EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

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

M. Högman, A. Thornadtsson, K. Bröms, C. Janson, K. Lisspers, B. Ställberg, H. Hedenström, A. Malinovschi

Please cite this article as: Högman M, Thornadtsson A, Bröms K, *et al*. Higher alveolar nitric oxide in COPD is related to poorer physical capacity and lower oxygen saturation after physical testing. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00263-2019).

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

M Högman[1], A Thornadtsson[1, 2], K Bröms[2,3], C Janson[1], K Lisspers[3,4], B Ställberg[3,4], H Hedenström[5], A Malinovschi[5]

Affiliations: [1]Dept. of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden,

[2]Center for Research & Development, Uppsala University/Region Gävleborg, Gävle, Sweden

[3]Dept. of Public Health and Caring Sciences, Family Medicine and Preventive Medicine, Uppsala University, Uppsala, Sweden

[4]Center for Clinical Research, Uppsala University, County Council Dalarna, Falun, Sweden

[5]Dept. of Medical Sciences, Clinical Physiology, Uppsala University, Uppsala, Sweden

Correspondence: Marieann Högman, Dept. Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, University Hospital, S 751 85 Uppsala, Sweden

E-post: marieann.hogman@medsci.uu.se

Take home message

Nitric oxide from the gas exchange area, but not from the airways, is increased in subjects with chronic obstructive pulmonary disease with low 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. To gain information regarding peripheral NO from the lung, different mathematical models have been used [1]. NO from the gas-exchange area is referred to as alveolar NO (C_ANO). In symptomatic asthmatic subjects the C_ANO has been shown to be increased [2]. 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 negatively correlate to the distance travelled in 6-minute walking tests [5]. Of interest, is that in athletes hypoxemia develops due to prolonged exercise [7], and in marathon runners who are regularly exposed to hypoxemia 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 hypoxemia 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 are described in Högman *et al.* 2018 [9]. In short, patients in stable condition who had been previously diagnosed by physician with 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 non-linear 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 SpO_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 second Chair-stand- test (CST) [10, 11]. Peripheral oxygen saturation (SpO_2) was measured with the WristOx2® Model 3150 (Nonin Medical B.V., Amsterdam, Netherlands). SpO_2 analyses were made using the resting value before and the mean value after the two physical tests. Grouping variables were used for SpO_2 with the 25^{th} percentile of 91%, CST with the 25^{th} percentile of 10 repetitions, and 30WT with the 75^{th} percentile of 20 seconds or more walking time. Non-parametric tests, i.e. Mann-Whitney U test and Spearman´s rho (SPSS, v. 24 for Windows, SPSS Inc., Chicago, MI, USA) were used for all statistical calculations. A p-value of $p<0.05$ was considered significant. Data are given in median (25^{th}, 75^{th} percentile) with the exception of age and lung function (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: FEV_1-% predicted 54 ± 16, and FVC-% predicted 67 ± 16. In smokers (n=48) F_ENO_{50} was significantly lower 8 (5, 14) ppb compared to 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 SpO_2, p=0.46. Therefore, subjects were not divided by smoking status in the remaining analyses. The 30WT was 18 (16, 21) seconds and the CST had 12 (10, 14) repetitions. SpO_2 was significantly lower after physical testing compared to the resting value, 93 (91, 94) and 95 (93, 96) percent, respectively, p<0.001. Significant correlations were found between C_ANO and SpO_2 (rho=-0.29, p<0.001), the difference in SpO_2pre-SpO_2post (rho=0.25, p=0.001), age (rho=0.19, p=0.012), 30WT (rho=0.17, p=0.03) and CTS (rho=-0.16, p=0.044) but not to blood eosinophil levels. F_ENO_{50} was correlated to lung function, FEV_1 % predicted (rho=0.16, p=0.044), FVC % predicted (rho=0.16, p=0.034) and blood eosinophil levels (rho=0.24, p=0.002).
When stratifying subjects into SpO_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 SpO_2 ≤91% had fewer repetitions in the CST 10 (9, 12) and 13 (11, 15), respectively, p=0.001, and a longer time for the 30WT 19 (18, 23) and 17 (16, 20) seconds, respectively, p<0.001.

Place Figure 1 here

This study has found that C_ANO, but not F_ENO, is increased in subjects with low SpO_2 after physical testing. Subjects with a low SpO_2 did worse in the physical tests. Unlike F_ENO, C_ANO is not affected by smoking. Subjects who had a SpO_2 value of ≤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 O_2 saturation analysis, but it has been shown that SpO_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 if C_ANO has a potential to be a prognostic biomarker of pulmonary performance.

References

1. Horvath I, Barnes PJ, Loukides S, Sterk PJ, Högman M, Olin AC, Amann A, Antus B, Baraldi E, Bikov A, Boots AW, Bos LD, Brinkman P, Bucca C, Carpagnano GE, Corradi M, Cristescu S, de Jongste JC, Dinh-Xuan AT, Dompeling E, Fens N, Fowler S, Hohlfeld JM, Holz O, Jobsis Q, Van De Kant K, Knobel HH, Kostikas K, Lehtimaki L, Lundberg J, Montuschi P, Van Muylem A, Pennazza G, Reinhold P, Ricciardolo FLM, Rosias P, Santonico M, van der Schee MP, van Schooten FJ, Spanevello A, Tonia T, Vink TJ. A European Respiratory Society technical standard: exhaled biomarkers in lung disease. The European respiratory journal. 2017;49(4).

