Higher alveolar nitric oxide in COPD is related to poorer physical capacity and lower oxygen saturation after physical testing

To the Editor:

Exhaled nitric oxide (F_{ENO}) is an inflammatory marker used in asthma management but its clinical role in chronic obstructive pulmonary disease (COPD) is less defined. F_{ENO} represents the NO production in the airways. Various mathematical models have been used to gain information regarding peripheral NO from the lung [1]. NO from the gas exchange area is referred to as alveolar NO (C_{ANO}). C_{ANO} has been shown to be increased in symptomatic asthmatic subjects [2]; whereas in COPD, there is an alveolar destruction with emphysema and higher values of C_{ANO} have been reported [3–5]. However, in subjects with severe emphysema, there was no increase in C_{ANO} and, therefore, the clinical value of C_{ANO} is not clear [6]. C_{ANO} has been found to correlate negatively to the distance travelled in 6-min walking tests [5]. It is of interest that in athletes, hypoxaemia develops due to prolonged exercise [7] and in marathon runners who are regularly exposed to hypoxaemia during strenuous training, C_{ANO} values have been reported to be increased [8]. COPD patients frequently report dyspnoea with exertion, and our hypothesis was that repeated hypoxaemia could lead to an increase in C_{ANO}. We therefore investigated C_{ANO} in a Swedish study [9].

The study design and the methods used were previously described by Högman *et al.* [9]. In short, patients in a stable condition who had been previously diagnosed by a physician as having COPD were recruited. The COPD diagnosis was confirmed at the study visit by a post-bronchodilator spirometry (SpiroPerfect spirometer; Welch Allyn, Skaneateles Falls, NY, USA). F_{ENO} at exhalation flows of 20, 100 and 300 mL·s^{-1} were measured in duplicate for the nonlinear modelling of NO exchange [1], which was in addition to 50 mL·s^{-1} ($F_{ENO_{50}}$). The Eco Medics CLD 88 (Eco Medics, Duernten, Switzerland) NO analyser was used with the Högman-Meriläinen algorithm software. Resting oxygen saturation measured by pulse oximetry (S_{pO_2}) and $F_{ENO_{50}}$ measurements were performed before any other tests. The physical tests, performed in random order, were the 30-m walking distance at maximal speed (30WT) and the 30-s chair-stand test (CST) [10, 11]. S_{pO_2} was measured with the WristOx2 Model 3150 (Nonin Medical BV, Amsterdam, the Netherlands). S_{pO_2} analyses were made using the resting value before and the mean value after the two physical tests. Grouping variables were used for S_{pO_2} with the 25th percentile of 91%, CST with the 25th percentile of 10 repetitions and 30WT with the 75th percentile of ⩾20 s walking time. Nonparametric tests, *i.e.* Mann–Whitney U-test and Spearman's ρ (SPSS version 24 for Windows; SPSS Inc., Chicago, IL, USA), were used for all statistical calculations. A p-value <0.05 was considered significant. Data are presented as median (interquartile range) with the exception of age and lung function (which are presented as mean±SD).

In total, 170 COPD subjects (61% female), aged 68±8 years, had $F_{ENO_{50}}$ levels of 13 (8–19) ppb and C_{ANO} levels of 1.4 (0.7–2.3) ppb. Lung function measurements were: forced expiratory volume in 1 s (FEV_1) 54 ±16% predicted and forced vital capacity (FVC) 67±16% predicted. In smokers (n=48), $F_{ENO_{50}}$ was significantly lower 8 (5–14) ppb than in ex-smokers 15 (11–22) ppb (p<0.001) but for C_{ANO}, no difference was found (1.3 (0.7–2.1) and 1.4 (0.7–2.4) ppb, respectively; p=0.46). This was also the case for S_{pO_2}

