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Letter to the Editor

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Fractional Exhaled Nitric Oxide in Normoxic Adult Patients With COVID-19 Infection in the Emergency Department: A Preliminary Observation

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To the Editor

Current concepts suggest that local elaboration of nitric oxide (NO) modulates, in part, the intense pro-inflammatory phenomena observed in lungs of patients with certain respiratory viral infections [1]. To that end, fractional exhaled NO (FeNO) monitoring is proposed as simple, portable, noninvasive, cost-effective, point-of-care biomarker of pulmonary inflammation in patients with viral-induced acute lung injury [1-3]. However, the effects of acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 (COVID-19)) infection on FeNO levels in human subjects requiring supplemental oxygen therapy is controversial. For instance, Exline et al [2] reported high FeNO levels in hospitalized, mechanically-ventilated patients with COVID-19 infection. By contrast, Lior et al [3] showed recently that FeNO levels were decreased in hospitalized patients with severe COVID-19 infection and that admission FeNO < 11.8 ppb heralded adverse outcomes.

To the best of our knowledge, no studies to date have determined FeNO levels in normoxic patients with COVID-19 infection seen in the emergency department. We posit that under these circumstances FeNO could be used as noninvasive biomarker to identify infected patients at greater risk of disease progression and/or worse prognosis and to devise a care plan accordingly. To begin to address these issues, we determined FeNO levels in normoxic adult patients with rapid polymerase chain reaction (PCR) test-documented COVID-19 infection seen in the emergency department of a large, tertiary care hospital in Chicago, IL, USA. None required supplemental oxygen nor received COVID-19-related medications at the time FeNO was determined.

A hand-held NIOX VERO® Airway Inflammation Monitor (Circassia Pharmaceuticals Inc., Morrisville, NC, USA) was used to determine FeNO levels in 18 eligible patients, 64 ± 15 years (mean ± standard deviation (SD); 17 males) presenting to the Emergency Department of Jesse Brown VA Medical Center and in 18 healthy, non-smoking volunteers between December 2020 and June 2021. The US Food and Drug Administration (FDA)-cleared NIOX VERO® monitor deploys an electrochemical sensor technology as analytical method and an external quality control procedure to ascertain reliability of measured values [4]. In each subject, FeNO determination conformed with the American Thoracic Society (ATS) clinical practice guidelines [5]. Although these patients presented with respiratory complaints, such as persistent cough and dyspnea, all were able to perform adequate FeNO measurements as instructed.

Data are reported as means ± SD. Statistical analysis was performed using paired Student's *t*-test. $P < 0.05$ was considered statistically significant. The study was approved by Jesse Brown VA Medical Center institutional review board (IRB) (approval number: 1574706-1).

Arterial oxygen saturation (SpO_2) in patients with COVID-19 was 96±3% during FeNO testing. FeNO levels in patients and healthy volunteers were 18.11 ± 10.07 and 13.33 ± 4.64 ppb, respectively (P = not significant (NS)). Fourteen patients (78%) were subsequently hospitalized of which one died.

Our small, single-site, prospective study shows that FeNO levels in normoxic adult patients presenting to the emergency department with COVID-19 infection are similar to those of healthy, non-smoking volunteers. This observation is noteworthy because most our patients (14/18) were subsequently hospitalized attesting to the severity of their illness. However, the small sample size precludes meaningful evaluation of FeNO as a simple, bedside, noninvasive biomarker of risk stratification of normoxic patients with COVID-19 infection seen in the emergency department.

The reason(s) underlying the discrepant reports about FeNO levels in hospitalized patients with COVID-19 infection is uncertain [2, 3]. Conceivably, differences in patient characteristics, such as age, sex, race/ethnicity, disease severity, and therapeutic interventions at the time of FeNO testing could account, in part, for these observations. For instance, hypoxia has been shown to increase FeNO levels while short-term hyperoxia decreases FeNO levels for several hours in human subjects [6, 7].

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In summary, we propose that larger, well-controlled, prospective studies are warranted to determine the utility of point-of-care FeNO monitoring as noninvasive biomarker of risk stratification of patients with COVID-19 infection seen in the emergency department.

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Conflict of Interest

The authors declare no conflicts of interest.

Informed Consent

All the informed consents were obtained.

Author Contributions

Zane Z. Elfessi: literature review, study design, investigation, data curation, analysis, interpretation, writing and editing. Brendan K Steadman: investigation, data curation, and editing. Israel Rubinstein: conceptualization, supervision, analysis, interpretation, writing and editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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