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The effect of isolated nocturnal oxygen desaturations on serum hs-CRP and IL-6 in patients with chronic obstructive pulmonary disease

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Abstract

Introduction: A majority of patients with chronic obstructive pulmonary disease (COPD) die of cardiovascular disease (CVD), yet the mechanisms responsible for this association are not fully understood. It remains unknown if isolated nocturnal oxygen desaturation (iNOD) could be one of the potential pathways by which the 'inflammatory COPD' phenotype leads to CVD.

Objectives: We aimed to evaluate if COPD patients who meet the Medicare guidelines for nocturnal oxygen therapy (iNOT+) had higher serum hs-CRP and IL-6 than those who did not meet the guidelines for iNOT (iNOT−).

Methods: Patients with moderate to severe COPD (ie FEV1 < 80% and FEV1/FVC < 70), who were not on oxygen, underwent nocturnal oximetry on room air. Serum IL-6 and hs-CRP were collected the morning after the nocturnal oximetry testing.

Results: A total of 28 patients were included in the study, 8 of whom had more than 5 minutes and 5% of their sleep time spent at oxygen saturation less than 88% and constituted the iNOT+ group. Only serum hs-CRP was significantly higher in iNOT+ than iNOT− ($P = 0.050$). There was

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AUTHOR CONTRIBUTIONS

Madalina Macrea designed and performed the research/study; analysed the data; and wrote the paper.
Robert Owens analysed the data and wrote the paper.
Martin Thomas participated in writing the paper.
Dan Smith participated in writing the paper.
Kris Ann Oursler designed the research study; analysed the data; and wrote the paper.
Atul Malhotra was involved in the study design overview and wrote the paper.

CONFLICT OF INTEREST

All authors have stated explicitly that there are no conflicts of interest in connection with this article.

no difference in the rate of COPD exacerbations at one and three months, or five-year survival between the groups ($P > 0.3$).

Conclusion: COPD patients who have more than 5 minutes and 5% of their sleep time spent at oxygen saturation less than 88% have increased hs-CRP, which is associated with increased risk of future CVD.

Keywords

COPD; hs-CRP; nocturnal hypoxia

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is predicted to be the third most common cause of death in the world by the year 2020.[1] A majority of COPD patients die of cardiovascular disease (CVD),[2,3] yet the mechanisms responsible for this association largely remain unknown. The classical clinical parameters that have been studied as predictors of cardiovascular mortality in this population include the severity of airflow limitation as measured by FEV_1, exercise performance, severity of dyspnea and a low body mass index (BMI).[4,5] Although isolated nocturnal oxygen desaturation (iNOD) in this population is a commonly encountered phenomenon,[6–9] its relationship with CVD is uncertain.

There are several mechanisms in COPD that lead to iNOD, with alveolar hypoventilation and worsening ventilation-per-fusion mismatch likely accounting for most of the oxygen desaturations.[10] Given the physiology of the oxyhemoglobin dissociation curve, most COPD patients with resting daytime hypoxemia will have NOD as well.[11] In patients with at-rest daytime oxygen saturation of 88% and less, the benefits of long-term oxygen therapy have been well defined.[12] However, for COPD patients who have isolated nocturnal desaturations without resting daytime hypoxemia, the effects of iNOD on the cardiovascular system and cardiovascular mortality are still unknown. Although the Medicare definition for iNOD is clear (< 88% for > 5 minutes during the night), the paucity of data on negative outcomes may contribute to substantial variation in physicians' interpretation of the overnight oximetry testing and the prescription of supplemental nocturnal oxygen.[13]

Most recently, the 'systemic COPD' phenotype has emerged and is characterized by a high proportion of the COPD patients having CVD and systemic inflammation.[14] The ECLIPSE Investigator Group found that in COPD patients, higher serum high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) levels were associated with three-year all-cause mortality.[15] However, in none of these cohorts were sleep parameters or overnight oximetry investigated, so it remains unknown if iNOD could be one of the potential pathways by which the 'systemic COPD' phenotype leads to extrapulmonary (ie cardiovascular) disease. This question remains un-answered after the recent Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation,[16] as iNOD data were not measured.