2. Lehtimäki L, Kankaanranta H, Saarelainen S, Hahtola P, Järvenpää R, Koivula T, Turjanmaa V, Moilanen E. Extended exhaled NO measurement differentiates between alveolar and

bronchial inflammation. American journal of respiratory and critical care medicine. 2001;163:1557-61.

3. Brindicci C, Ito K, Resta O, Pride NB, Barnes PJ, Kharitonov SA. Exhaled nitric oxide from lung periphery is increased in COPD. EurRespirJ. 2005;26(1):52-9.

4. Williamson PA, Clearie K, Menzies D, Vaidyanathan S, Lipworth BJ. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. Lung. 2011;189(2):121-9.

5. McCurdy MR, Sharafkhaneh A, Abdel-Monem H, Rojo J, Tittel FK. Exhaled nitric oxide parameters and functional capacity in chronic obstructive pulmonary disease. J BreathRes. 2011;5(1):016003.

6. Bazeghi N, Gerds TA, Budtz-Jorgensen E, Hove J, Vestbo J. Exhaled nitric oxide measure using multiple flows in clinically relevant subgroups of COPD. Respiratory medicine. 2011;105(9):1338-44.

7. Hopkins SR, Gavin TP, Siafakas NM, Haseler LJ, Olfert IM, Wagner H, Wagner PD. Effect of prolonged, heavy exercise on pulmonary gas exchange in athletes. Journal of applied physiology. 1998;85(4):1523-32.

8. Thornadtsson A, Drca N, Ricciardolo F, Högman M. Increased levels of alveolar and airway exhaled nitric oxide in runners. Upsala journal of medical sciences. 2017;122(2):85-91.

9. Högman M, Sulku J, Ställberg B, Janson C, Bröms K, Hedenström H, Lisspers K, Malinovschi A. 2017 Global Initiative for Chronic Obstructive Lung Disease reclassifies half of COPD subjects to lower risk group. Int J Chron Obstruct Pulmon Dis. 2018;13:165-73.

10. Andersson M, Moberg L, Svantesson U, Sundbom A, Johansson H, Emtner M. Measuring walking speed in COPD: test-retest reliability of the 30-metre walk test and comparison with the 6-minute walk test. Prim Care Respir J. 2011;20(4):434-40.

11. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 1999;70(2):113-9.

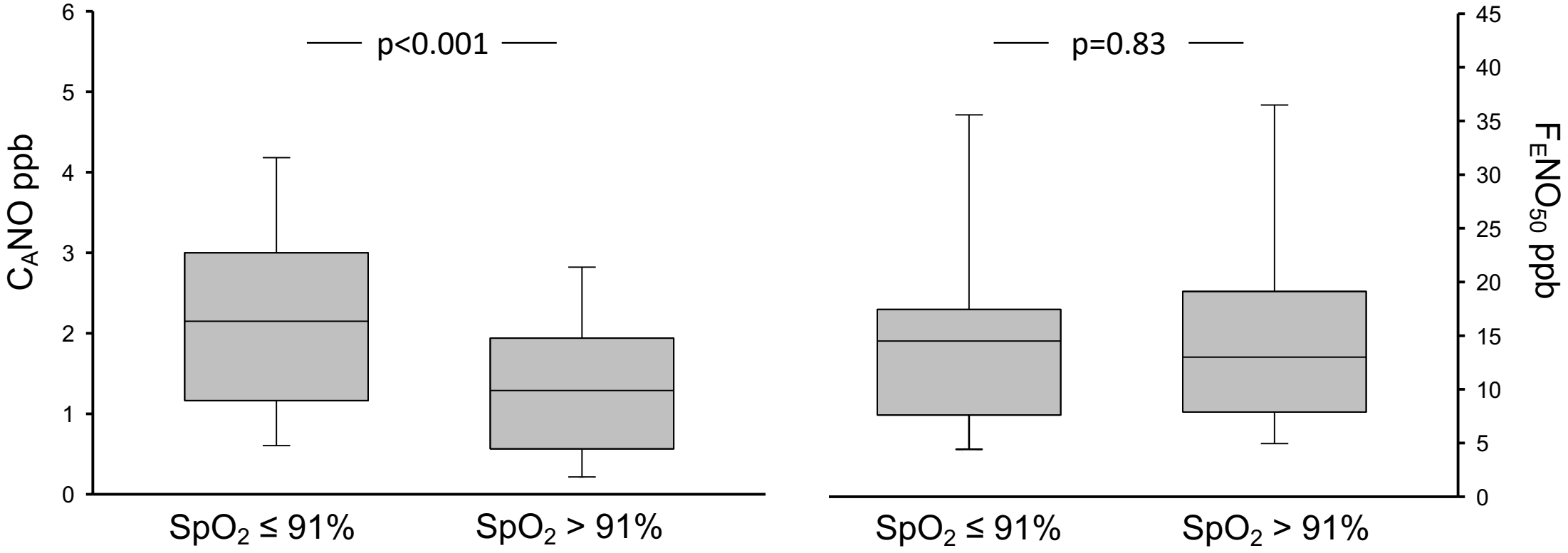

Figure 1. C_ANO was significantly higher statistically in the group with SpO_2 ≤91 %, while no difference was found in F_ENO_{50}.
In the boxplots the horizontal line in each box corresponds to the median value, the upper and lower margins correspond to the 25th and 75th percentiles, the whiskers correspond to the 10th and 90th percentiles.