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Exhaled nitric oxide is not increased in pulmonary sarcoidosis

Paolo Cameli, Elena Bargagli, Paola Rottoli
Department of Medical and Surgical Sciences and Neurosciences, Respiratory Disease and Lung Transplantation Section, Le Scotte Hospital, Siena, Italy

Abstract. *Background:* Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker of airway inflammation and nitrosative stress. Previous studies have suggested a possible role of FeNO in the management of patients with pulmonary sarcoidosis, but published data are discordant. *Objectives:* To assess the clinical usefulness of FeNO and alveolar concentration of NO (CalvNO) in sarcoidosis. *Methods:* We measured FeNO50-100-150 and CalvNO in 31 patients with pulmonary sarcoidosis, 32 patients affected by idiopathic pulmonary fibrosis (IPF) and 30 healthy controls. *Results:* Sarcoidosis group reported FeNO50-100-150 and CalvNO levels comparable to healthy controls, while IPF patients showed significantly higher values of FeNO50-100-150 and CalvNO than sarcoidosis (all p<0.05) and controls groups (all p<0.05). *Conclusion:* Exhaled nitric oxide is not a useful biomarker in the management of patients affected by pulmonary sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 39-40)*

Key words: infliximab; cutaneous sarcoidosis; pulmonary; sarcoidosis; sarcoidosis activity and severity index; tumor necrosis factor-alpha

In 2004, Ziora et al. reported a mild increase of fractional exhaled nitric oxide (F_ENO) in twenty-seven sarcoidosis patients compared to eleven controls (p=0.05) and suggested a potential role of activated macrophages and CD4 lymphocytes in inducible NO synthase upregulation (1). Literature data on F_ENO in sarcoidosis is still limited and contradictory (2, 3). We recently analyzed F_ENO in sarcoidosis patients compared with idiopathic pulmonary fibrosis (IPF) and healthy controls. F_ENO levels at 50, 100 and 150 ml/s flow rates ($F_ENO_{50-100-150}$) were measured in 31 patients with sarcoidosis (17 stage II and 14 stage III), 32 patients with IPF and 30 healthy controls. IPF and sarcoidosis were diagnosed according to international guidelines (4, 5). The subjects gave their informed consent to the study. We used a chemiluminescence analyzer (model Hypair F_ENO medisoft Exp'air, 2010) according to ATS recommendations (6) for measurement of F_ENO. The alveolar concentration of NO ($Calv_{NO}$) was calculated using both Tsoukias and George (7) and Condorelli's methods (8).

IPF patients were older and smoked more packs/year of cigarettes than sarcoidosis patients (p<0.05 and p<0.01, respectively). No significant differences were found between $F_ENO_{50-100-150}$ and $Calv_{NO}$ in sarcoidosis patients and healthy subjects. IPF patients reported $F_ENO_{50-100-150}$ and $Calv_{NO}$ levels significantly higher than controls and sarcoidosis

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Corresponce: Cameli Paolo,
UOC Malattie Respiratorie e Trapianto di Polmone,
Dipartimento di Scienze Mediche, Chirurgiche e
Neuroscienze, Policlinico Le Scotte
Viale Bracci, 53100 Siena (Italy)
Tel. +39 0577 586710
Fax +39 0577 280744
E-mail: paolocameli88@gmail.com

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Table 1. Comparisons between sarcoidosis, IPF and healthy subjects performed by Kruskall-Wallis test and Dunn's post hoc test. Data expressed as mean ± standard deviation (SD). No correlations were found between NO parameters and lung function tests

Parameters	Sarcoidosis	IPF	Controls	p value
N°	31	22	30	
Age (years)	55.7 ± 12.6	64.8 ± 10.4*	62.0 ± 4.7	< 0.05
BMI (Kg/m^2)	23.2 ± 3.5	25.0 ± 3.5	24.4 ± 2.9	ns
Ex-smokers	5	12*	7	ns
Tobacco use (packs/year)	1.8 ± 5.7	10.2 ± 12.2*	5.2 ± 3.7	0.001
F_ENO_{50} (ppb)	15.8 ± 5.8	22.3 ± 8.5†	15.8 ± 4.1	0.001
F_ENO_{100} (ppb)	14.1 ± 5.3	18.2 ± 6.8†	13.1 ± 2.9	0.006
F_ENO_{150} (ppb)	11.8 ± 4.1	15.3 ± 7.7†	10.8 ± 2.9	0.04
$Calv_{NO}$ (ppb)[¶]	6.0 ± 3.1	11.8 ± 6.6†	4.7 ± 2.3	< 0.0001
$Calv_{NO}$ (ppb)[§]	5.4 ± 3.7	10.7 ± 5.9†	4.3 ± 2.1	< 0.0001

BMI, Body Mass Index
F_ENO, fractional exhaled nitric oxide
$Calv_{NO}$, alveolar concentration of nitric oxide
* $p < 0.05$ with respect to sarcoidosis group
† $p < 0.05$ with respect to controls and sarcoidosis group.
[¶] two-compartment model by Tsoukias and George (7)
[§] trumpet model with axial diffusion (TMAD) by Condorelli et al. (8)

patients (p=0.001, p=0.006, p=0.04 and p<0.0001, respectively) (Table 1). No correlations were found between eNO levels and radiological stages in sarcoidosis patients. 11/31 sarcoidosis patients were taking oral corticosteroids (mean dose: 12.08 ± 4.24 mg/day, expressed in prednisone equivalent) but no significant differences were found between treated and untreated patients.

Our study reports contrasting results with those of Ziora et al. (1), denying a role of NO in the pathogenesis of pulmonary sarcoidosis. Our results are in line with O'Donnell et al. (2) and Wilsher and coworkers (3), who reported no increase of F_ENO in sarcoidosis patients and no correlations with morphological disease extent. Moreover, our sarcoidosis patients didn't show increased $Calv_{NO}$ levels, suggesting that it cannot represent a marker of sarcoidosis severity or activity; the higher levels of F_ENO and $Calv_{NO}$ reported in patients with IPF, instead, are probably due to oxidative/nitrosative stress (9, 10).

In conclusion, eNO did not represent a reliable biomarker for pulmonary sarcoidosis, while it has to be further analyzed as a potential bioindicator of IPF. Although attractive, Ziora's theory of a potential involvement of NO in the inflammatory granulomatous pathophysiology of sarcoidosis cannot be confirmed.

Take-home messages: Exhaled nitric oxide is not a considerable biomarker in sarcoidosis.

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