FeNO analysis in IPF

Subjects: Pathology

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Fractional exhaled nitric oxide is a non-invasive and reproducible biomarker that has demonstrated an interesting potential for differential diagnosis and prognostic estimation of patients affected by idiopathic pulmonary fibrosis. In particular, alveolar concentration of nitric oxide appeared to be a reliable indicator of severity of lung fibrosis and proved its efficacy in the early detection of patients with a fast progression of disease.

Fractional exhaled nitric oxide (FeNO) is a well-known and widely accepted biomarker of airways inflammation in asthmatic patients. Recent evidences underlined the potential value of an extended analysis of FeNO, including a multiple-flows assessment, as a useful tool for the management of patients with interstitial lung However, the multiple-flows assessment of FeNO can provide a reliable measurement of bronchial and alveolar production of NO, supporting its potential value as biomarker also in peripheral lung diseases, such as interstitial lung diseases (ILD).

The possibility to measure a biomarker of airway inflammation with a non-invasive, reproducible and economic technique led to the development of exhaled NO analyzers able to measure the NO burden in the airways. The procedure for the quantification of FeNO was standardized in 2005 [1]. To provide a more accurate evaluation of NO dynamics in distal airways and alveolar space, an extended analysis of FeNO has been proposed and the last technical standard document by ERS officially endorsed this procedure for future research[2].

Here, we performed a systematic review of literature in order to report all the available evidences concerning the rationale and the potential usefulness of extended FeNO analysis in the clinical management of idiopathic pulmonary fibrosis (IPF).

Keywords: exhaled nitric oxide ; biomarker ; idioapthic pulmonary fibrosis

1. Nitric oxide and lung fibrosis: rationale

The role of NO in the pathogenesis and or pathophysiology of IPF and in general of ILDs is not fully understood: although oxidative stress is well recognized as an essential component for the development of lung fibrosis, particularly in IPF [3][4], the impact of NO and related nitrosative stress still need to be fully clarified. IPF is the most common and severe among idiopathic interstitial pneumonia (IIP), showing a tipically progressive impairment of lung volumes and diffusion capacity due to aberrant fibrogenesis and collagen deposition in the distal airspaces [5]. The hypothesis that NO was directly involved also in lung fibrogenesis was firstly reported by Jung et al, who demonstrated an increased production of nitrate and nitrites in bronchoalveolar lavage (BAL) of bleomycin-induced lung fibrosis, associated to a significant overexpression of NOS2 [6]. More specifically, Pullamssetti et al. demonstrated on murine and human models of IPF an aberrant expression of dimethylarginine dimethylaminohydrolases (DDAHs) in fibrotic lungs, leading to an uncontrolled activity of iNOS2 through the inhibition of asymmetric dimethylarginine (ADMA) [7]. The significance of this alteration was further confirmed by the inhibition of DDAH through a specific enzymatic inhibitor, which led to a reduction of epithelial proliferation and collagene production by resident fibroblasts in bleomycin-induced lung fibrosis [7].

Still, the role of NO in lung fibrogenesis remains controversial: a recent paper by Noguchi et al. showed that triple knockout of the three isoforms of NOS (epithelial, neuronal and inducible) led to a significant deterioration of lung fibrosis, that could be reverted with supplemental NO [8], suggesting a potential protective role of this molecule.

2. Extended FeNO analysis in IPF: current evidences

Data concerning the potential role of multiple-flow analysis of FeNO in IPF has been growing in the last years.

Extended exhaled NO assessment was firstly described in IPF patients in 2011 by Schildge, who observed significant variations of CaNO among many ILD subgroups. Few other studies have investigated the dynamics of multiple-flows exhaled NO in IPF, reporting in the majority of cases a significant higher CaNO in respect with healthy subjects [9][10]; only

one study showed similar CaNO levels between IPF and healthy controls, but the study was limited by sample size, different smoking status and sex prevalence [11].

The potential value of eNO in the differential diagnosis of IPF is surely intriguing but still largely unexplored. Two papers implemented multiple-flows eNO assessment in their study design, showing promising results of CaNO in the discrimination of a specific ILD or ILD subgroup from other diseases with similar clinical and radiological features [10][12].

No focused papers have been published to evaluate eNO parameters among different IIPs; however, some studies didn't observe any significant differences between IPF and idiopathic non specific interstitial pneumonia (NSIP) [13][14][10].

In summary, extended eNO assessment seems to have a potential to be implemented in the diagnostic pathway of IPF, thanks also to its reproducibility, non-invasivity and relatively low costs are definitely good properties of

Concerning the severity assessment of disease, many studies found an inverse correlation between CaNO values and FVC and DLCO, suggesting a potential value of this biomarker in the monitoring of disease progression [10][13][15]; one study reported also a significant correlation of CaNO with Composite Physiological Index (CPI), further supporting its potential as severity biomarker in this setting [16].

No data is available regarding the potential counfonding effect of antifibrotic treatment on CaNO values and concerning the potential role of extended eNO analysis in predicting the response to therapy in IPF patients.

Multiple-flows FeNO analysis is surely a interesting technique that could allow respiratory physicians to obtain reproducible and non-expensive biomarker for the management of diffuse lung diseases. Among these, IPF is a devastating disease, characterized by a progressive clinical course, leading to chronic respiratory failure and death in few years. No biomarker has been widely accepted in the clinical practice in both diagnostic and prognostic estimation. On this field, CaNO demonstrated a intriguing potential in discriminating idiopathic ILDs from CTD-ILDs and in estimating survival and disease progression in terms of FVC deterioration, suggesting its possible implementation in the clinical management of IPF, thanks to its reproducibility, repeatibility and non-invasive nature. Further data is needed to confirm these findings and better understand the real potential of this promising technique on this field.

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