



Does untreated obstructive sleep apnea cause secondary erythrocytosis?



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ABSTRACT

Background: The current literature suggests a relationship between obstructive sleep apnea (OSA) severity and hematocrit. However, the degree that OSA contributes to clinically significant erythrocytosis is uncertain. The aim of this study is to evaluate this association in a large study sample controlling for multiple confounders.

Methods: We evaluated consecutive subjects with suspected untreated OSA using multivariate analysis to test the associations between apnea-hypopnea index (AHI) and hematocrit. Subjects were evaluated with sleep studies, comprehensive sleep questionnaires, and detailed electronic medical record reviews to document their medical comorbidities, and demographic and laboratory information.

Results: 1604 consecutive veterans (age 57.6 ± 13.4 years, 92% male) were included in the analysis with 77.4% diagnosed with OSA. However, few included subjects (1.6%) had clinical erythrocytosis. OSA severity defined by AHI was not associated with hematocrit or clinically significant erythrocytosis. Rather, awake oxygen saturation (-0.17 points, $p < 0.001$) and mean nocturnal oxygen saturation (-0.08 points, $p = 0.04$) were inversely proportional to hematocrit (per standardized Z-score). Other factors including active tobacco, increased alcohol ingestion and exogenous testosterone therapy were associated with higher hematocrit. Although AHI was not predictive of erythrocytosis, having severe OSA was predictive of nocturnal hypoxemia (adjusted OR 7.4, $p < 0.001$).

Conclusions: Hematocrit levels and presence of erythrocytosis appear not associated with OSA severity, but rather with hypoxemia as measured by awake and to a lesser extent mean nocturnal oxygen saturation. Nocturnal oximetry may provide diagnostic utility in the evaluation of unexplained secondary polycythemia and polysomnography may be warranted in those with unexplained nocturnal hypoxemia and erythrocytosis.

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1. Introduction

Erythrocytosis is characterized by an absolute increase in red cell mass [1,2] and is classified as primary (e.g. polycythemia vera), or secondary due to circulating erythropoiesis-stimulating factors. A well described etiology for secondary erythrocytosis includes sustained hypoxemia caused by a variety of conditions including chronic obstructive pulmonary disease (COPD) and tobacco use [3–6].

Obstructive sleep apnea (OSA) is a highly prevalent condition associated with decrements in oxyhemoglobin saturation during sleep [7]. Several hematologic guidelines recommend an evaluation for OSA in the work up of secondary erythrocytosis [1,8,9]. However, whether untreated OSA causes clinically significant erythrocytosis is not well established, with many studies reporting no clear relationship between OSA severity and hematocrit [10–14]. The largest study to date ($n = 263$ subjects) reported no relationship between untreated OSA and clinically significant erythrocytosis [15].

This and other studies have generally failed to control for pertinent confounding factors including comorbid respiratory disorders, smoking status, or awake hypoxemia. Thus, the extent that

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Abbreviations list

AHI	Apnea Hypopnea Index
BMI	Body Mass Index
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CHF	Congestive Heart Failure
CPAP	Continuous Positive Airway Pressure
CAD	Coronary Artery Disease
DM	Diabetes Mellitus
OSA	Obstructive Sleep Apnea
SpO ₂	Pulse Oxygen Saturation
WBC	White Blood Cell Count

untreated OSA contributes to clinically significant erythrocytosis remains uncertain. The aim of this study was to delineate the relationship between untreated OSA and erythrocytosis in a large sample taking into account well established confounders.

2. Methods

Consecutive patients aged 21 to 95 referred to the Veterans Affairs Palo Alto Healthcare System's Pulmonary-Sleep Section for suspected OSA who completed formal sleep study testing between February 2010 and July 2014 were retrospectively analyzed. Eligible subjects completed a structured prospectively collected questionnaire detailing medical comorbidity and habits, and had an available hematocrit within 12-months prior to the sleep study or 3-months after (and prior to any OSA therapy). Exclusion criteria included: inadequate sleep study data, supplemental oxygen provided during sleep study testing, a sleep questionnaire/study completed during a period of hospitalization, a diagnosis of polycythemia vera, or prior OSA diagnosis and/or current use of continuous positive airway pressure therapy (CPAP). The study protocol was approved by the Stanford University's institutional review board (protocol ID #22385) and was in accordance of the Declaration of Helsinki.

