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Hand-held fractional exhaled nitric oxide measurements as a non-invasive indicator of systemic inflammation in Crohn's disease

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Abstract

Background and aims: Active inflammatory bowel disease (IBD) is associated with increased activity of inducible nitric oxide synthase (iNOS), which increases both mucosal and plasma nitric oxide (NO) levels. Increased fractional exhaled nitric oxide (FeNO) levels have been described in patients with IBD. Currently, hand-held FeNO measurement devices are available, enabling a fast in-office analysis of this non-invasive disease activity marker. In this pilot study, we investigated the utility of in-office FENO measurements in patients with Crohn's disease (CD).
Methods: Fifty CD patients and 25 healthy controls (HC) were included, all of whom were free of atopic or pulmonary disorders and respiratory symptoms at the time of inclusion. The Crohn's disease activity index (CDAI) was calculated, and the inflammatory parameters and fecal calprotectin levels were assessed. FeNO was measured with a hand-held device.
Results: A significant increase in FeNO (median, [interquartile range]) was observed in steroid-free CD patients with clinically active disease (CDAI>150; 22 [8] ppb) compared with CD patients in clinical remission (CDAI<150; 11 [6] ppb; $P<0.001$) and HC's (17 [9] ppb; $P<0.05$). Active CD patients treated with corticosteroids had significantly lower FeNO compared with active CD patients without steroids (12 [10] ppb vs 25 [19] ppb; $P<0.05$). FeNO displayed a strong correlation with the CDAI ($R=0.68$; $P<0.001$). Fair correlations were found between FeNO and several systemic inflammatory markers, but no significant correlation was found with fecal calprotectin.

Abbreviation: (F)eNO, (Fractional) exhaled nitric oxide.

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Conclusion: This pilot study suggests that hand-held FeNO measurements could be an attractive non-invasive indicator of systemic inflammation in Crohn's disease.

1. Introduction

Crohn's disease (CD) is a systemic inflammatory disease that primarily affects the gastrointestinal tract, although in many cases, extraintestinal manifestations of the disease are observed.[1]

Objective measurements of disease activity in CD are important because CD patients may have irritable bowel-like symptoms even when their disease is in complete remission. In addition, patients with documented disease activity will benefit from a switch or intensification of their therapy. Currently, validated clinical disease activity indices (e.g., the Harvey–Bradshaw index and the Crohn's disease activity index [CDAI]) and serum inflammatory parameters are used to screen for disease activity.[2,3] The CDAI appears to be a valid instrument of assessment, although it cannot be used in all patient subgroups with CD (e.g., children). The CDAI has a consistent correlation with diagnostic markers of mucosal inflammation in CD. It is a very useful tool for trials, but a full clinical assessment is needed to demonstrate disease.[4,5] In the case of doubt, endoscopy is performed to assess the severity and extent of mucosal inflammation. Due to the invasive nature of the latter, there is a medical need for non-invasive alternatives to reliably assess disease activity in CD.

In this context, the measurement of fecal calprotectin has increasingly entered clinical practice as a reliable marker of active disease in patients with IBD.[6] Although fecal calprotectin concentrations theoretically can be measured in less than 30 min, this procedure still requires the collection and manipulation of stool samples, making it less useful for in-office, point-of-care testing. The ideal non-invasive marker would be measured during the consultation.

Nitric oxide is an indispensable cellular messenger molecule involved in a variety of processes, and it has a 'bimodal' character, displaying both cytotoxic and cytoprotective behaviors.[7] NO and its different effects are found in various parts of the body, e.g., the respiratory, immune, and digestive systems.[8] CD patients have been shown to have high rectal NO concentrations and increased NO metabolites in their serum and urine due to increased activity of the inducible form of nitric oxide synthase (iNOS). Overproduction of rectal NO can be measured during the active disease phase, but in patients in remission, a significant decrease has been demonstrated.[9] As investigated by Koek et al.[10] and Ozyilmaz et al.,[11] the levels of FeNO also appear to increase with disease activity in patients with IBD.

Although in the past the measurement of FeNO required sophisticated equipment, currently, hand-held devices are available, allowing the analysis of FeNO in less than 2 min and requiring only a single exhaled breath.[12] The same technique is currently used to measure FeNO as a biomarker in the diagnosis and monitoring of asthma patients.[13]

The aim of this study was to confirm that FeNO levels, as measured by hand-held devices, are elevated in CD patients without any respiratory complaints or disorders. Secondly, we wanted to assess the correlation between FeNO and different established disease activity parameters in CD, including clinical indices, inflammatory blood markers, and fecal calprotectin.

2. Materials and methods

Fifty patients with CD and 25 healthy individuals were included. All patients were recruited at the outpatient clinic of the Gastroenterology Department of the Ghent University Hospital. The diagnosis of CD was made by a gastroenterologist, based on medical history, physical examination, radiological criteria, and endoscopic and histological findings. Individuals with known allergies, atopic eczema, hay fever, asthma, and other lung disorders (including common respiratory tract infections) were excluded from the study population because these disorders are known to increase FeNO levels.[14] This study was approved and accepted by the Ethics Committee of the Ghent University Hospital (Nr 2009248). All subjects provided written informed consent.

Using a questionnaire, the smoking habits, age, gender, body length and weight, past medical history, CD duration, and use of medication were recorded. Disease-related symptoms were recorded to determine the Crohn's disease activity index (CDAI). Patients with a CDAI score higher than 150 were considered to have active disease, and those below 150 to be in remission.[15] Routine laboratory parameters, such as white blood cell count (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured. All CD patients were asked to provide a stool sample to determine the fecal calprotectin levels, as measured by ELISA (Bühlmann, Schönenbuch, Switzerland).

The FeNO measurement was performed using a hand-held analyzer, the NIOX MINO (Aerocrine, Sweden). During a single-breath exhalation, the NIOX MINO measures FeNO in 100 s with an electrochemical sensor. All FeNO measurements were performed in concordance with the ATS/ERS recommendations.[14]

Statistical analysis was performed using SPSS statistics 17.0. For the comparison of the means of normally distributed variables, a one-way analysis of variance (ANOVA) was performed, with the Scheffé-test for pairwise comparisons. The Mann–Whitney U test was used to compare nonparametric mean values, and the correlations were studied with Spearman's rank-based correlation coefficient. The data are expressed as median (interquartile range), the test results are considered significant for P-values less than 0.05.