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# Effects of rescue inhaled nitric oxide on right ventricle and pulmonary circulation in severe COVID-related acute respiratory distress syndrome

Manuela Bonizzoli, MD\*, Chiara Lazzeri, MD, Giovanni Cianchi, MD, Cristiana Guetti, MD, Giorgio Enzo Fulceri, MD, Filippo Socci, MD, Adriano Peris, MD

Intensive Care Unit and Regional ECMO Referral Centre, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

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## ABSTRACT

**Purposes:** To assess the effects of inhaled Nitric Oxide (iNO) on right ventricle dimension and function and systolic pulmonary arterial pressures in severe Acute Respiratory Distress (ARDS) due to Sars-Cov2 (COVID) infection. **Materials and methods:** We assessed the effects of iNO on right ventricle dimension and function and systolic pulmonary arterial pressures in 12 consecutive COVID-related ARDS patients by means of serial echocardiographic exams (baseline, 12 and 24 h since iNO start). **Results:** Inhaled NO administration did not influence systolic pulmonary arterial pressures nor RV dimension and function. No changes were detectable in ventilatory data with iNO administration. Considering the negligible effect on oxygenation, iNO use was discontinued in all cases. **Conclusions:** In COVID-related severe ARDS iNO administered as rescue therapy is not able to ameliorate oxygenation nor pulmonary hypertension, as assessed by serial echocardiograms. This finding may be explained by the diffuse loss of hypoxic pulmonary vasoconstriction with increased perfusion around alveolar consolidations which characterizes COVID-related severe ARDS.

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## 1. Introduction

Inhaled nitric oxide therapy (iNO) has been proposed as a rescue therapy in patients with Sars-CoV2 (COVID)-related Acute Respiratory Distress Syndrome (ARDS) [1] but no beneficial effects has so far been reported [2]. In the United States clinical trials have begun and a phase 2 clinical trial of inhaled NO is being conducted for mechanically ventilated patients with COVID-related ARDS to assess the effects of this drug [3–5].

The rationale for iNO use relies mainly on its antiinflammatory properties, which consist chiefly in reducing inflammatory cell-mediated lung injury through the inhibition of neutrophil activation. It also exhibits selective pulmonary vasodilation, thus lowering pulmonary vascular resistance and reducing ventilation/perfusion matching.

Echocardiography proved to be a promising clinical tool in COVID-related ARDS, by documenting that right ventricle (RV) dilatation and dysfunction and increased systolic pulmonary hypertension do represent prognostic indicators in these patients [6,7].

We assessed, by means of serial echocardiographic exams, the effects of iNO administered as rescue therapy on RV dimension and function and systolic pulmonary arterial pressures in 12 consecutive patients with severe COVID-related ARDS patients.

## 2. Methods

In our case series study, we enrolled all patients with COVID-related ARDS refractory to conventional treatment (protective ventilation and pronation) submitted to iNO and consecutively admitted to our ICU (which is an ECMO referral center, Azienda Ospedaliero-Universitaria Careggi) from 1st April 2020 to 31st March 2021. The study protocol was approved by our Ethical Committee (n.17024, approved on March 31st 2020). The written informed consent for each patient was waived for emerging infectious disease. Data were prospectively recorded and retrospectively analyzed.

On ICU admission we measured: Troponin T (pg/ml), N-terminal-pro Brain Natriuretic Peptide (NT-BNP, pg/ml), C-reactive Protein (CRP, mg/dl) creatinine (mg/dl), Lactate dehydrogenase (LDH, UI/L), D-dimer (ng/ml), and interleukin 6 (IL-6, pg/ml)

According to our protocol [6,8,9], a transthoracic echocardiographic examination was performed before (Time 1) and during iNO administration (12 h after iNO initiation – Time 2- and 24 h since iNO start – Time 3). A tank with 450 ppm NO in nitrogen was connected to the

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\* Corresponding author at: Intensive Care Unit and Regional, ECMO Referral Centre Emergency Department, Largo Brambilla 3, 50134 Florence, Italy.  
E-mail address: [manuelabonizzoli@gmail.com](mailto:manuelabonizzoli@gmail.com) (M. Bonizzoli).

inspiratory limb of the ventilatory circuit; NO was delivered during the inspiratory phase using a digital system (Optikonox, Air Liquide, Milan, Italy). iNO was administered at 40 ppm. A positive response to iNO was defined as an improvement in oxygenation, as indicated by an increase in P/F ratio. Echocardiographic exams were performed by three intensivists (CG, FS, CL).

