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Increased alveolar nitric oxide concentration is related to nocturnal oxygen desaturation in obstructive sleep apnoea

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ABSTRACT

Purpose: To assess distal/alveolar inflammation in patients with suggestive symptoms of obstructive sleep apnoea (OSA) using exhaled nitric oxide (NO) measured by two-compartment model (2-CM) after correction for axial NO back-diffusion (trumpet model).
Methods: Ninety five patients suspected for OSA prospectively underwent pulmonary function test, overnight polysomnography (PSG), and exhaled NO measurement. Patients with apnoea–hypopnoea index (AHI) < 5/hour were included in non-OSA group. Exhaled NO was repeatedly measured after PSG in 21 OSA patients and 8 non-OSA subjects.
Results: Alveolar NO concentration (C_{ANO}) was significantly higher in OSA patients (n = 71; 4.07 ± 1.7ppb) as compared with non-OSA subjects (n = 24; 2.24 ± 1.06ppb; p < 0.0001) whilst maximal bronchial NO flux (J'_{awNO}) and fractional exhaled NO (F_{ENO}) did not differ between the two groups. C_{ANO} was strongly associated to AHI (r = 0.701; p < 0.0001) and to recording time with SaO_2 < 90% (ST-90%; r = 0.659; p < 0.0001) in OSA patients but not in non-OSA persons. The area under ROC curve for screening patients with OSA and significant nocturnal oxygen desaturation (ST-90% > 1%) was 0.865 ± 0.036 (95% IC, 0.793–0.937; p < 0.0001). C_{ANO} at 4.5 ppb could detect these patients with specificity of 94% and sensitivity of 46%. Increase of C_{ANO} measured after PSG was significantly related to oxygen desaturation index (ST-90%) in OSA patients.
Conclusions: Increased alveolar NO concentration was related to the severity of nocturnal oxygen desaturation in patients with OSA, linking the distal airway inflammation to intermittent hypoxia. (250 words)

1. Introduction

Obstructive sleep apnoea (OSA) is an independent risk factor for cardiovascular morbidity and mortality [1], due to increased production of reactive oxygen species and pro-inflammatory cytokines, resulting from chronic intermittent hypoxia–reoxygenation [2]. Oxidative stress and inflammation cause endothelial dysfunction leading to cardiovascular diseases [3]. Thus, evaluation of pulmonary inflammation might be useful to screen for OSA and to predict its severity.

Nitric oxide (NO) plays an important role both as a physiological modulator of vascular tone and as a pathological pro-inflammatory biomarker implicated in many lung disorders [4]. NO can be easily measured in the exhaled air, and there are theoretical grounds to hypothesise that concentration of exhaled NO (F_{ENO}) may change in the two principal pathological processes observed in OSA: pulmonary inflammation and endothelial dysfunction. Increased exhaled NO reflects lung inflammation by over-expression of the inducible NO synthase (NOS) as observed in asthma and systemic sclerosis (SSc) [5,6], whilst reduced exhaled NO levels can be found in cardiovascular disorders associated with endothelial dysfunction such as pulmonary hypertension [7] and chronic heart failure [8], due to decreased endothelial NOS expression and activity.

In patients with OSA, lung inflammation and vascular injuries usually co-exist with, however, different degrees of severity. F_{ENO}, which reflects NO production from the large airways, has been found either

Abbreviations: 2-CM, two-compartment model; AHI, apnoea–hypopnoea index; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; C_{ANO}, alveolar nitric oxide concentration; F_{ENO}, fractional exhaled nitric oxide; J'_{awNO}, maximal bronchial nitric oxide flux; NOD, nocturnal oxygen desaturation; OSA, obstructive sleep apnoea; PSG, polysomnography; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity; ST-90%, percentage of recording time with SaO_2 < 90% on total sleep time.

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unchanged [9] or increased [10–17] in patients with OSA. F_{ENO} is however a poor marker of NO production in the distal parts of the lungs, i.e. small airways and alveolar spaces. The two-compartment model (2-CM) allows quantification of maximal bronchial NO flux (J'_{awNO}) and steady-state alveolar NO concentration (C_{ANO}) [18]. Using this simplified model, two studies reported a decrease of C_{ANO} in patients with OSA [10,15] suggesting endothelial dysfunction that might be linked to systemic hypertension [10]. We hypothesised that in patients with advanced OSA and vascular diseases, distal/alveolar NO production might decrease [10,15] but in patients with moderate OSA and associated lung inflammation, C_{ANO} might increase as observed in patients with systemic sclerosis [6].

It is recently suggested that taking into account NO axial back-diffusion, related to the trumpet shape of the cross-sectional area of the tracheal tree [18], can better characterise the proximal and distal exhaled NO origins in healthy subjects [19] and SSc patients [20].

In this prospective study, we aimed to assess the distal/alveolar inflammation in patients with suggestive symptoms of OSA, using this novel approach. We also studied the variation of exhaled NO after overnight PSG recording in OSA and non-OSA patients to see whether this variation was associated with sleep apnoea parameters.

2. Methods

2.1. Study population

All subjects (≥18 years-old) were recruited from our Sleep Research Unit, Department of Physiology, Cochin Hospital, Paris, France. They were consecutively referred for OSA diagnosis with suggestive symptoms (American Association of Sleep Medicine, AASM criteria) during a period of 2 years, from January 1, 2009 to December 31, 2010 [21]. The study was approved by the Ethics Committee of our institution and informed consents were obtained from all participants.

