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Respiratory Medicine 193 (2022) 106745

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Can FeNO be a biomarker in the post-COVID-19 patients monitoring?

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ARTICLE INFO

Keywords:
Post-COVID-19
FeNO
biomarker

ABSTRACT

The nature of the inflammatory and fibrotic processes found in patients with post-COVID-19 syndrome makes it possible to speculate that in such patients fractional exhaled nitric oxide (FeNO) may be a useful biomarker. Consequently, we set out to verify the consistency of this hypothesis. We consecutively enrolled 68 post-COVID patients after being hospitalized for persistent clinical manifestations within 2 months from disease onset and 29 healthy volunteers as control group. None of post-COVID patients had bronchial asthma or were being treated with a corticosteroid. Only 19 out of 68 post-COVID-19 patients reported a FeNO value > 25 ppb. The mean FeNO value in post-COVID-19 patients was 18.55 ppb (95% CI: 15.50 to 21.58), while in healthy subjects it was 17.46 ppb (95% CI: 15.75 to 19.17). The mean difference was not statistically significant (P = 0.053). However, the mean FeNO value of post-COVID-19 patients was higher in men than in women (20.97 ppb; 95% CI: 16.61 to 25.33 vs 14.36 ppb; 95% CI: 11.11 to 17.61) with a difference between the two sexes that was statistically significant (P = 0.016). Mean FeNO was 14.89 ppb (95% CI: 10.90 to 18.89) in patients who had been treated with systemic corticosteroids because of their COVID-19, and 20.80 ppb (95% CI: 16.56 to 25.04) in those who had not taken them, with a difference that was statistically significant (P = 0.043). The data generated in this study suggest that measurement of FeNO is not useful as a biomarker in post-COVID-19 patient. However, this hypothesis needs solid validation with additional specifically designed studies.

1. Introduction

A high proportion of patients recovering from COVID-19 reported persistence of symptoms, particularly fatigue and dyspnea, even 2 months after being discharged [1]. This delayed recovery of symptoms has been termed "post-COVID-19 syndrome" or "long COVID" [2]. The pathogenesis of post-COVID syndrome remains largely unknown. Evidence suggests that prolonged inflammation, nervous system dysfunction, endothelial damage, and thromboembolism have a key role in the pathogenesis of most post-COVID manifestations [3]. Furthermore, there is increasing evidence that fibrotic changes and interstitial lung abnormalities may result from COVID-19 infection in some cases, although we still do not know whether the fibrosis is stable or progressive [4].

The high proportion of patients who develop the post-COVID-19 syndrome is the reason for the frenetic search for biological markers that are clinically useful in predicting a severe disease course in COVID-19 patients and also responses to treatment [5].

Although not yet widely implemented, fractional exhaled nitric oxide (FeNO) has emerged in recent years as a potentially useful biomarker for the assessment of airway inflammation in both undiagnosed patients with nonspecific respiratory symptoms and in those with established airway disease [6]. FeNO is widely accepted as a non-invasive biomarker of inflammation and oxidative stress in the lungs [7]. There are also reports of increased FeNO fraction values in interstitial lung disease with concentrations of alveolar NO (CaNO) that correlate with 6-min walking distance, oxygen saturation recovery time, total lung capacity, and forced vital capacity (FVC) [8].

; NO, nitric oxide; FeNO, fractional exhaled NO; CaNO, concentration of alveolar NO; FVC, forced vital capacity; iNOS, inducible NO synthase; FEV1, forced expiratory volume in one second; ppb, parts per bilion; ERS, European Respiratory Society; ATS, American Thoracic Society; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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https://doi.org/10.1016/j.rmed.2022.106745
Received 2 November 2021; Received in revised form 11 January 2022; Accepted 17 January 2022
Available online 26 January 2022

The nature of the inflammatory and fibrotic processes found in patients with post-COVID-19 syndrome makes it possible to speculate that in such patients FeNO may be a useful biomarker. However, the impact of respiratory viruses on FeNO levels has not yet been clarified.

In children with an acute asthma exacerbation, FeNO levels rise to a greater extent in those whose exacerbation is not virus-induced [9]. In contrast, another study has observed an increase in FeNO levels following human rhinovirus 16 infection in asthmatics [10]. In addition, respiratory syncytial virus has been shown to induce inducible NO synthase (iNOS)-mediated expression of Kruppel-like transcription factor 6 in human alveolar epithelial type 2 cells [11].

These observations suggest that FeNO and CaNO could be considered markers of epithelial damage in the proximal and distal airways, respectively, during viral infections e.g. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [12].

