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Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19 pneumonia

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Dear Editor,

Patients with ARDS due to COVID-19 are characterised by poor oxygenation with a various extent of pulmonary alterations [1]. Ventilation strategies for COVID-19 patients have been suggested basing on the pathophysiological evidence to date [1]; however, there are no data regarding the use of inhaled nitric oxide (iNO). We report herein our experience of iNO administration in COVID-19 mechanically ventilated patients with refractory hypoxaemia and/or right ventricular (RV) dysfunction. Refractory hypoxaemia was defined as $PaO_2/FiO_2 < 100$ despite high PEEP (≥ 10 cmH_2O) and prone position. RV dysfunction was defined as acute *cor pulmonale* at echocardiography with hemodynamic impairment requiring infusion of inotropic drugs [2].

The NO/nitrogen mixture was introduced into the inspiratory limb of the ventilator tubing. Respiratory and haemodynamic parameters were collected immediately before iNO administration (t_0) and after 15–30 min (t_1). Responders were defined by an increase of $PaO_2/FiO_2 >$ 20% compared to t_0 [3].

Results in the text are shown as median [IQR] or number (%). Wilcoxon test for paired samples and Mann-Whitney test, as appropriate (MedCalc version 19.2 MedCalc Software), were performed considering $p < 0.05$ as significant.

iNO was used in sixteen out of 72 (22.2%) consecutive mechanically ventilated patients (66.0 [59.6–69.7] years old; 93% male). All patients required iNO for refractory hypoxaemia of whom 4 (25%) had also superimposed RV dysfunction, in 1 case associated with pulmonary embolism. The iNO dosage was 25 [20–30] parts per million (ppm).

Respiratory parameters at t_0 and t_1 are shown in Table 1. Overall, iNO did not improve oxygenation in our population. Only 4 (25%) patients were responders, of whom 3 have superimposed RV dysfunction, showing a median increase of PaO_2/FiO_2 of 26.9% [24.1–45.5]. A trend towards a larger improvement of oxygenation was observed in patients with RV dysfunction as compared with those without (PaO_2/FiO_2 increase 24.1% [9.2–43.5] vs. 3.3% [−10.8–11.5], $p = 0.069$). Additionally, in responders, PaO_2/FiO_2 was 125.9 [82.2–259.2] at t_1 and did not change ($p = 0.875$) 24 h later (146.4 [102.2–225.1]).

iNO is a free radical gas that diffuses across the alveolar-capillary membrane into the subjacent smooth muscle of pulmonary vessels enhancing endothelium-dependent vasorelaxation and improving oxygenation by increasing blood flow to ventilated lung units [3]. In previous studies, iNO was effective in improving PaO_2/FiO_2 and oxygenation index, although it failed in reversing acute lung injury, reducing mechanical ventilation days and mortality [4].

In our population, the improvement of oxygenation in responders was probably magnified by an iNO-induced decrease of RV afterload, enhancing cardiac output and finally leading to an increase of mixed venous oxygen saturation.

Although the reason why patients with refractory hypoxaemia without RV dysfunction were not responder is yet to be determined, some speculation can be done. Severe endothelial injury with cytoplasmic vacuolization

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Table 1 Patients respiratory and hemodynamic parameters at the two time points

Parameter	Pre iNO (t_0)	Post iNO (t_1)	*p* value
SBP, mmHg	127.0 [114.0–137.5]	119.0 [110.0–138.0]	0.454
MAP, mmHg	83.5 [80.5–93.5]	78.0 [74.5–85.5]	0.144
HR, bpm	89.5 [80.5–99.7]	88.0 [75.0–100.0]	0.159
pH	7.27 [7.22–7.35]	7.31 [7.24–7.36]	0.049
$PaCO_2$, mmHg	59.8 [52.5–76.5]	60.9 [50.8–65.7]	0.002
PaO_2, mmHg	79.7 [58.9–87.2]	77.1 [63.5–88.6]	0.252
PaO_2/FiO_2	91.7 [62.1–109.2]	91.5 [67.1–106.7]	0.274
MetHb, %	1.18 [1–1.3]	1.3 [1.1–1.4]	0.16
FiO_2	87.5 [80–95]	87.5 [80–95]	1
PEEP, cmH_2O	13.0 [10.0–15.0]	13.0 [10.0–15.0]	1
MV, L/min	9.7 [8.1–11.3]	10.3 [8.7–11.4]	0.204
Peak pressure, cmH_2O	30.5 [27.5–33.5]	30.5 [26.0–33.0]	0.641

Results in the table are shown as mean [CI 95%]
SBP systolic blood pressure, *MAP* mean arterial pressure, *HR* heart rate, *bpm* beats per minutes, *MetHb* methemoglobin, *PEEP* positive end-expiatory pressure, *MV* minute volume

and cell detachment in pulmonary middle-small arteries can make the pulmonary vessels less reactive to iNO stimulation [1, 5, 6]. This could also explain the loss of hypoxic vasoconstriction and lung perfusion regulation. However, whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus, part of the ARDS pathophysiology or the intertwine of both is still undetermined. Moreover, prone position and iNO were used in refractory hypoxaemia as an escalating treatment strategy. Therefore, a positive response to the prone position may have precluded the enrolment in our study of patients that could positively respond to iNO.

Conclusion

Overall, iNO did not improve oxygenation in COVID-19 patients with refractory hypoxaemia, when administered as a rescue treatment after prone position. A subgroup of patients with RV dysfunction was better iNO responders probably due to the haemodynamic improvement associated with RV unloading.

The word count of our manuscript is just beyond the limit suggested by the editorial rules as we felt that the fluency and completeness would be sacrificed in further shorten the text. However, we are willing to cut some part if strongly advised by the editorial office.

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Authors' contributions

All authors contributed equally to the data collection and redaction, writing and final revision before submission of the paper. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Informed consent was collected following the ad hoc procedures defined by the local Ethics Committee of Fondazione Policlinico San Matteo IRCCS for the COVID-19 pandemic.

Competing interests

FM received fees for lectures from GE Healthcare, Hamilton Medical, SEDA SpA, outside the present work. SM received fees for lectures from GE Healthcare, outside the present work. GT received fees for lectures by GE Healthcare, outside the present work. MP, VD and GR have nothing to disclose.

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