We excluded patients with advanced cardiovascular diseases or respiratory disorders, current smokers, patients with upper or lower respiratory infections, and those receiving oral corticosteroids within the last 4 weeks since these factors could modify exhaled NO.

All patients underwent thorough physical examination with medical history and pulmonary function tests before inclusion. On the examination day, exhaled NO was measured in the afternoon, then patients were submitted to overnight in-laboratory polysomnography (PSG). On the next morning, exhaled NO was re-evaluated in 21 patients with OSA (defined as AHI ≥5/hour) and 8 patients without OSA. We included 30 healthy non-smokers (mainly from our medical staff and students) having exhaled NO measurement as controls.

2.2. Lung function measurement

Pulmonary function tests (PFT), assessing forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and total lung capacity (TLC) (MasterScreen® Body; VIASYS Healthcare GmbH, Hoechberg, Germany), were performed according to the international recommendations [22]. Blood gas analysis was done on the same day.

2.3. Exhaled NO measurement

Exhaled NO was measured using a chemiluminescent NO analyser (EndoNO 8000®; SERES, Aix-en-Provence, France), according to ATS/ERS recommendations [23]. NO analyser was calibrated daily with a standard NO source (100 ppb, Air Liquid, Paris, France). Exhaled NO measurement was strictly performed in all subjects during the medical visit preceding the PSG recordings, as previously described [20,24]. Patients who cannot perform a regular exhalation of more than 8 seconds to obtain a steady-state alveolar NO concentration during 3 seconds were excluded from the study [24].

Correction of J'_{awNO} and C_{ANO} using the trumpet (TP) model to take into account axial NO back-diffusion was then applied for all measurements [19]. We used the linear relationship to express the variation of V'_{NO} (pl/s: picolitre/second) as a function of V'_E (ranging from 100 to 250 ml/s):

$$V'_{NO} = \left(C_{ANO(TP)} + J'_{awNO(TP)} \cdot 0.00078\right) \cdot V'_E + J'_{awNO(TP)} / 1.7$$

The slope of this linear relationship S and the intercept I was obtained by plotting the V'_{NO} against V'_E, allowing the calculation of $C_{ANO(TP)}$ and $J'_{awNO(TP)}$ from the $C_{ANO(2CM)}$ and $J'_{awNO(2CM)}$ as previously described [18,20].

2.4. Polysomnography

All patients underwent overnight polysomnography (PSG) using a Medcare data-acquisition system (Rembrandt Analysis Manager, Buffalo, NY, USA) with standard electrodes and sensors according to AASM recommendations [25]. Briefly, electroencephalography electrodes applied at A2-C4, C4-C3, C3-A1, and C3-O1, two electro-oculography, submental and anterior tibial electromyography channels were recorded. For respiratory parameters, thoracic and abdominal movements by inductance plethysmography, thermistors and nasal pressure cannulas were used simultaneously. Arterial oxygen saturation (SaO_2) was measured using pulse oximeter. To establish sleep stages, recorded nocturnal PSG were visually scored on the basis of 30-second epochs, using Rechtschaffen and Kales criteria, by two independent medical doctors with more than 10 year-experience in sleep medicine [26]. Apnoea was defined as a complete cessation of oro-nasal airflow ≥10 seconds. Hypopnoea was defined as an important reduction in airflow (≥50%) for ≥10 seconds or moderate reduction (<50%) associated with EEG arousals and/or oxygen desaturation (SaO_2 decrease ≥3%). The apnoea–hypopnoea index (AHI) was defined as the addition of apnoea episodes and hypopnoea episodes per hour during sleep. Patients with OSA (AHI ≥5) were divided into mild-to-moderate group (5 ≤ AHI <30) and severe one (AHI ≥30) [26]. Subjects with AHI <5 constituted the non-OSA group. For the nocturnal oxygen desaturation (NOD), we recorded the mean SaO_2, nadir SaO_2 and the percentage of recording time with SaO_2 <90% on total sleep time (ST-90%). Patients with significant NOD were defined as ST-90% of more than 1% [27].

2.5. Statistical analysis

Data were analysed using SPSS 16.0 (Chicago, IL, USA). Values were expressed as mean ± standard derivation (SD) for continuous parameters, number and percentage for categorical variables. Normal distribution was determined using Kolmogorov–Smirnov test. Comparisons were made by Student's *t*-test or Mann–Whitney test for quantitative variables and Chi-square test or Fisher's exact test for qualitative variables, as appropriate. Exhaled NO levels before and after PSG were compared using Wilcoxon matched-pairs rank test. Linear correlations between C_{ANO} with AHI and ST-90% were done using Spearman's method. A multivariate linear regression was used to examine the association of AHI with C_{ANO} and BMI. Statistical significance was two-sided at $p < 0.05$.

Diagnostic performance of C_{ANO} for detecting patients with OSA (AHI ≥5/hour) and significant NOD (ST-90% > 1%) was done by the ROC curve. Overall discriminatory ability of ROC curve was determined by the area under ROC curve (mean ± SD; [95% CI]).