dead space fraction. Accordingly, the ventilatory ratio, a proxy of dead space, performs at least as well as the Pa_{O_2}/FI_{O_2} ratio in predicting mortality among patients with COVID-19 with ARDS (8). Di Fenza and colleagues report a subgroup analysis that stratified patients according to ARDS severity, with the greatest benefit appearing in patients with the most severe hypoxemia (Pa_{O_2}/FI_{O_2} ratio <100). Because part of the positive effects of NO administration is expected to be related to its vasoactive properties, it would be interesting to assess if NO could provide a significant clinical advantage in patients with a high versus a low ventilatory ratio (i.e., high vs. low alveolar dead space). This *post hoc* analysis, combined with the results stratified according to ARDS severity, may help clinicians identify patients with the highest likelihood of clinical benefit from NO as administered in this important randomized trial. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Eleuteri *et al.*: High-Dose Inhaled Nitric Oxide in Acute Hypoxemic Respiratory Failure: Need for Patient Phenotyping?

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From the Authors:

We thank Eleuteri and colleagues for recognizing the importance of our study on the role of high-dose inhaled nitric oxide (iNO) in improving systemic oxygenation in patients with COVID-19 (1). We appreciate the opportunity to engage in a meaningful dialogue about our work and have provided responses to each of the three comments raised by Eleuteri and colleagues.

First, maintaining oxygenation remains the cornerstone of the management of acute respiratory distress syndrome (ARDS). Several large, robust clinical trials support that maneuvers which improve oxygenation are associated with a decreased risk of mortality in patients with ARDS (2–4). Although multiorgan failure contributes significantly to mortality in patients with ARDS, including those with COVID-19, addressing hypoxemia remains a crucial aspect of patient care. It is conceivable that certain subgroups of patients with ARDS, particularly Black patients with nitric oxide cyclic guanosine 3′,5′-monophosphate system suppression or those with specific clinical characteristics or phases of ARDS, might derive more substantial advantages from iNO therapy. Exploring these nuances in patient selection and refining treatment protocols could be pivotal in unraveling the full therapeutic potential of iNO.

Second, we agree that NO production is increased in inflammatory conditions through the inducible nitric oxide synthase

*L.B. and P.A. contributed equally and are considered co–senior authors of this work.

†Dr. Berra filed a patent application on June 7, 2021, for nitric oxide delivery in COVID-19 disease: PCT application number: PCT/US2021/036269.

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Table 1. Change in Inflammatory Markers at 48 Hours, Stratified by Study Arm

Marker	Group (*n*)	Unadjusted Analysis: Mean (95% CI)†	Unadjusted Analysis: Group Difference (95% CI)	Unadjusted Analysis: *P* Value	Adjusted Analysis*: Mean (95% CI)†	Adjusted Analysis*: Group Difference (95% CI)	Adjusted Analysis*: *P* Value
CRP	NO (32)	31.8 (−3.5, 67.2)	27.8 (−22.5, 78.2)	0.27	33.8 (1.0, 66.7)	29.6 (−15.1, 74.3)	0.18
	Control (31)	4.0 (−31.9, 39.9)			4.2 (−31.5, 39.8)		
Ferritin	NO (30)	−50.2 (−454.1, 353.7)	−24.1 (−605.3, 557.2)	0.93	−176.9 (−587.9, 234.1)	−169.7 (−737.9, 399.4)	0.55
	Control (28)	−26.1 (−444.1, 391.9)			−7.7 (−445.1, 429.7)		

Definition of abbreviations: CI = confidence interval; CRP = C-reactive protein; NO = nitric oxide.
*Adjusted for age, age^2, sex, race, and body mass index.
†Values depict least squares mean and 95% confidence interval.

pathway (5). This induction of NO synthesis and production of reactive oxygen species in inflammation serves as a mediator of the immune response (5). However, iNO is unlikely to play a role in the inflammatory response because of its rapid degradation (6). On the contrary, iNO has been shown to have potent antiinflammatory action, which improves allograft function after liver transplant (7, 8) and reduces kidney injury in cardiac surgery (8). Specifically, during hemolysis, NO has been shown to react rapidly with plasma-free oxyhemoglobin to form methemoglobin, thereby reducing the oxidative burden (6). This antioxidant action of iNO led to the hypothesis that iNO reduces the risk of postoperative risk of acute kidney injury in cardiac surgery patients in whom cardiopulmonary bypass was used (9). Cardiopulmonary bypass is associated with hemolysis, and the increase in oxyhemoglobin leads to precipitation of acute kidney injury secondary to oxidative damage (9). Administration of iNO was hypothesized to convert oxyhemoglobin into methemoglobin and reduce the risk of postoperative acute kidney injury (9). This randomized controlled trial of 240 patients showed that iNO reduced the risk of postoperative acute kidney injury in cardiac surgery patients by 22% through its hypothesized antioxidant action (9). Furthermore, longitudinal measures of inflammatory markers such as C-reactive protein (CRP) and ferritin were only available in a subset of the current study population. Among the 63 patients with CRP values and 58 patients with ferritin values, we found that the change in CRP (mean difference by treatment group, 29.6; 95% confidence interval, −15.1, 74.3) and ferritin (mean difference by treatment group, −169.7; 95% confidence interval, −737.9, 399.4) concentrations at 48 hours were similar in both study arms (Table 1). Further studies are needed to assess the role of inflammatory markers in guiding the selection of patients with ARDS who would benefit the most from treatment with iNO therapy.