In any case, upregulation of iNOS, which leads to an increase in the concentration of NO, is induced by pro-inflammatory cytokines that are highly upregulated in patients with COVID-19. It has been shown that in SARS-CoV-2 infection, tumour necrosis factor α and interferon γ synergistically induce iNOS and NO, which subsequently induce cell death [13].

Considering the prolonged inflammation that characterises post-COVID-19 syndrome and its possible impact on NO production, we aimed to test whether FeNO, which has the advantage of being standardized, quick, non-invasive, simple, and easy to reproduce, could be considered a valid biomarker in patients with post-COVID-19 syndrome.

2. Patients and methods

2.1. Patients

In this prospective study, convalescent (post-) COVID-19 patients were consecutively selected for entry into the study after being admitted within less than 2 months after the onset of COVID-19 to the Istituti Clinici Scientifici Maugeri IRCCS, Telese Terme, Benevento, Italy, or the Ospedale Universitario "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy, to undergo a pulmonary rehabilitation program or to continue appropriate medical care. All patients had two consecutive negative SARS-CoV-2 swab tests before their admission in our wards. An additional control group of 29 healthy volunteers enrolled among hospital staff from January 2021 to April 2021 was also included in the analysis. All volunteers tested negative for SARS-CoV-2 at study entry and had no history of positive nasopharyngeal swab at periodic monitoring of hospital staff.

Exclusion criteria for cases and controls were: age < 18 years; history of atopy and/or asthma; previously documented eosinophilic airway inflammation; peripheral blood eosinophil count at admission $> 500/\mu L$ ($>0.5 \times 10^9/L$); current smokers or ex-smokers; history of chronic obstructive pulmonary disease; history of bronchial asthma; any respiratory condition other than COVID-19; history of cardio- or cerebrovascular events; any condition associated with poor compliance with the study protocol or inadequate understanding of the study procedures; being treated with systemic or inhaled corticosteroids.

The study, which was reported following the Strengthening the Reporting of Observational Studies in Epidemiology recommendations to limit known sources of bias [14], was conducted in accordance with the 1975 Declaration of Helsinki of the World Medical Association. The Institutional Review Board of Istituto Nazionale Tumori, Fondazione Pascale, Naples, Italy approved this study with reference number ICS11/20. All patients provided written informed consent to use their de-identified data.

2.2. Study procedures

After informed consent signature, the main demographic and clinical information pertaining to the acute phase of COVID-19, pulmonary function, and ongoing treatments were collected for all post-COVID-19 patients. For control subjects, persistently anonymized data were analyzed after collection.

Forced expiratory volume in 1 s (FEV_1) and FVC were measured with an automated instrument (Vmax Encore, Vyasis Healthcare, Milan, Italy, at the Istituti Clinici Scientifici Maugeri IRCCS, Telese Terme, Benevento, and Minispir, Medical International Research, Rome, Italy, at the Ospedale Universitario "San Giovanni di Dio e Ruggi d'Aragona", Salerno), always following the protocols of the American Thoracic Society/European Respiratory Society (ATS/ERS) [15]. A value above 80% of predicted was considered normal for both variables.

2.3. Fractional exhaled nitric oxide (FeNO)

FeNO was measured in both centers with Hyp'AirFeNO electrochemical analyzer (MediSoft, Sorinnes, Belgium). This analyzer guaranteed repeatable measurements of FeNO in the range of 0–600 parts per billion (ppb) and did not require external calibration. FeNO measurements were performed in all participants according to ATS/ERS guidelines [16]. Briefly, all evaluations were performed at a standardized exhalation flow rate of 50 ml/s. To perform a valid exhalation maneuver, the flow parameters were controlled by both audio and visual feedback supplied by manufacturers, allowing the participant to maintain a constant exhaled breath flow rate. FeNO measurements were obtained in duplicate. Subjects were instructed to avoid exercise and consumption of nitrate-rich diets at least 2 h before measurement.

2.4. Statistical analysis

Statistical analysis was performed using Prism 8 software package (GraphPad Software Inc, USA). Data were expressed as mean and 95% confidence interval (CI) (standard errors have been reported in figures). Comparison between healthy subjects and convalescent COVID-19 patients was made with unpaired *t*-test and Welch's correction. Relationships between continuous variables were examined using simple regressions with Pearson's correlation coefficient (r). All results were expressed as 2-tailed values, P values < 0.05 being statistically significant.

3. Results

Sixty-eight post-COVID patients were admitted into the study. The control group included 29 healthy volunteers. The main demographic and clinical characteristics of the study participants have been reported in Table 1.