The right ventricle size is assessed by the RV end-diastolic area (EDA) and the ratio between EDAs of the right and left ventricles was calculated (RVEDA/LVEDA). Systolic pulmonary artery pressure (sPAP) is obtained using the simplified Bernoulli's equation:  $4 \cdot (V_{\max} \text{ tricuspid regurgitation})^2 + \text{central venous pressure (CVP)}$ . Each measure is performed three times, and the mean value was recorded. Tricuspid Annular Plane Excursion (TAPSE) is measured, as the difference of displacement during diastole and systole.

RV dilatation and dysfunction (RVDys) was defined in presence of RVEDA/LVEDA >0.6 and TAPSE <15 mm. The ratio TAPSE/sPAP was calculated to assess right ventricle/pulmonary artery coupling, as index of RV function [10].

Lung ultrasound score (LUS) was measured as previously described [9]. The following point scoring system was employed by region and ultrasound pattern as: A = 0 point, B1 = 1 point, B2 = 2 points, C = 3 points. Thus, a LUS of 0 is normal, and 36 would be the worst.

All ultrasound (lung and cardiac) procedures are performed using the necessary protective equipment for professionals [6,8,9].

### 2.1. Statistical analysis

Data have been stored in a dedicated data-base and analyzed with SPSS for Windows 20.0 (SPSS Inc., Chicago, IL). *P* value less than 0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean  $\pm$  standard deviation (SD) or median (range), as needed. The variations in time domain have been analyzed by means of repeated measures ANOVA.

## 3. Results

Our series includes 12 consecutive patients with COVID-related ARDS treated with iNO therapy. Clinical characteristics and biochemical data are depicted in Table 1. Males were more frequent (8/12, 66%) and comorbidities were common, as indicated by Charlson's index. Renal replacement therapy was needed in three patients (3/12, 25%). Inhaled NO was started 36 h (median, range 6–96) since ICU admission.

**Table 1**  
Study population clinical characteristics.

Parameter	Value
Number	12
Age (mean $\pm$ SD)	61.7 $\pm$ 17
Gender (males, n, %)	8 (66%)
BMI (mean $\pm$ SD)	29 $\pm$ 4
Charlson's index (mean $\pm$ SD)	4 $\pm$ 3
Time from symptoms' onset to ICU (days, median, IQR)	8.5 (7–10)
SOFA (median, IQR)	6 (5–8)
Mechanical Ventilation duration (days, median, IQR)	10 (8–19.5)
ICU death (n,%)	7 (58%)
LOS (days, median, IQR)	11.5 (9–21)
<i>Biochemical data</i>	
Creatinine (mg/dl, median, IQR)	0.83 (0.66–1.75)
LDH (IU, median, IQR)	373 (336–378)
D-dimer (ng/ml, median, IQR)	2412 (1660–8116)
CRP (median, IQR)	129 (32–158)
IL-6 (pg/ml, median, IQR)	110 (33–137)
Troponin (pg/ml median, IQR)	16 (8–75)
NT pro BNP (pg/ml median, IQR)	1650 (674–3162)

BMI: body mass index; ICU: intensive care unit, SOFA: LOS: length of stay, LDH: lactose dehydrogenase, CRP: C Reactive Protein, IL-6: interleukin-6, NT-pro-BNP: N-terminal pro brain natriuretic peptide; SD: standard deviation, IQR: interquartile range.

Table 2 shows echocardiographic findings and ventilatory data, obtained by serial assessments, during iNO administration, before start (Time 1) and during administration (at 12 and 24 h since iNO start). All patients showed P/F values <150. At baseline, RV dilatation and dysfunction was detectable in one third of the entire population (4/12, 33%), while reduced LVEF (< 50%) was observed in three patients (3/12, 25%) due to preexistent heart disease.

