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Inhaled nitric oxide minimally improves oxygenation in COVID-19 related acute respiratory distress syndrome

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Editor—Inhaled nitric oxide (iNO) diffuses across the alveolar capillary membrane and acts on vascular smooth muscle to increase vasodilation, resulting in increased blood flow to ventilated alveoli and improved oxygenation. Despite the lack of conclusive evidence demonstrating survival benefit, iNO is used as a rescue strategy in refractory hypoxaemia.[1,2] Patients with coronavirus disease 2019 (COVID-19) related acute respiratory distress syndrome (ARDS) have a significant burden of vascular endothelial injury and pulmonary microthrombi compared with patients with ARDS not caused by COVID-19.[3,4] We therefore hypothesised that patients with COVID-19 related ARDS would have a blunted increment in PaO_2/FiO_2 ratio in response to iNO compared with patients with ARDS not caused by COVID-19.

We conducted a single-centre retrospective case–control study of patients with ARDS treated with iNO at University College London Hospital (UCLH) between March 1 and June 30, 2020. Data on consecutive patients with ARDS not caused by COVID-19 receiving iNO over the previous 2 yr were used for comparison. Data were extracted from electronic healthcare records on patient characteristics, ventilatory parameters, highest iNO dose, fluid balance on the day of iNO initiation, steroid use, and change in PaO_2/FiO_2 ratio over 24 h. A 24 h period was chosen to both allow time to titrate the iNO dose to maximal effect, and to assess whether there was sustained benefit. Data and materials are available upon reasonable request.

As this was a retrospective observational study, we did not define any sample size. Anonymised data were used for analysis. Complete case analysis was used where there was missing data. Continuous and categorical variables are reported as median (inter-quartile range) and *n* (%), respectively. For comparison of continuous variables, Mann–Whitney *U*-test was used for comparison between two groups. Categorical data were compared using the χ^2 test. Statistical analysis was performed and graphs constructed using Prism (GraphPad Software, version 5.0d; GraphPad Software, Inc., San Diego, CA, USA). Ethical reporting of observational data on critical care patients at UCLH is covered by the National Research Ethics Service (14/LO/103).

Of 154 patients admitted with COVID-19, 99 (64%) received invasive mechanical ventilation (IMV). Of those requiring IMV, 27 (27%) received inhaled NO. Comparison was made against 91 patients with ARDS not caused by COVID-19, of whom 20 (22%) received iNO. Seven (35%) patients with ARDS not caused by COVID-19 and six (22%) patients with COVID-19 related ARDS who received iNO were excluded from the final analysis as they did not survive 24 h from iNO initiation.

Among the patients with ARDS not caused by COVID-19, nine patients had bacterial pneumonia, one had intra-abdominal sepsis, one had fungal chest infection, and two had viral influenza after chemotherapy. The time from admission to ICU to use of iNO was similar between patients with COVID-19 and ARDS not caused by COVID-19 (Supplementary data). Patients in both groups were treated with ARDS-net lung protective ventilation.

Patients in both groups were of similar age and had a similar PaO_2/FiO_2 ratio on initiation of iNO (Supplementary Table 1). More males were in the COVID-19 related ARDS group. There were no differences between groups in maximal dose of iNO, mode of ventilation, mean airway pressure, PEEP,

pulmonary compliance, driving pressure, tidal volume, fluid balance, or use of steroids in the 24 h from initiation of iNO. However, the increment in PaO_2/FiO_2 ratio after iNO was significantly lower in COVID-19 related ARDS patients compared with ARDS not related to COVID-19 (3% [−17% to 26%] *vs* 47% [6−54%]; $P<0.05$) (Fig. 1; Supplementary Table S1).

Venous thromboembolism (VTE) was diagnosed in seven (35%) COVID-19 patients. Seven patients underwent CT pulmonary angiography, of which two patients had evidence of pulmonary emboli. A further 10 patients underwent lower limb Doppler ultrasonography, of whom five patients had a diagnosis of deep vein thrombosis.

Only eight (40%) patients with COVID-19 related ARDS had an increment in PaO_2/FiO_2 ratio >10% compared with 10 patients (77%) with ARDS not related to ARDS ($P=0.07$). Baseline PaO_2/FiO_2 ratio, dose of iNO, use of steroid, prone position ventilation, C-reactive protein, D-dimer levels, N-terminal B-type natriuretic peptide (NT-BNP) levels, fluid balance, driving pressure, days from ICU admission to iNO, pulmonary compliance, diagnosis of VTE, or BMI did not discriminate between COVID-19 patients who responded to iNO or not (Supplementary Fig. S1).

The potential benefit of iNO in reducing pulmonary shunt in COVID-19 related ARDS has been postulated.[5] However, we found that the increase in PaO_2/FiO_2 ratio in COVID-19 ARDS patients in response to iNO was significantly lower compared with ARDS patients without ARDS, consistent with another published series.[6] Pulmonary vascular endothelial dysfunction and microthrombi are hallmarks of COVID-19-induced lung damage, and this may impair iNO-induced pulmonary vasodilation.[4,7] In contrast, patients with coronavirus-related severe acute respiratory syndrome, where increased thrombosis was not a hallmark, demonstrated significant PaO_2/FiO_2 ratio improvements in response to iNO.[8]

Early in the COVID-19 disease process, hypoxaemia develops despite good pulmonary compliance, and a pulmonary vasculopathy is implicated.[9] Later on, compliance decreases to that seen with 'classical' ARDS.[9,10] Our COVID-19 patients who received iNO did so as a rescue treatment late in the disease, 12 days after ICU admission. Although no differences were seen in D-dimer values between responders and non-responders, levels were significantly elevated in most patients. The benefits of iNO in COVID-19 related ARDS may extend beyond its effects on pulmonary vasculature.[11] However, the theoretical