Hence, the objective of our study was to investigate the relationship of systemic biomarkers of inflammation and iNOD in COPD patients. We hypothesized that COPD patients who

meet the Medicare guidelines for nocturnal oxygen therapy (iNOT+) would have higher serum hs-CRP and IL-6 than those who did not meet the guidelines for NOT (iNOT−).

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a cohort study of patients with COPD followed at the Salem Veterans Affairs Medical Center (Salem, Virginia) between January 2009 and June 2011. Inclusion criteria included a pulmonary function test showing moderate to severe COPD (i.e. FEV1 < 80% and FEV1/FVC < 70). Exclusion criteria included history of obstructive sleep apnea, oral glucocorticoid use, awake room air oxygen saturation < 88% or any oxygen therapy. All consecutive subjects who met these eligibility criteria and agreed to participate in the study subsequently underwent domiciliary nocturnal oximetry on room air. Demographic and clinical data (including the one-and three-month COPD-related exacerbations and five-year survival status) were extracted from the Electronic Medical Record (EMR). The Charlson Comorbidity Index (CCI)[17] and Framingham (FH) 10-year cardiovascular risk[18] were calculated based on EMR data. Patients who were prescribed NOT after nocturnal pulse oximetry testing were included in the iNOT+ group. The study was approved by the local Institutional Review Board (IRB), and written informed consent was obtained from the patients.

2.2 | Nocturnal and diurnal oximetry

Overnight domiciliary pulse oximetry was carried out on one night using a portable oximeter with a finger probe and an eight-hour memory (Siemens Micro2 plus). Patients were instructed to commence recording on entering bed to sleep and to discontinue recording once fully awake. The following were recorded: mean oxygen saturation; percentage of sleep time spent at an O_2sat < 88%; minutes of sleep time spent at an O_2sat < 88%; and longest sleep time spent at an O_2sat < 88%. Patients with > 5 minutes and 5% of their sleep time with oxygen saturation < 88% were considered iNOT+. Diurnal oximetry data were collected from EMR and included the oxygen saturations recorded during the outpatient visits completed by patients in the 12 months prior and 12 months after their blood collection for hs-CRP and IL-6.

2.3 | Laboratory methods

Morning fasting blood samples were collected for serum IL-6, hs-CRP and lipid profile the morning after the nocturnal oximetry testing. Assays were performed in a single run by the Salem VAMC laboratory.

2.4 | Statistical analysis

Continuous variables were evaluated for normal distribution by the Shapiro-Wilk test. Comparison of continuous data between iNOT groups were performed using *t* tests for data with normal distribution or the Wilcoxon-Mann-Whitney test for data with a skewed distribution. Correlation coefficients between serum hs-CRP and IL-6 and variables depicting patient status were calculated using the Spearman correlations. A two-sided *P* value of ≤0.05 was considered statistically significant.

3 | RESULTS

A total of 28 patients with moderate to severe COPD but without OSA or current oxygen therapy were included in the study. Four patients had incomplete data for hs-CRP and IL-6 and were excluded from further analysis, leading to an analytical set of 24 patients. Patient baseline characteristics including nocturnal oximetry findings are detailed in Table 1. The hs-CRP and IL-6 values by iNOT group are listed in Table 2.

The mean diurnal oxygen saturations recorded during the outpatient visits completed by these patients in the 12 months prior and 12 months after their blood collection for hs-CRP and IL-6 were similar at 95%, with a range between 92% and 99%. Eight patients had more than 5 minutes and 5% of their sleep time spent at oxygen saturation less than 88% and constituted the iNOT+ group. The remaining 16 patients were classified as iNOT-. The daytime oxygen saturations (%, mean ± SD) registered during the 12 months prior and 12 months after the hs-CRP and IL-collection were 95 ± 1, and 91 ± 1, respectively. The lowest oxygen saturation over the 24-month period was 91%. Serum hs-CRP was significantly higher in iNOT+ than iNOT− (Table 2). There was no difference in IL-6 by group. BMI, COPD severity (FEV1) and comorbidity (CCI) severity and smoking were not associated with hs-CRP or IL-6 (P values > 0.07) in univariate analysis.

