The Discrepant Role of Fractional Exhaled Nitric Oxide in SARS-CoV-2 Infection

Betancor D[1], Olaguibel JM[2,3], Sastre J[1,3]

[1]*Allergy Department, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain*

[2]*Allergy Department, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain*

[3]*CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain*

To the Editor:

We appreciate the correspondence of Drs Elfessi and Rubinstein [1]. The many studies performed on the effect of fractional exhaled nitric oxide (FeNO) in COVID-19 infection have yielded discrepant results and no conclusions. While some studies demonstrated the accurate diagnostic capacity of FeNO measurement in COVID-19, others conclude that there is no association between FeNO and this viral infection.

Inclusion criteria vary widely not only for affected patients (eg, symptomatic respiratory disease [2], mild/severe COVID-19 [3], and critical illness [4]), but also for healthy control groups [5,6]. Moreover, the use of different FeNO measurement devices could also interfere with the results. To the best of our knowledge, our study [2] is the only one to compare patients' FeNO levels during acute infection and recovery in the same patients, in addition to a control group, during the COVID-19 pandemic.

While Balci et al [5] and Yang et al [6] demonstrated significantly higher FeNO levels than in healthy controls, a significant difference was found in the median FeNO value in COVID-19 patients between the studies (31.7 [14.8] and 18.3 [7.1] ppb, respectively), with similar control FeNO values (15.5 and 15.6 ppb). This finding supports the previously demonstrated high variability in FeNO, also suggested by Elfessi and Rubinstein [1]. Exline et al [4] reported higher levels of NO and ammonia in mechanically ventilated COVID-19 patients than in mechanically ventilated COVID-19–negative patients. The isolated NO value in this study is not measured; therefore, its involvement without ammonia is unknown. Other studies [3] evaluated only positive COVID-19 patients and demonstrated lower FeNO values in patients with severe disease than in those with mild disease, suggesting that FeNO is a predictor of the severity of COVID-19. The authors also demonstrated that FeNO ≤11.8 ppb is predictive of severe outcomes. This finding contrasts with ours [2], which indicate no significant differences in FeNO values according to disease severity. Three studies with hospitalized post–COVID-19 populations performed 3 to 6 months after the initial infection

report different results [7-9]. Lindahl et al [7] and Salem et al [8] found normal FeNO values, although their samples were small (20 patients in each one). Cameli et al [9] demonstrated higher distal FeNO values (350 mL/s) in patients than in healthy controls. However, they did not observe any significant differences in proximal FeNO.

Additionally, medical treatment, especially corticosteroids in moderate-severe COVID-19, has previously demonstrated a significant effect on FeNO levels. Patient medication data were collected in only 2 studies [2,3], although neither provided a statistical analysis. Some authors did report clinical characteristics that could interfere with FeNO levels (eg, age, sex, body mass index, and smoking) [10]. However, other characteristics that may have some influence, such as previous food intake, history of atopy, and concurrent respiratory infections, were not included. All of these could confound the analysis of FeNO values.

A positive correlation has been reported between FeNO and atopy [10]. In addition to compiling data in our previous study [2], we also analyzed FeNO levels in atopic patients with COVID-19 infection (positive SARS-Cov-2 RT-PCR and/or antigen test). Of the 82 patients included, 19 (23.2%) reported atopy and 63 (76.8%) were nonatopic. There were no differences in demographic characteristics. FeNO levels did not vary significantly between the groups during acute infection (12.7 [8.4] ppb for atopic patients vs 11.3 [9.1] ppb for nonatopic patients; $P>.05$) or during the early recovery period (23.2 [16.4] ppb vs 18.0 [21.9] ppb, respectively; $P>.05$). No patient had FeNO levels higher than 50 ppb, and 4 patients, all from the nonatopic group, had FeNO levels higher than 30 ppb. We concluded that measurement of FeNO does not define atopy status in patients with SARS-CoV-2 infection during symptomatic or early recovery.

Discrepant FeNO results have also been observed in other viral respiratory tract infections [11]. The explanation for these variable results is controversial. The SARS-CoV-2 virus binds to the host cells through the angiotensin-converting enzyme 2 (ACE2) receptor. Respiratory epithelial cells, which highly express ACE2, are the portal of entry for the virus. FeNO is produced in airway epithelial cells, mainly by inducible nitric oxide synthase (iNOS). Given that ACE2 diminishes iNOS signalling, a negative correlation was hypothesized between COVID-19 infection and airway NO production and, therefore, FeNO values. As a result of this finding, treatment with NO has proven beneficial for COVID-19 patients, with increased susceptibility to SARS-CoV-2 infection reported in those with low airway NO levels [12]. By contrast, NO is usually increased in viral infections as a response mechanism of proinflammatory cytokine signaling and acts by inhibiting its replication and entry into the host cell.