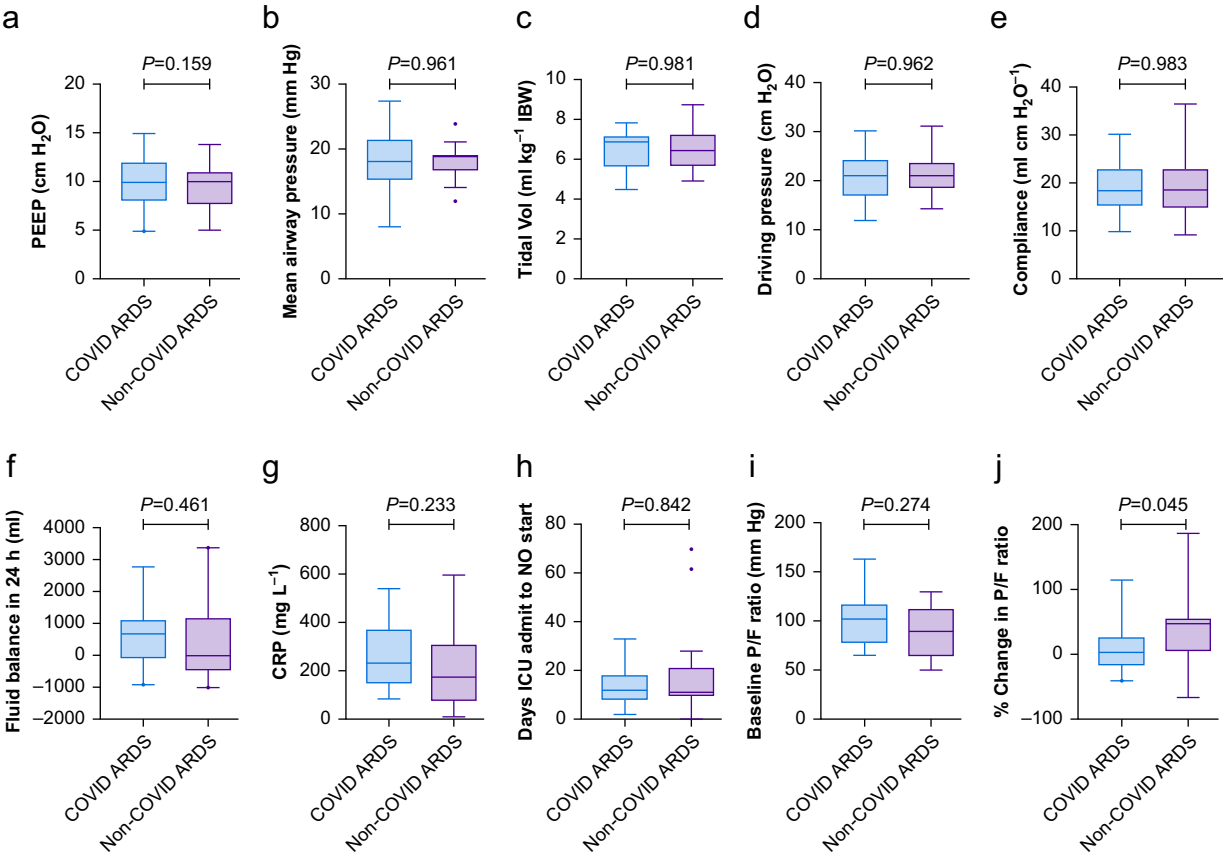

Fig 1. Baseline patient characteristics, C-reactive protein (CRP), and PaO_2/FiO_2 ratio in ARDS patients with and without COVID-19. There are no differences in ventilatory parameters, CRP, or baseline PaO_2/FiO_2 ratio between acute respiratory distress syndrome (ARDS) patients with and without COVID-19 who received inhaled nitric oxide (iNO). The increase in PaO_2/FiO_2 ratio of COVID-19 ARDS patients in response to iNO was significantly lower compared with non-COVID ARDS. IBW, ideal body weigh; PF ratio, PaO_2/FiO_2 ratio.

benefits of iNO in inhibiting early-stage viral replication are unlikely to have benefited patients in whom iNO was administered 12 (8–18) days after ICU admission.

As with all retrospective analyses, we acknowledge the possibility of residual confounding, and that results are associative. The small number of COVID-19 related ARDS patients included also warrants caution in interpreting the findings. CT imaging was not performed on all patients because of clinical instability or lack of a clear indication; thus, the presence of major emboli may have been missed in some patients. Alternatively, lack of identification by CT does not exclude the presence of multiple pulmonary microthrombi contributing to increased pulmonary vascular resistance and right heart dysfunction. Echocardiography was not performed systematically to assess impact on cardiac anatomy and function, but NT-BNP levels were significantly elevated and raised pulmonary pressures were commonplace findings when measured. NT-BNP and D-dimer values were not routinely collected in ARDS patients before the COVID-19 pandemic so comparisons cannot be made.

In summary, more than half of patients with refractory hypoxaemia secondary to COVID-19 ARDS did not show an increase in PaO_2/FiO_2 ratio in response to iNO. This response was much lower compared with a cohort with ARDS not related to COVID-19. Further work is required to ascertain if this lack of response to iNO is diagnostic for degree of pulmonary thromboembolism.

Authors' contributions

Study design: NA
Data collection: AL, CM, RS, SB
Statistics: NA
Drafting manuscript: NA
Finalising manuscript: MS, NA

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.10.011.

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Response of US hospitals to elective surgical cases in the COVID-19 pandemic

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