Third, we agree that COVID-19 ARDS is associated with microvascular thrombosis and microangiopathy, leading to profound perfusion abnormalities, as highlighted in our article (10). We were interested in investigating the impact of iNO on the ventilatory ratio in our trial participants (1). We found that iNO did not improve the ventilatory ratio at 48 hours (1). In addition, we also present a *post hoc* analysis of the effect of iNO on improving oxygenation at 48 hours stratified by the ventilatory ratio. The study population was stratified using the median ventilatory ratio of 1.54 into low ($n = 42$ in the treatment arm and 48 in the control arm) and high ($n = 45$ in the treatment arm and 47 in the control arm) ventilatory ratio. We found that the probability that iNO would increase the Pa_{O_2}/FI_{O_2} ratio at 48 hours was similar in both study groups, at 94.2% in the low ventilatory ratio group and 98.6% in the high ventilatory ratio group (Figure 1). Therefore, patients with severe ARDS (Pa_{O_2}/FI_{O_2} ratio, <100 mm Hg) may reap the greatest

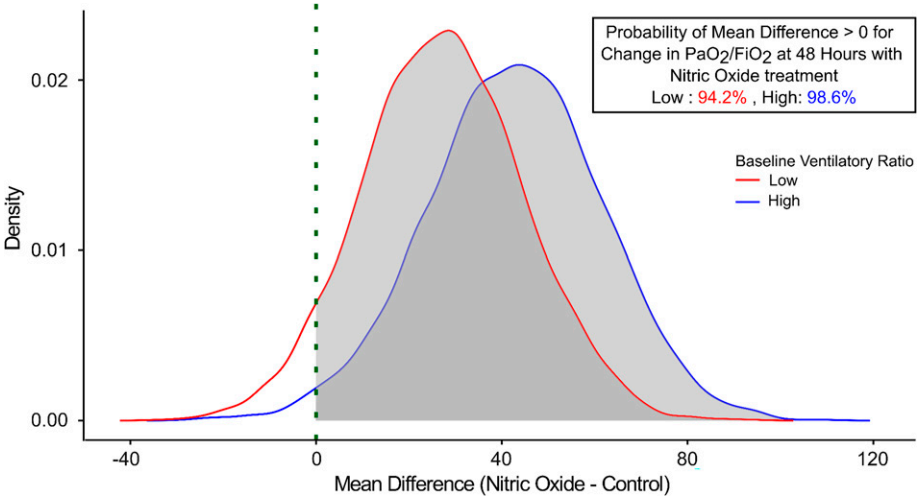

Figure 1. Posterior probability curves for change in Pa_{O_2}/FI_{O_2} ratio at 48 hours with inhaled nitric oxide therapy stratified by ventilatory ratio.

benefit of iNO therapy, regardless of their ventilatory ratio. Precision phenotyping of ARDS based on various factors, such as clinical, physiological, and molecular markers, to better understand and tailor treatment approaches for specific subtypes or manifestations of the condition is warranted. ■

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Erratum: Idiopathic Pulmonary Fibrosis Is Associated with Common Genetic Variants and Limited Rare Variants

In the article by Peljto and colleagues published in the December 15, 2023 issue of the *Journal*, the authors incorrectly assigned sex to a small proportion of subjects in the validation cohort. The corrected data resulted in a change of the sex variable for 74 of 916 cases included in the validation analyses. Since some of the analyses adjusted for sex, there were minor changes to the *P* values reported in the article; there were no changes to the values published for the discovery cohort. The incorrect *P* values appear in the fourth column of Table 2 and the fourth and sixth columns of Table 3. The corresponding *P* values in the Results section have also been updated. The authors state that none of the conclusions of the article have changed.

For the convenience of our readers, the *Journal* is replacing the online version of the article with a corrected version. ■

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