COVID-19 stage could also affect FeNO value. The first stages of the disease are characterized by antiviral activity secondary to the activation of epithelial cells to produce cytokines and upregulate iNOS and, therefore, NO concentration. Concurrently, excessive NO is converted into peroxynitrite and other substances, damaging human immune cells, promoting COVID-19 infection, inhibiting NO production, and reducing NO concentration.

We agree with Elfessi and Rubinstein [1] that more studies with larger samples are needed. Our sample of 88 patients [2] is surpassed only by that of Balci et al [5], with 102 patients. Samples in other studies are highly variable, ranging from 20 patients [7-9] to 56 patients [3].

In conclusion, the role of FeNO in SARS-CoV-2 infection is controversial. Differences in clinical characteristics, disease stage at measurement, treatment, device, and patients' characteristics could confound FeNO measurement. More studies are needed to elucidate the role of FeNO in this viral infection.

Funding

Conflicts of Interest

Dr Betancor reports a Rio Hortega Research Grant outside the submitted work.

Dr Olaguibel reports grants and personal fees from everSens and AstraZeneca and personal fees from Mundipharma outside the submitted work.

Dr Sastre reports grants and personal fees from SANOFI and personal fees from GSK, NOVARTIS, AstraZeneca, Mundipharma, and FAES FARMA outside the submitted work.

References

1. Elfessi Z, Rubinstein I. Monitoring fractional exhaled nitric oxide levels in adult patients with acute symptomatic COVID-19 infection: non sequitur? J Investig Allergol Clin Immunol. 2022;32(5):415-415.
2. Betancor D, Valverde-Mongue M, Gomez-Lopez A, Barroso B, Ruete L, Olaguibel JM, et al. Evaluation of fractional exhaled nitric oxide during SARS-CoV-2 infection. J Investig Allergol Clin Immunol. 2022;32:301-3.
3. Lior Y, Yatzkan N, Brami I, Yogev Y, Riff R, Hekselman I, et al. Fractional exhaled Nitric Oxide (FeNO) level as a predictor of COVID-19 disease severity. Nitric Oxide. 2022;1;124:68-73.
4. Exline MC, Stanacevic M, Bowman AS, Gouma PI. Exhaled nitric oxide detection for diagnosis of COVID-19 in critically ill patients. PLoS One. 2021;16:e0257644.
5. Balcı A, Yildiz E, Selendili O, Günay E. A predictive and prognostic marker in COVID-19 patients: exhaled nitric oxide (FENO). Acta Med Mediterr. 2021:37:841-6.
6. Yang L, Zhou W, Ma J, Sun L, Zhai D, Ren GQ, et al. Ultrafast preliminary screening of COVID-19 by machine learning analysis of exhaled NO. Res Sq. 2021;30. Preprint.
7. Lindahl A, Reijula J, Malmberg LP, Aro M, Vasankari T, Mäkelä MJ. Small airway function in Finnish COVID-19 survivors. Respir Res. 2021;26;22(1):237.
8. Salem AM, Al Khathlan N, Alharbi AF, Alghamdi T, AlDuilej S, Alghamdi M, et al. The Long-Term Impact of COVID-19 Pneumonia on the Pulmonary Function of Survivors. Int J Gen Med. 2021;14:3271-80.
9. Cameli P, Bargagli E, Bergantini L, d'Alessandro M, Giugno B, Gentili F, et al. Alveolar Nitric Oxide as a Biomarker of COVID-19 Lung Sequelae: A Pivotal Study. Antioxidants (Basel). 2021;10(9):1350.
10. Olin AC, Rosengren A, Thelle DS, Lissner L, Bake B, Torén K. Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. Chest. 2006;130(5):1319-25.
11. Wang T, Dong H, Jiang W, Li Y, Sun H, Huang L, et al. Viral etiology and atopic characteristics in high-risk asthmatic children hospitalized for lower respiratory tract infection. Transl Pediatr. 2020;9(4):541-50.
12. Francistiová L, Klepe A, Curley G, Gulya K, Dinnyés A, Filkor K. Cellular and Molecular Effects of SARS-CoV-2 Linking Lung Infection to the Brain. Front Immunol. 2021;13;12:730088.

▌ **Diana Betancor**

Allergy Department
Hospital Universitario Fundación Jiménez Díaz
Av Reyes Catolicos, 2
28040 Madrid, Spain
E-mail: diana13_b@hotmail.com