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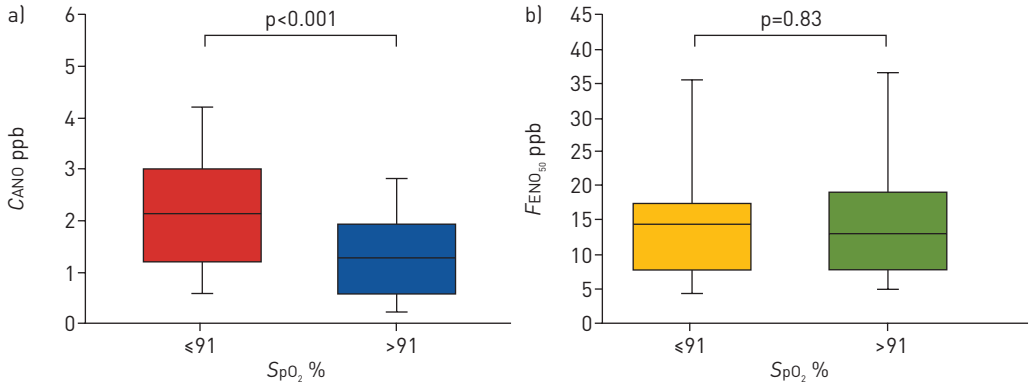

FIGURE 1 a) Alveolar nitric oxide content (C_{ANO}) was statistically significantly higher in the group with oxygen saturation measured by pulse oximetry (S_{pO_2}) ⩽91% b) while no difference was found in exhaled nitric oxide fraction measured at 50 mL·s^{-1} ($F_{ENO_{50}}$). In the boxplots, the horizontal line in each box corresponds to the median value, the upper and lower margins correspond to the 25th and 75th percentiles, and the whiskers correspond to the 10th and 90th percentiles.

(p=0.46). Therefore, subjects were not stratified by smoking status in the remaining analyses. The 30WT was 18 (16–21) s and the CST had 12 (10–14) repetitions. S_{pO_2} was significantly lower after physical testing compared to the resting value (93% (91–94%) and 95% (93–96%), respectively; p<0.001). Significant correlations were found between C_{ANO} and S_{pO_2} (ρ=−0.29, p<0.001), the difference in S_{pO_2} pre- and post-physical testing (ρ=0.25, p=0.001), age (ρ=0.19, p=0.012), 30WT (ρ=0.17, p=0.03) and CTS (ρ=−0.16, p=0.044) but not to blood eosinophil levels. $F_{ENO_{50}}$ was correlated to lung function, FEV1 % predicted (ρ=0.16, p=0.044), FVC % predicted (ρ=0.16, p=0.034) and blood eosinophil levels (ρ=0.24, p=0.002).

When stratifying subjects into S_{pO_2} ⩽91% (n=47) or >91% (n=123), there was a difference in C_{ANO} (p<0.001) but not in $F_{ENO_{50}}$ (p=0.83) (figure 1). Subjects with S_{pO_2} ⩽91% had fewer repetitions in the CST (10 (9–12) and 13 (11–15), respectively; p=0.001) and longer times for the 30WT (19 (18–23) and 17 (16–20) s, respectively; p<0.001).

This study has found that C_{ANO}, but not F_{ENO}, is increased in subjects with low S_{pO_2} after physical testing. Subjects with a low S_{pO_2} performed worse in the physical tests. Unlike F_{ENO}, C_{ANO} is not affected by smoking. Subjects who had S_{pO_2} ⩽91% had a higher C_{ANO}; this could suggest that in COPD subjects, there is a potential for the lung to adapt to dyspnoea. We did not perform arterial oxygen saturation analysis but it has been shown that S_{pO_2} accurately reflects arterial oxygen saturation with exercise. Further research is needed to explore the reason for the increase in C_{ANO} in COPD subjects. Longitudinal studies of C_{ANO} in COPD subjects are needed to understand whether C_{ANO} has the potential to be a prognostic biomarker of pulmonary performance.

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