inflammation, the major underlying mechanisms of a wide array of chronic pathological conditions [18]. Water-pipe use generates greater amounts of CO, mainly because of the use of charcoal. The amount of CO inhaled in one session of water-pipe smoking is substantial. Carbon monoxide exhaled after a water-pipe session is estimated to be higher than the amount exhaled after smoking an entire pack of cigarettes [19]. CO is readily absorbed in the lungs and can form a tight but reversible bond with haemoglobin to cause tissue hypoxia. The affinity of CO for haemoglobin and myoglobin is 250 and 40 times greater respectively than for oxygen [20].

Electronic cigarette (E-Cigarette)-Induced Polycythemia

The electronic cigarette (e-cigarette) developed with recent technology and believed to be less hazardous than conventional tobacco. E-cigarettes are battery-operated devices that heat an e-liquid and produce an aerosol that the users inhale, while conventional tobacco produces smoke by burning tobacco leaves [21]. E-cigarettes have been increasingly among smokers who want to stop smoking. They create the simulation of smoking, which can help users to reduce conventional tobacco consumption as they switch from conventional cigarettes to e-cigarettes [22]. However, based on the reported cases, we have doubts about whether e-cigarette use is truly safe or more harmful than has been believed. It is well known that conventional tobacco may cause many kinds of diseases, one of which is polycythemia [1]; but there are few case reports on the relationship between e-cigarettes and polycythemia [23]. As secondary polycythemia might cause critical vaso-occlusive events, it is important to pay attention to e-cigarette smokers’ polycythemia. E-cigarettes might involve some carbon monoxide as in a conventional tobacco dose but till now, it is unclear how e-cigarette use might cause polycythemia.

Therapy in Secondary Smoker’s Polycythemia

Secondary polycythemia doesn’t always require treatment. By reviewing the literatures, there are reasonable management recommendations in symptomatic smoker’s polycythemia (such as cases of cerebral infarction) include volume resuscitation (eg, intravenous fluids) in an attempt to lower hematocrit values and blood viscosity, low-dose aspirin therapy or bloodletting (phlebotomy) and smoking cessation but further investigations are still needed to clarify the optimal management strategy.

Smoking Cessation

Treatment of smoker’s polycythemia is usually directed towards the cessation of smoking. Smoking cessation resulted in a significant decrease in hematocrit and haemoglobin levels [24]. This highlights the importance of smoking cessation as one of the treatment steps for treating different cardiovascular disorders in smoker’s polycythemia. The hope would be that once the patient has stopped smoking, his secondary polycythemia will resolve,

reducing the need for treatment of the secondary polycythemia itself.

Bloodletting

Phlebotomy (Venesection)

Phlebotomy is one of the recommended first-line treatments for patients with polycythemia. Phlebotomy helps to reduce hematocrit (HCT) levels to less than 45%. However, a study evaluating the need for additional phlebotomies in 533 patients with polycythemia vera (PV) showed that a higher intensity of treatment with phlebotomy was related to an increased risk of thrombotic events: patients requiring ≥ 3 phlebotomies per year had a higher risk of thrombosis compared with patients needing ≤ 2 phlebotomies per year (20.5% vs 5.3% at 3 years; $P < .0001$) [25]. However, analysis of the ECLAP and CYTO-PV studies suggested that; there is no correlation between the intensity of the phlebotomy regimen and the risk of thrombosis in patients with PV [26]. Many patients with secondary polycythemia are treated with phlebotomy based on recommendations for PV despite the lack of evidence demonstrating whether or not secondary polycythemia patients share this increased risk. While the pro-thrombotic state in PV has been associated with JAK2 allele burden, leukocytosis, and hypercoagulability, similar changes have not been reflected in secondary polycythemia [27]. Repeated phlebotomies result in an iron deficiency that can cause other symptoms. Therefore, smoking cessation for patients with carboxyhemoglobin in polycythemia is important and proper treatment [28].

Wet Cupping Bloodletting (Hijama)

Hijama means wet cupping in Arab and Muslim culture [29]. The mechanism of Hijama therapy is not clear, but some suggest that placement of cups on selected points on the skin produces hyperemia or hemostasis, which results in a therapeutic effect [30,31]. Wet cupping bloodletting is not like venous bloodletting. In wet cupping bloodletting, the blood is drawn from capillary tubes and some lymph fluid, modifying its concentration and eliminating waste materials [32].

Low-Dose Aspirin

The ECLAP study demonstrated that treatment with aspirin prevented thrombotic complications in patients with PV [26]. Low-dose aspirin reduced the risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, and death from cardiovascular causes (HR, 0.40 [95% CI, 0.18–0.91]; $P = .03$). Consistent with these findings, in the ECLAP study, low-dose aspirin will be associated with a lower risk of cardiovascular events in secondary polycythemia patients whether or not share this increased thrombotic risk.

Strategies to mitigate secondary smoker's polycythemia

Suggested strategies to mitigate the effects of secondary smoker's polycythemia include spreading awareness through social media as regard smoking can induce polycythemia.

Conclusions and Recommendations

Cigarette smoking has been associated with many health

problems, and one of these is polycythemia. Secondary smoker's polycythemia can significantly increase the viscosity of blood and increasing the risk of vaso-occlusive events. Cardiovascular thrombosis is a rare initial presentation of polycythemia but it is important to be diagnosed early because treatment can reduce mortality and morbidity significantly.

To that effect, carefully designed epidemiological studies (young vs old, male vs female, second-hand smoke, concurrent use of other addictive substances) are needed to assess the health risk of polycythemia in smoker across all regions and cultures. Cerebral ischemic stroke in a healthy individual with no or minimal cerebrovascular risk factors should raise suspicion for polycythemia, initiating further hematologic workup. More research focusing on pathological mechanisms and effects of secondary smoker's polycythemia and intervention strategies are needed.

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