The mean FeNO value in post-COVID patients was 18.55 ppb (95% CI: 15.50 to 21.58), while in the healthy subjects it was 17.46 ppb (95% CI: 15.75 to 19.17) (Fig. 1A). The mean difference in FeNO between post-COVID patients and healthy subjects was not statistically significant ($P = 0.053$).

In 19 of our 68 post-COVID patients, the FeNO value was > 25 ppb (Fig. 1B), which the ATS committee on interpretation of FeNO levels for

Table 1
Functional parameters in healthy subjects (control group and in post-COVID patients. Values are mean.

	Control group n = 29	Post-COVID patients N = 68	P value
Age, years (95% CIs)	47.2 (43.7–50.7)	53.6 (49.4–57.8)	
Women, (%)	10 (34.5)	25 (36.8)	
FEV_1% predicted (95% CIs)	96.9 (94.0–99.9)	87.3 (82.3–92.2)	<0.01
FVC% predicted (95% CIs)	99.4 (96.7–102.1)	85.9 (80.6–81.2),	<0.0001

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

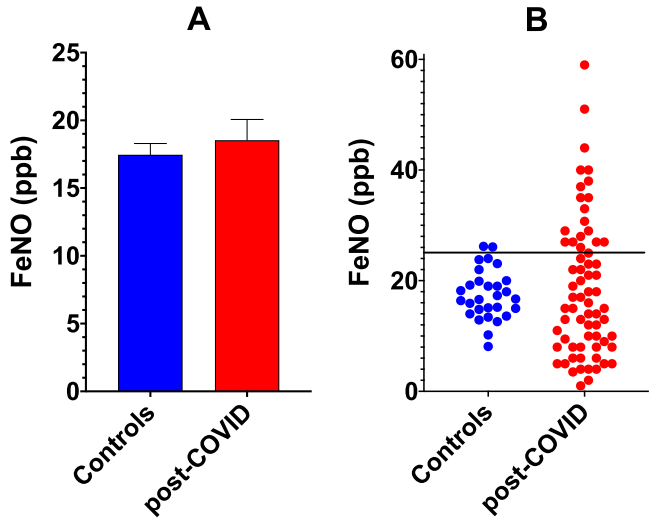

Fig. 1. Comparison of mean FeNO values between healthy subjects (controls) and post-COVID-19 patients (A) and distribution of individual values taking into account the cut off suggested by the ATS to define a test as possibly positive (B). ATS, American Thoracic Society; FeNO, fractionated exhaled nitric oxide; ppb, parts per billion.

clinical applications [17] indicates has a low probability of eosinophilic inflammation and responsiveness to corticosteroids, and only in 2 it was > 50 ppb, a value indicating that eosinophilic inflammation and responsiveness to corticosteroids are likely. However, the Japanese Respiratory Society suggests that the mean normal value is 15.4 ppb [18] and 36 of our patients exceeded this threshold. Among the 29 healthy subjects, 2 had a FeNO > 25 ppb and 18 a FeNO > 15.4 ppb. We did not give importance to these values because the Japanese Respiratory Society itself states that the normal upper limit is approximately 37 ppb. Only 9 post-COVID 19 patients had a FeNO ≥35 ppb, while no control exceeded 26.2 ppb.

Mean FeNO value of post-COVID patients was higher in men (20.97 ppb; 95% CI: 16.61 to 25.33) than women (14.36 ppb; 95% CI: 11.11 to 17.61) (Fig. 2). The difference between the two sexes was statistically significant (P = 0.016). In contrast, in the control group there was no substantial difference (P = 0.534) between men and women (men; 17.05 ppb, 95% CI: 15.01 to 19.09; women: 18.24 ppb, 95% CI: 14.61 to 21.87). There was no significant difference (P = 0.924) in mean FeNO values between patients up to 65 years of age (18.64 ppb; 95% CI: 15.08 to 22.21) and those over 65 years of age (18.31 ppb; 95% CI: 12.02 to 24.60) (Fig. 2). FeNO was 14.89 ppb (95% CI: 10.90 to 18.89) in the 26 patients who had been treated with systemic corticosteroids because of their COVID-19, and 20.80 ppb (95% CI: 16.56 to 25.04) in the 42 who had not taken them, with a difference that was statistically significant (P = 0.043) (Fig. 2). The difference in mean FeNO values between 23 patients who were taking O_2 and the 45 who were not on O_2 treatment was not statistically significant (P = 0.250), although there was a trend toward higher values in those on O_2 therapy (21.29 ppb; 95% CI: 14.75 to 27.84) compared with those not on O_2 treatment (17.13 ppb; 95% CI: 13.84 to 20.43) (Fig. 2).

