CHEST

Exertional Hypoxemia in Stable COPD Is Common and Predicted by Circulating Proadrenomedullin

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BACKGROUND: The prevalence of exertional hypoxemia in unselected patients with COPD is unknown. Intermittent hypoxia leads to adrenomedullin (ADM) upregulation through the hypoxia-inducible factor-1 pathway. We aimed to assess the prevalence and the annual probability to develop exertional hypoxemia in stable COPD. We also hypothesized that increased ADM might be associated with exertional hypoxemia and envisioned that adding ADM to clinical variables might improve its prediction in COPD.

METHODS: A total of 1,233 6-min walk tests and circulating proadrenomedullin (proADM) levels from 574 patients with clinically stable, moderate to very severe COPD enrolled in a multinational cohort study and followed up for 2 years were concomitantly analyzed.

RESULTS: The prevalence of exertional hypoxemia was 29.1%. In a matrix derived from a fitted-multistate model, the annual probability to develop exertional hypoxemia was 21.6%. Exertional hypoxemia was associated with greater deterioration of specific domains of health-related quality of life, higher severe exacerbation, and death annual rates. In the logistic linear and conditional Cox regression multivariable analyses, both FEV_1% predicted and proADM proved independent predictors of exertional hypoxemia ($P < .001$ for both). Adjustment for comorbidities, including cardiovascular disorders, and exacerbation rate did not influence results. Relative to using FEV_1% predicted alone, adding proADM resulted in a significant improvement of the predictive properties ($P = .018$). Based on the suggested nonlinear nomogram, patients with moderate COPD (FEV_1% predicted = 50%) but high proADM levels (> 2 nmol/L) presented increased risk (> 30%) for exertional desaturation.

CONCLUSIONS: Exertional desaturation is common and associated with poorer clinical outcomes in COPD. ADM improves prediction of exertional desaturation as compared with the use of FEV_1% predicted alone.

TRIAL REGISTRY: ISRCTN Register; No.: ISRCTN99586989; URL: www.controlled-trials.com

CHEST 2014; 146(2):328-338

Manuscript received August 21, 2013; revision accepted February 10, 2014; originally published Online First April 10, 2014.

ABBREVIATIONS: 6MWD = 6-min walk distance; 6MWT = 6-min walk test; ADM = adrenomedullin; BODE = BMI, airway obstruction, dyspnea, and exercise capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; proADM = proadrenomedullin; PROMISE-COPD = Predicting Outcome Using Systemic Markers in Severe Exacerbations of COPD; QoL = quality of life; Sao_2 = peripheral oxygen saturation; SF-36 = Short-Form 36; SGRQ = St. George's Respiratory Questionnaire

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Exertional hypoxemia portends a poor prognosis for patients with COPD.[1,2] Hypoxemia is associated with the development of pulmonary hypertension,[3] systemic inflammation,[4] and skeletal muscle[5] and neurocognitive dysfunction.[6] Supplemental oxygen appears to enhance exercise performance,[7] decrease the level of dyspnea,[8] improve health-related quality of life (QoL),[9] and sustain cerebral function[10] during activity in individuals with COPD who are normoxemic at rest but who desaturate with exertion. Indeed, because of the great heterogeneity of the population with COPD, ventilation and blood gas parameters vary with time and activity, and, in fact, values obtained during exercise may be most revealing of the need for long-term oxygen therapy.[11]

The prevalence of exertional hypoxemia in patients with COPD is unknown.[12] Differences in the definition of desaturation, mode of exercise, and characteristics of the patient population make it difficult to compare previous studies and apply them to clinical practice. The form of exertion may also affect the detection of exercise-induced desaturation in individuals with COPD.[13] These difficulties have driven multiple attempts to correlate various clinical tests with exertional desaturation.[14-18]

Plasma proadrenomedullin (proADM) is the stable, biologically inactive mid-regional fragment of the adrenomedullin (ADM) prohormone and, as such, a surrogate for the mature protein.[19,20] Intermittent hypoxia leads to ADM upregulation through the hypoxia-inducible factor-1 pathway, which interacts with nuclear factor-κB to promote the expression of inflammatory genes.[21-24] There is mounting evidence suggesting that systemic inflammation correlates with clinical outcomes in COPD.[25] Accordingly, ADM was associated with all-cause mortality in patients with stable and exacerbated COPD.[26,27] This observation led us to hypothesize that proADM might be associated with exertional hypoxemia in COPD. Additionally, we envisioned that adding proADM to clinical variables might improve exertional hypoxemia prediction compared with use of the latter alone.

The primary aim of the present analysis was to evaluate the prevalence and the annual risk to develop exertional hypoxemia during the 6-min walk test (6MWT) among clinically stable patients with COPD in a large, multinational, multicenter, prospective, longitudinal, observational cohort. We also describe the accuracy of a concomitant estimation of the circulating ADM alone or in combination with clinical variables to predict exertional hypoxemia.

Materials and Methods

Study Design and Ethics

Conducted in 11 centers in eight European countries, the Predicting Outcome Using Systemic Markers in Severe Exacerbations of COPD (PROMISE-COPD) study evaluated variables potentially identifying poor outcomes in patients with moderate to very severe COPD. Such disease was defined as postbronchodilator $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted (ie, GOLD [Global Initiative for Chronic Obstructive Lung Disease] grade II-IV airway obstruction); COPD exacerbation was defined as an acute change from baseline in one or more of dyspnea, cough, and sputum, beyond normal day-to-day variation and possibly warranting medication change.

The study and its analyses were designed and conducted to take an inclusive, exploratory, hypothesis-generating approach. Enrollees had an initial baseline examination and then were followed for at least 2 years in scheduled semiannual visits. Additionally, as necessary, patients made outpatient visits or were hospitalized for treatment of acute exacerbation of COPD, and follow-up visits were specified for 4 weeks after exacerbation onset. Patients were treated as clinically warranted, without restriction, throughout the study period.

PROMISE-COPD, an investigator-initiated and -driven study, complied with the Helsinki Declaration and Good Clinical Practice Guidelines, was approved by the participating centers' ethics committees (EKBB 295/07), and was registered at www.controlled-trials.com under the identifier ISRCTN99586989. Patients provided prior written informed consent for all study assessments.

Patients

Six hundred thirty-eight patients with COPD were consecutively recruited and followed at pulmonary departments of primary to tertiary care hospitals between November 2008 and October 2011. Patients had to meet the following inclusion criteria: (1) at baseline, clinically stable moderate to very severe COPD based on anamnesis, physical examination, and spirometry performed ≥ 4 weeks after resolution of the latest exacerbation; (2) age ≥ 40 years; (3) smoking history ≥ 10 pack-years. Exclusion criteria were: (1) a non-COPD condition (eg, bronchiectasis, asthma, or pulmonary fibrosis) as the main respiratory disease; (2) rapid

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FUNDING/SUPPORT: PROMISE-COPD was an investigator-initiated study primarily funded by the Clinic of Pulmonary Medicine and Respiratory Cell Research of the University Hospital Basel, Switzerland and by the Swiss National Foundation [Grant PP00-P3_128412/1]. Thermo Scientific Biomarkers (formerly BRAHMS AG), Hennigsdorf, Germany, provided all reagents for those analyses gratis and, through an unrestricted research grant, funded all costs of transporting blood samples to the central biomarker testing facility at University Hospital Basel.

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DOI: 10.1378/chest.13-1967