There was no correlation between serum hs-CRP or IL-6 and several measures of iNOD (mean oxygen saturation, percentage of sleep time spent at an O_2sat < 88% and minutes of sleep time spent at an O_2sat < 88%). There was a significant correlation though (rho = 0.68, P = 0.028) between serum hs-CRP and the longest duration of time spent continuously at less than 88% oxygen saturation (LongO_2sat) when LongO_2sat was more than 1 minute.

There was no difference in the rate of COPD exacerbations at one and three months or the five-year survival between the groups (P > 0.3). At 5 years, only 15 (62%) of the patients were alive. The serum IL-6 levels (mean ± SD pg/mL) were higher in non-survivors than survivors (5.17 ± 3 vs 2.7 ± 3, P = 0.03). There was however a non-significant trend towards a difference between these groups in serum hs-CRP (8.24 ± 6 vs 9.3 ± 15 mg/dL, P = 0.089).

4 | DISCUSSION

To the best of our knowledge, our study is the first to study the effect of iNOD on serum hs-CRP and IL-6 in COPD patients. Our results show that COPD patients who met the Medicare definition for isolated nocturnal oxygen therapy have increased serum levels of hs-CRP compared with those who do not require nocturnal oxygen therapy per Medicare Guidelines criteria despite similarity in baseline pulmonary and cardiac disease, obesity, smoking status and overall comorbidity. Our results, if reproduced in larger studies, may promote a major change in the current clinical practice by providing evidence that iNOD is associated with biomarkers of cardiovascular disease and thus nocturnal oximetry testing in patients with COPD and increased hs-CRP should be included as standard of care. In the meantime, our study might help decrease the existing variation in physicians' prescription of supplemental nocturnal oxygen in this population.

Chronic obstructive pulmonary disease is a major risk factor for atherosclerosis and development of CVD above and beyond the established risk factors of smoking, dyslipidemia or hypertension.[19] The exact mechanisms linking COPD to heart disease are yet to be determined. Sleep pathophysiology presents a plausible link between nocturnal hypoxia, systemic inflammation and the process of atherosclerosis. Hypoxia participates directly in the process of atherosclerosis by various mechanisms, including upregulating cell adhesion molecules[20] and increasing foam cell production and CRP levels.[21,22] CRP is an acute phase protein primarily produced by hepatocytes under the stimulation of IL- 6 and has the ability to initiate or augment the atherosclerotic process through numerous pathways, including upregulating other inflammatory cytokines, activating complement and promoting the uptake of low-density lipoproteins by macrophages.[23] hs-CRP is an ideal serologic marker given its stability over prolonged periods and lack of diurnal variation,[24] and it is a stronger predictor than LDL of future cardiovascular risk.[9]

Levels of serum hs-CRP however are influenced by several commonly encountered clinical factors. Thus, it is important to note that both study groups had a similar degree of overall comorbidity (CCI score), smoking, obesity status, and baseline pulmonary (FEV1) and cardiac disease. Medicare does not cover hs-CRP testing as a screening test for the general population or for monitoring response to therapy. However, it accepts hs-CRP testing for certain categories of patients such as those with two or more CVD major risk factors, including age (men > 50 years; women > 60 years) and current cigarette smoking.[25] Hence, considering this demographic, an overwhelming number of patients with COPD would qualify for serum hs-CRP testing under Medicare and if it is found to be increased lead to consideration for nocturnal oximetry testing.