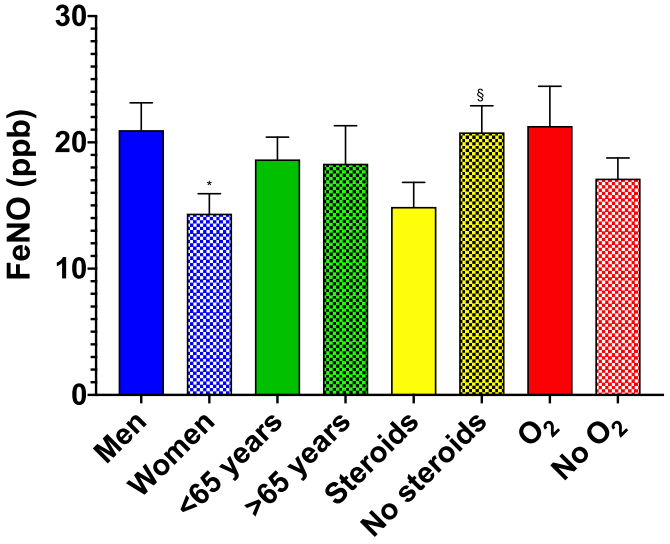

Fig. 2. FeNO values in post-COVID-19 patients considering sex, age group, previous steroid use and O_2 supplementation. FeNO, fractionated exhaled nitric oxide; steroids, corticosteroids. *P = 0.016 vs men; §P = 0.043 vs no steroids.

Functional parameters (FEV_1% predicted and FVC% predicted) showed statistically lower mean values in post-COVID patients compared with those in the control group (Table 1). It must be noted that the spirometric data refer to 62 patients because other 6 subjects were unable to perform the pulmonary function test when they were admitted to our wards.

FeNO values of our patients correlated significantly with the FEV_1% predicted and FVC% predicted baseline values (r = 0.26, P = 0.037; and r = 0.28, P = 0.026, respectively) (Fig. 3), but they did not correlate with the age (r = 0.10, P = 0.929) although in patients up to 65 years r was 0.00 (P = 0.981) and become 0.25 (P = 0.278) in patients over 65 years of age.

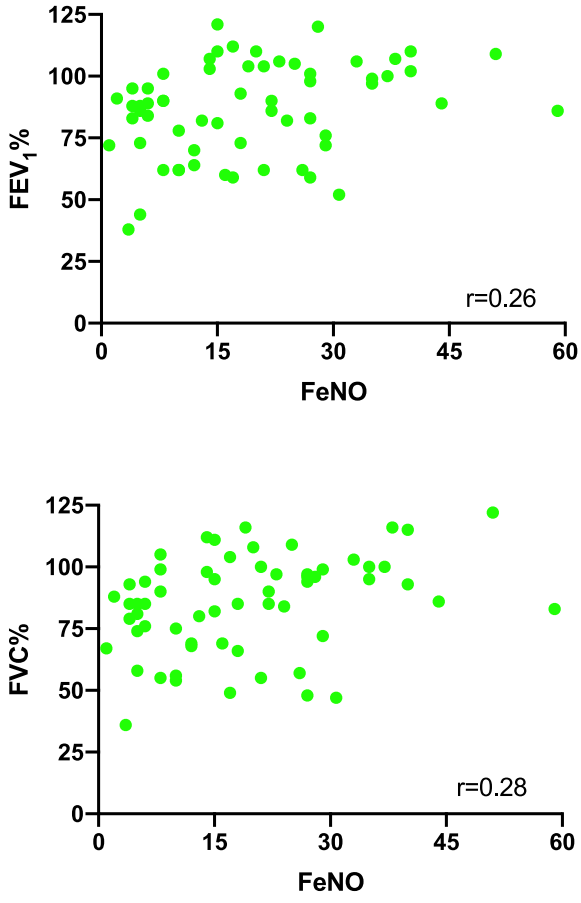

Fig. 3. Relationship between FEV_1 or FVC% predicted and FeNO in post-COVID-19 patients. Pearson's correlation coefficient (r) value is indicated.

4. Discussion

The data generated in this study suggest that measurement of FeNO is not useful as a biomarker of post-COVID-19 patient monitoring. This conclusion correlates well with the observation that eosinophils do not play a protective or exacerbating role during SARS-CoV-2 infection [19]. In addition, it is eosinopenia that is very common and often pronounced in cases of SARS-CoV-2 infection [20].