OSA Assessment. All patients received either an in-lab type-1 polysomnogram or a portable type-3 sleep study consistent with the American Academy of Sleep Medicine's guidelines [16]. Selection of portable versus in-lab testing depended on availability, pretest OSA probability, and consideration of comorbid medical disorders. Portable testing utilized an Embletta X100 (Embla, Broomfield, CO) that includes nasal pressure transducer, thoracoabdominal movement detection, pulse oximeter (SpO₂), single-lead electrocardiogram, actigraphy, and body position. Polysomnography utilized Alice-5 (Respironics, Murrysville, PA), that includes all data channels recorded on the type-3 study with the addition of electroencephalogram, electrooculogram, and electromyogram. Sleep studies were considered adequate if they recorded a minimum of 2-h of high quality data including SpO₂, nasal pressure, and thoracoabdominal movements. Studies with between 2 to 6-h of high quality data were considered adequate but of poorer quality. The apnea-hypopnea index (AHI) was calculated as the number of apneas (>90% reduction in thermistor flow for ≥ 10 s) plus hypopneas ($\geq 30\%$ reduction in nasal pressure amplitude accompanied by a $\geq 4\%$ SpO₂ reduction for ≥ 10 s) per hour [17]. Sleep apnea severity was defined as mild (5–14.9 events/hour), moderate (15–29.9 events/hour), or severe (≥ 30 events/hour).

Medical Record and Questionnaire Review. Included patients

completed a comprehensive sleep questionnaire detailing demographics, medical comorbidities, habits (e.g. tobacco, alcohol, illicit drugs), and medications. Medical comorbidities, medications, habits and demographics were separately abstracted from the electronic medical record (EMR) and compared to responses on the questionnaire. All discrepancies were reconciled by a separate and comprehensive review of the entire EMR. Additionally, the most recent vital signs, diagnostic studies and laboratory testing including chemistry and hematologic data were also abstracted from the EMR.

We defined hypertension as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or having a clinical diagnosis of hypertension and currently prescribed an antihypertensive medication; diabetes mellitus (DM) as an HgA1C $\geq 7.0\%$, or having a diagnosis of diabetes and currently prescribed a glucose lowering agent; chronic kidney disease (CKD) as a creatinine >1.3 mg/dl; and congestive heart failure (CHF) as a left ventricular ejection fraction $<55\%$. A diagnosis of coronary artery disease (CAD) was confirmed by review of prior diagnostic testing, documented myocardial infarction, cardiac intervention, or clinical diagnosis by a cardiologist. A diagnosis of lung disease was confirmed by EMR review by a pulmonologist who considered prior pulmonary function testing, chest radiography, smoking history, and reported clinical respiratory symptoms and documented physical examination findings. Cerebrovascular disease (CVD) was defined as having brain imaging consistent with current/past stroke, documented neurologic deficits, or a clinical diagnosis by a neurologist in the EMR.

Analyses. We performed univariate and multivariate analyses using Statistical Package for the Social Sciences version 22 for Windows (SPSS, Chicago, IL, USA). We define erythrocytosis as a hematocrit $\geq 51\%$ in men and $\geq 48\%$ in women [1,2]. Additionally, we also evaluate predictors of a hematocrit $\geq 48\%$ in all included subjects. We compared categorical variables using a chi-square test and continuous variables with a 2-tailed Wilcoxon-Mann-Whitney test (or Kruskal Wallis test as appropriate). Multivariate linear (dependent variable hematocrit) and logistic (dependent variable hematocrit $\geq 48\%$ vs $<48\%$) regressions were used to evaluate the association between demographics, clinical data, and erythrocytosis. Covariates in these models included well established causes of erythrocytosis as well as factors associated with erythrocytosis identified from our univariate analyses. Model-1 in our stepwise multivariate regression was controlled for age, age², gender, body mass index (BMI), AHI, nocturnal mean SpO₂, awake SpO₂, and included the interaction term AHI*nocturnal-mean-SpO₂. Model-2 was controlled for all Model-1 covariates as well as covariates associated with hematocrit levels (i.e. active malignancy, active tobacco, alcohol use, CKD, CHF, COPD, DM, diuretic use, hepatic dysfunction, supplemental oxygen, testosterone use, and white blood cell count (WBC)). Model-3 was controlled for all Model-1 covariates as well as covariates associated with OSA (i.e. CAD, CHF, CKD, DM, and hypertension). Model-4 was controlled for all covariates in Models 1 through 3. Values are reported as mean \pm standard deviation. For single comparisons, we considered a two-sided *P*-value <0.05 as statistically significant. For multiple group comparisons, we applied a Bonferroni correction.

3. Results

Of 2813 consecutive patients completing adequate sleep evaluations, 800 were excluded for prior OSA diagnosis and/or using CPAP, 264 for having a hematocrit that was drawn greater than 12-months before or 3-months after the sleep study, nine for receiving

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