All patients showed systolic pulmonary arterial hypertension. Inhaled NO administration did not influence systolic pulmonary arterial pressures, RV dimension and function nor RV/pulmonary arterial coupling as indicated by TAPSE/sPAP. No changes were detectable in ventilatory data with iNO administration. Only one patient showed an increase in P/F values from time 1 to time 3. Nevertheless, this patient developed on day 2 worsening hypoxemia and ECMO support was needed. Considering the negligible effect on oxygenation, iNO use was discontinued in all cases. As shown in Table

In our series, four patients needed ECMO support, among whom two patients survived and were discharged from ICU and then returned home. Seven patients were not eligible for ECMO support due to age and comorbidities and died during ICU stay.

## 4. Discussion

The main finding of the present investigation, performed in COVID-related severe ARDS, is that iNO administration is not able to ameliorate oxygenation nor pulmonary hypertension, as assessed by serial echocardiographic examinations performed before and during iNO administration.

It can be hypothesized that the lack of iNO effects on pulmonary vasculature and oxygenation in COVID related ARDS may be explained by the diffuse loss of hypoxic pulmonary vasoconstriction with increased perfusion around alveolar consolidations, previously described in COVID-related ARDS, especially in more advanced disease conditions [1]. Our series is characterized by COVID disease severity as inferred by the low P/F ratio, high LUS values and echocardiographic data, that is the presence of increased systolic pulmonary arterial pressure in all patients, RV Dys in about one third of patients and low values of RV/pulmonary arterial coupling.

Our findings are in keeping with those by Ferrari et al. [10] who documented negligible effects on oxygenation of iNO in ten mechanically ventilated patients with severe ARDS due to COVID disease. We extend these findings by assessing the iNO effects on pulmonary circulation, RV chamber and RV/pulmonary arterial coupling by serial echocardiograms performed at 12 and 24 h since iNO start. Differently from Ferrari et al. [10], serial echocardiograms allowed the assessment of heart-lung interactions by means of measurements of RV dimensions/function and pulmonary arterial pressures. The lack of changes in RV chamber and systolic pulmonary arterial pressures, and especially in RV/pulmonary arterial coupling indirectly confirm that iNO has negligible effects on pulmonary circulation in these patients.

To date, iNO administration in COVID-ARDS is still subject of debate since data are scarce and heterogeneous, mainly due to variable doses used and difference in selection population criteria (in primis disease severity). In a small group of mild ARDS (P/F < 150) due to COVID disease, lower iNO doses (10 ppm) were associated with an increase in PaO<sub>2</sub>/FiO<sub>2</sub> over 20%, during over 30 min following its administration, in the 65% of the overall population (34 patients). No effect of iNO use was observed in patients with acute cor pulmonare [11]. On the contrary, two other reports concluded in the absence of effectiveness of iNO [2,3]. Tavazzi et al. [12] reported their experience of iNO therapy (25 ppm) in 16 COVID mechanically ventilated patient with refractory hypoxemia (P/F <100) and/or RV dysfunction (4 patients). The administration of iNO failed to improve oxygenation in their population, though four (25%) patients were responders, among whom three had RV dysfunction. In our series four patients (33%) showed RV dysfunction but iNO failed to improved oxygenation in these patients. Further research

