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ORIGINAL ARTICLE

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Effects of inhaled nitric oxide in COVID-19–induced ARDS – Is it worthwhile?

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Background: Changes in pulmonary hemodynamics and ventilation/perfusion were proposed as hallmarks of Coronavirus disease 2019 (COVID-19)–induced acute respiratory distress syndrome (ARDS). Inhaled nitric oxide (iNO) may overcome these issues and improve arterial oxygenation.

Methods: We retrospectively analyzed arterial oxygenation and pulmonary vasoreactivity in seven COVID-19 ARDS patients receiving 20 ppm iNO for 15-30 minutes.

Results: The inhalation of NO significantly improved oxygenation. All patients with severe ARDS had higher partial pressures of oxygen and reduced pulmonary vascular resistance. Significant changes in pulmonary shunting were not observed.

Conclusion: Overall, iNO could provide immediate help and delay respiratory deterioration in COVID-19–induced moderate to severe ARDS.

1 | INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic progresses and it`s clear that a COVID-19–induced acute respiratory distress syndrome (ARDS) significantly differs from other causes of ARDS. Gattinoni et al proposed two different types of disease. L-type disease is characterized by low elastance, low lung weight and low ventilation to perfusion (VA/Q) ratios due to the loss of hypoxic pulmonary vasoconstriction. This may progress to H-type disease, which resembles "typical ARDS" with low compliance and high lung weight.[1] Hereby, deranged pulmonary vasoreactivity may not only be related to vasodilation, but also vasoconstriction, coagulation disorders and microthrombi. Elevated d-dimers are commonly found.[2] In this regard, therapeutic benefits may be achieved via the administration of inhaled nitric oxide (iNO). It acts as a selective pulmonary arterial vasodilator, alleviating the ventilation/perfusion ratio.[3] However, to date no ARDS survival benefit from iNO was found and its effectiveness remains controversial.[4]

Abbreviations: ARDS, acute respiratory distress syndrome; C_aO_2, arterial oxygen content; C_cO_2, end-pulmonary-capillary oxygen content; COVID-19, coronavirus disease 2019; C_VO_2, mixed venous oxygen content; FiO2, fraction of inspired oxygen; iNO, inhaled nitric oxide; mPAP, mean pulmonary arterial pressure; PEEP, positive end-expiratory pressure; ppm, parts per million; PVR, pulmonary vascular resistance; Q_s, pulmonary Shunt (mL/min); Q_t, cardiac output (mL/min); SVR, systemic vascular resistance.

2 | METHODS

We retrospectively analyzed changes in pulmonary vasoreactivity, pulmonary shunt fraction and arterial oxygenation in seven COVID-19 patients treated with iNO. The study was observational in design and the decision for iNO treatment was at the discretion of the attending physician. The institutional ethics board of the university of Würzburg waived the need for informed consent. Severe acute respiratory syndrome coronavirus 2 infection was verified by real-time reverse transcriptase chain reaction according to the World Health Organization interim guidance.[5] All patients suffered from ARDS due to COVID-19 pneumonia according to the Berlin classification.[6] In 5 cases severe ARDS was present. All patients were treated with lung protective mechanical ventilation (fraction of inspired oxygen [F_iO_2] = 1.0, positive end expiratory pressure [PEEP] = 14 [interquartile range 13-15]) and were in supine position at the time of iNO application. Inhaled NO was administered at a concentration of 20 ppm for the duration of 15-30 minutes prior to data acquisition.

Editorial Comment

Inhaled nitric oxide has been a therapeutic option for trying to improve gas exchange in the lungs when oxygenation is a problem. In this small retrospective assessment of a treatment series, nitric oxide inhalation in COVID-19 ARDS patients had a positive effect on arterial oxygenation, but at the same time little effect on measured pulmonary shunt. This article is accompanied by an editorial.