Our data are not dissimilar to those of Cameli et al. who reported mean FeNO values of 17.3 ppb in 20 post-COVID patients and 15.8 ppb in 22 healthy subjects [21]. However, while in our population we found no predominant pulmonary fibrotic changes on radiological investigation, in Cameli's group such changes and ground glass opacities were associated with high CaNO levels although no further significant differences were observed between other FeNO parameters and CT scan data.

In a small Finish study, mean FeNO value was 21.7 ppb three to six months after hospital discharge [22]. Seven out of 20 patients had slightly elevated FeNO of 25–50 ppb, and none of the participants had an abnormal FeNO of more than 50 ppb.

In a study conducted in Saudi Arabia, the median FeNO value measured in 20 patients at least 3 months post-recovery was 19 ppb, while in a control group of 30 individuals it was 16 ppb [23].

Our data do not allow us to understand whether FeNO values are elevated in patients with COVID-19, with possible differences in the presence rather than absence of pneumonia or acute respiratory distress syndrome, and then decrease in the post-COVID phase.

The documentation that FeNO mean values in post-COVID patients were quite similar to those in the control group suggests that COVID-19 does not induce chronic bronchial inflammation or predispose to chronic obstructive diseases. This hypothesis, which needs solid validation with additional specifically designed studies, contrasts with the evidence of persistent inflammation 5 months after the onset of olfactory symptoms in patients with COVID-19 who recovered from their olfactory dysfunction compared with patients who did not experience anosmia [24]. However, in the same study it was also demonstrated the presence of comparable FeNO and CaNO between COVID-19 patients with and without olfactory dysfunction. This suggests that the increase in residual inflammation accompanying olfactory loss is limited only to the olfactory epithelium probably due to the increased expression of both angiotensin-converting enzyme 2 and transmembrane protease serine 2 in the ciliated and goblet cells of the nasal cavity compared with the lower airway and alveolar epithelial cells. It has been suggested that nasal NO levels be measured in patients with post-acute COVID-19 syndrome with persistent anosmia to evaluate ongoing background activation of iNOS by proinflammatory cytokines even after recovery [24]. This is an interesting possibility that could provide additional information about the level of airway inflammation [25]. However, its validity needs to be appropriately demonstrated.

The evidence that FeNO was significantly higher in males than in females corresponds to the accepted notion that sex is an important factor determining FeNO measurements [26], not necessarily because of lower NO production in women but because women have smaller lungs and consequently higher linear flow velocities in the airways, and it is known that FeNO decreases with increasing flow because it is highly flow-dependent [27]. This suggests that the significant difference we recorded between the sexes does not appear to be a consequence of suffering from COVID-19.

The documentation that FEV_1% and FVC% predicted mean values were statistically lower in post-COVID-19 patients compared with those in the control group confirms that COVID-19 pneumonia can cause significant alterations in lung function [28]. Our patients were examined within 8 weeks after the onset of COVID-19, and it was reported that 54% of COVID-19 survivors had abnormal lung function 10 weeks after diagnosis [29].

The fact that patients treated in the acute phase with corticosteroids had lower mean FeNO values than those not treated with such agents is another expected result. While we have no information on whether the use of corticosteroids was in accordance with the recommendations available for hospitalized patients with acute COVID-19 [30] because such treatment was administered in different hospital settings than in our facilities, it is known that treatment with systemic corticosteroids induces a drastic reduction in FeNO values, although in non-asthmatic subjects it is difficult to predict whether they rise again and, if so, after how long [31]. In any case, a small study found FeNO levels within the normal range during acute symptoms of SARS-CoV-2 infection, with some increase during the recovery phase, independently of disease severity or the patient's history of atopy. However, in patients treated with corticosteroids, a significant FeNO decrease during clinical evolution was more pronounced [32].

Overall, the preliminary data generated in this study suggest that measurement of FeNO is not useful as a biomarker in post-COVID-19 patient monitoring. A major limitation of this pilot study is the small sample, thus suggesting the need for larger studies specifically designed to test the usefulness of this biomarker in post-acute care and rehabilitation settings.

CRediT authorship contribution statement

Mauro Maniscalco: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing, All Authors read and approved the final version of the manuscript. **Pasquale Ambrosino:** Data curation, Investigation, All Authors read and approved the final version of the manuscript. **Remo Poto:** Data curation, Investigation. **Salvatore Fuschillo:** Investigation, All Authors read and approved the final version of the manuscript. **Sergio Poto:** Conceptualization, Investigation, Writing – review & editing, All Authors read and approved the final version of the manuscript. **Maria Gabriella Matera:** Formal analysis, Validation, Writing – review & editing, All Authors read and approved the final version of the manuscript. **Mario Cazzola:** Conceptualization, Formal analysis, Validation, Writing – original draft, All Authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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