**Table 2**  
Echocardiographic, ventilatory and hemodynamic data before and during iNO administration.

Parameter	Time 1	Time 2	Time 3	p
LVEF (% mean $\pm$ SD)	53 $\pm$ 8	54 $\pm$ 9	54 $\pm$ 6	F = 0.006, p = 0.939
RV dimension (mm, mean $\pm$ SD)	27 $\pm$ 4	27 $\pm$ 3	26 $\pm$ 3	F = 0.0577, p = 0.944
RV/LV (mean $\pm$ SD)	0.53 $\pm$ 0.16	0.53 $\pm$ 0.17	0.51 $\pm$ 0.16	F = 0.187, p = 0.829
TAPSE (mm, mean $\pm$ SD)	18 $\pm$ 6	19 $\pm$ 7	18 $\pm$ 7	F = 0.164, p = 0.985
RV dil/dysf (n, %)	4	4	4	
SPAP (mmHg, mean $\pm$ SD)	54 $\pm$ 7	58 $\pm$ 5	59 $\pm$ 7	F = 0.212, p = 0.135
TAPSE/SPAP (mm/mmHg, mean $\pm$ SD)	0.36 $\pm$ 0.16	0.32 $\pm$ 0.12	0.30 $\pm$ 0.12	F = 0.246, p = 0.782
pH (mean $\pm$ SD)	7.35 $\pm$ 0.05	7.33 $\pm$ 0.08	7.36 $\pm$ 0.04	F = 0.486, p = 0.616
LUS (mean $\pm$ SD)	29 $\pm$ 2	28 $\pm$ 3	29 $\pm$ 1	F = 0.951, p = 0.396
P/F (mean $\pm$ SD)	67 $\pm$ 26	82 $\pm$ 37	83 $\pm$ 42	F = 0.722, p = 0.493
PaO <sub>2</sub> (mean $\pm$ SD)	63 $\pm$ 18	74 $\pm$ 30	70 $\pm$ 23	F = 0.711, p = 0.498
PaCo <sub>2</sub> (mean $\pm$ SD)	58 $\pm$ 12	53 $\pm$ 10	53 $\pm$ 9	F = 0.814, p = 0.451
Lactate (mg/dl, mean $\pm$ SD)	1.83 $\pm$ 0.7	2.07 $\pm$ 0.7	1.95 $\pm$ 0.5	F = 0.270, p = 0.763
PEEP (mean $\pm$ SD)	11 $\pm$ 2	10 $\pm$ 3	11 $\pm$ 2	F = 0.004, p = 0.952
TV (ml) (mean $\pm$ SD)	451 $\pm$ 113	445 $\pm$ 71	471 $\pm$ 89	F = 0.302, p = 0.741
MAP (mmHg, mean $\pm$ SD)	76 $\pm$ 9	77 $\pm$ 5	75 $\pm$ 5	F = 0.184, p = 0.832
Noradrenaline (ug/kg/min) (mean $\pm$ SD)	0.19 $\pm$ 0.11	0.21 $\pm$ 0.13	0.22 $\pm$ 0.11	F = 1.420, p = 0.250

LVEF: left ventricular ejection fraction; RV: right ventricle; sPAP: systolic pulmonary arterial pressure, P/F: pO<sub>2</sub>/FIO<sub>2</sub> ratio, PEEP: pressure end-expiratory pressure, TV: tidal volume, LUS: lung ultrasound score, MAP: mean arterial pressure.

should probably be focused on assess iNO effect specifically in patients with RV dysfunction.

The novelty of our investigation relies, in our opinion, in the serial evaluations of RV and pulmonary circulation by means of combined cardiac and lung ultrasound during iNO administration.

In our series, the possibility that the lack of benefits of iNO may be related to severity of COVID-related ARDS cannot be ruled out. Future research should investigate the effects of iNO in mild-to moderate COVID-related ARDS, by means of combined lung and cardiac serial assessments.

A possible limitation of the present study is represented by the small number of patients, enrolled in a single center investigation. The small number of patients and COVID disease severity may have accounted for the lack of beneficial effects of iNO administration. Further research should be performed in larger cohorts of patients, specifically addressing the role of iNO in mild to-moderate COVID-related ARDS and/or the effects of higher iNO doses. However each patient was repeatedly assessed by serial echocardiographic examinations, performed at 12 and 24 h since iNO start, since our investigation was aimed at assessing iNO effects on RV and pulmonary circulation. Another possible limitation may be the use of echocardiography for the estimation of pulmonary arterial pressures, as opposed to a pulmonary artery catheter, but this is rather impractical during a pandemic setting.

#### Declaration of Competing Interest

No conflict of interest.

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