TABLE 1 Clinical and hemodynamic characteristics of Covid-19 ARDS patients with or without the administration of 20ppm iNO for 15-30 minutes. Data are Median and interquartile range (25% - 75%), n = 7

Parameters	Baseline values	+20 ppm iNO	*P*-value
Patient characteristics (n = 7)			
Body weight [kg]	84.0 (77.5-87.5)		
Hemoglobin (g/dL)	9.9 (8.6-10.7)	9.6 (9.0-9.8)	
Ventilator-derived			
Peak inspiratory pressure [mm Hg]	29.0 (28.5-30.5)	29.0 (28.5-29.5)	
Tidal volume [mL]	424.0 (390.5-467)	433.0 (407.0-478.5)	
Minute ventilation [L/min]	10.0 (8.7-12.9)	9.3 (8.8-13.3)	
Compliance [L/cm H_20]	33.1 (24-37.2)	34.1 (27.2-34.7)	
Pulmonary hemodynamics			
mPAP [mm Hg]	31 (30.0-43.0)	37.0 (29.0-40)	.2476
PCWP [mm Hg]	18.0 (14.5-20.5)	15.0 (13.0-20.5)	1.0000
Shunt fraction (Q_s/Q_t) [%]	39.0 (35.0-43.0)	40.0 (35.0-42.0)	.4375
PVR [dyn × s × cm^{-5}]	184.1 (153.5-237.4)	155.3 (153.1-227.5)	.125
Pulmonary vasoreactivity [%]		9.9 (–12.1-17.9)	
Gas exchange			
p_aO_2 [mm Hg] (F_iO_2 = 1.0)	78.2 (64.5-101.5)	105.0 (78.5-144.5)	**.0313**
p_aCO_2 [mm Hg]	57.0 (56.0-67.0)	58.1 (55.5-67)	.5807
s_aO_2 [%]	94.8 (92.2-99.2)	99.4 (95.4-99.8)	.0754
S_vO_2 [%]	79.8 (70.7-82.3)	81.2 (73.1-83.9)	.6250
Systemic hemodynamics			
Cardiac output [L/min]	7.5 (6.2-8.9)	7.8 (6.7-8.1)	
MAP [mm Hg]	76.0 (72.5-81.0)	78.0 (73.5-80.5)	
CVP [mm Hg]	17.0 (14.5-19)	13.0 (12.5-20.0)	.5807
SVR [dyn × s × cm^{-5}]	643.9 (532.2-784.2)	680.6 (561.4-780)	.5781

Abbreviations: BMI, body mass index; CVP, central venous pressure; F_iO_2, inspired fraction of oxygen; MAP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; p_aCO_2, arterial partial pressure of carbon dioxide; p_aO_2, arterial partial pressure of oxygen; P_{AW}, Mean Airway Pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; s_aO_2, fraction of *oxygen-saturated* hemoglobin in arterial blood; S_vO_2, fraction of *oxygen-saturated* hemoglobin in mixed venous blood; SVP, systemic vascular resistance.

Bold indicates significantly different vs baseline values.