We classified patients with iNOD based on the Medicare definition of nocturnal oxygen saturation less than 88% for more than 5% and 5 minutes of time. We have found no correlation between certain measures of iNOD such as mean oxygen saturation, percentage of sleep time spent at an O_2sat < 88% and minutes of sleep time spent at an O_2sat < 88%. We did find however a significant correlation (rho = 0.68, $P = 0.028$) between serum hs-CRP and the longest duration of time (LongO_2sat) spent continuously at less than 88% oxygen saturation when LongO_2sat was more than 1 minute. Thus, it is possible that the increase in the hs-CRP levels may be triggered by prolonged (ie more than 1 minute) rather than transient oxygen desaturations. We are also aware that the hs-CRP levels could be increased by numerous other conditions than hypoxia, such as age, obesity, smoking and burden of existent comorbidities. Therefore, we included these risk factors for increased hs-CRP in our analysis and found no statistically significant difference between the iNOT+ and iNOT− groups with respect to age, BMI, smoking status and CCI.

We found that only serum hs-CRP and not IL-6 was elevated in patients with iNOT+. While IL-6 is also a strong predictor of cardiovascular disease, its circadian rhythm with a nadir early morning could have spuriously resulted in lower than expected levels in this population.[26]

Our study has several limitations. First, in the exclusion criteria we assumed that patients were free of sleep disorders based on the lack of such diagnosis on the EMR active problem

list. As such, some of our patients could have had undiagnosed obstructive sleep apnea and hence overlap syndrome (OS). We agree that ideally all our patients would have had diagnostic polysomnography. Future work should focus on this possibility. Second, given the small sample size that included only men, our study needs to be reproduced in a larger and more heterogeneous population. These preliminary data support a larger study, and if the results are confirmed, an intervention trial that includes measures of overnight oximetry is warranted. Finally, because of the focus on nocturnal oximetry, we do not have data regarding the presence of hypercapnia in these subjects.

In summary, our study shows that COPD patients with isolated nocturnal oxygen desaturation (iNOD) based on the definition of oxygen saturation less than 88% for more than 5% and 5 minutes of time have increased hs-CRP, which is associated with increased risk of future cardiovascular disease. If further research demonstrates that hs-CRP and cardiovascular outcomes improve with iNOT, then our results are the first step in changing Medicare Guidelines towards including nocturnal oximetry testing as part of the standard of care in COPD patients with increased hs-CRP.

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TABLE 1

Patients' characteristics

Clinical parameter	**NOT+ (*n* = 8)**	**NOT− (*n* = 16)**	***P* value**
Age (year, mean ± SDs)	68 ± 8	70 ± 8	NS
Body mass index (kg/m^2, mean ± SD)	24.6 ± 5.9	24.6 ± 3.6	NS
Smoking (%)	25%	43%	NS
Lipid profile	98 ± 44	113 ± 0.50	NS
Triglycerides (mg/dl, mean ± SD)			
Comorbidities			
FEV1 (litres, mean ± SD)	1.3 ± 0.4	1.4 ± 0.4	NS
Cardiovascular disease (%)	25%	27%	NS
Congestive heart failure (%)	12%	16%	NS
Hypertension (%)	37%	55%	NS
Diabetes (%)	12%	16%	NS
Charlson comorbidity index (mean ± SD)	2.7 ± 0.9	3.6 ± 1.4	NS
NOD severity (mean ± SD)			
Mean O_2sat (%)	91 ± 0.9	93 ± 1.1	0.0005 *
Percentage of sleep time spent at an O_2sat < 88%	9.5 ± 4.3	0.43 ± 0.71	0.0001 *
Minutes of sleep time spent at an O_2sat <88%	42 ± 11	2.41 ± 3.5	0.0002 *

Abbreviations: FEV1, Forced expiratory volume in 1 second; NOD, nocturnal oxygen desaturation; NOT, nocturnal oxygen therapy group; O_2sat, oxygen saturation; SD, standard deviation;

*: statistically significant.

TABLE 2

Serum inflammatory markers

Serum inflammatory marker	NOT+ (mean ± SD)	NOT− (mean ± SD)	*P* value
hs-CRP (mg/L)	13.4 ± 15.2	6.6 ± 11	0.050 *
IL-6 (pg/ml)	4 ± 3.2	3.2 ± 3.4	NS

Abbreviations: hs-CRP: high sensitivity C-Reactive Protein; IL-6: interleukin 6;

*: statistically significant.