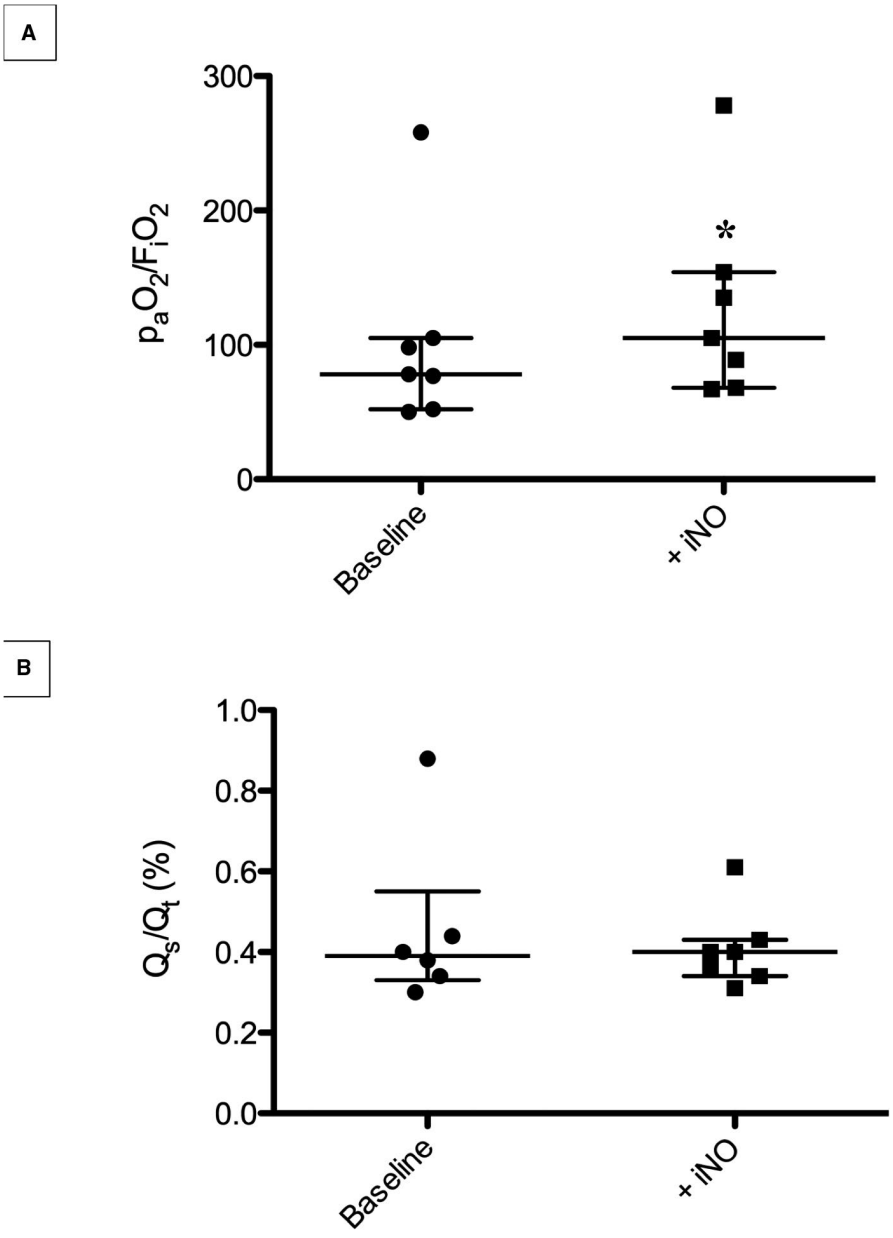

FIGURE 1 Inhaled nitric oxide (iNO) leads to significant improvement in arterial oxygenation (paO2) (A) without changes in pulmonary vascular shunting (Qs/Qt) (B). Seven patients with COVID-19 pneumonia were analyzed, of whom five suffered from a severe ARDS. All of these patients benefited from iNO concerning an ameliorated pulmonary gas exchange without beneficial effects onto pulmonary hemodynamics. *significantly different vs baseline ($P = .0156$)

iNO treatment was continued on an individual basis as deemed necessary by the attending physicians according to the German ARDS guidelines. Ventilator settings were not changed during the application of iNO. A balloon-tip thermodilution pulmonary artery catheter (Edwards Lifesciences Corp.,) was inserted via the right jugular or subclavian vein to allow continuous recording of cardiac output, central venous pressure and mean pulmonary arterial pressure (mPAP). Blood gas analysis was performed of both arterial and mixed venous blood (Radiometer ABL800 FLEX, Radiometer GmbH). Systemic blood pressure was monitored with an intraarterial line. Pulmonary vasoreactivity was defined by as a fall in mPAP and pulmonary vascular resistance (PVR) >20%.[7] Pulmonary shunt fraction was calculated as $Q_s/Q_t = (C_cO_2\text{-}C_aO_2)/(C_cO_2\text{-}C_vO_2)$. Data were analyzed with a Wilcoxon matched pairs signed-rank test (Prism 5 for Mac OS X, GraphPad Software).

3 | RESULTS

Our results indicate that iNO significantly improved arterial oxygenation in COVID-19–induced ARDS. Actually, all five patients suffering from a severe ARDS had a higher partial pressure of oxygen (p_aO_2) subsequent to the administration of iNO. There was no effect on the partial pressure of carbon dioxide (p_aCO_2) (median p_aCO_2 57.0 mm Hg vs 58.1 mm Hg). Moreover we did not observe significant effects onto pulmonary vasoreactivity or a change in pulmonary shunting (Table 1 and Figure 1). The observed pulmonary shunt fraction of 40% is consistent with data reported from other causes of ARDS.[8] A fraction of 30%-40% can be expected according to the observed median p_aO_2/F_iO_2 ratio (Figure 1). The mPAP was unchanged (means of 36.6 ± 9.0 mm Hg vs 34.4 ± 7.9 mm Hg after iNO [medians of 31 mm Hg vs 37 mm Hg, respectively]) and

pulmonary vascular resistance (PVR) only decreased by 9.9%. As can be expected in severe sepsis and ARDS, systemic vascular resistance (SVR) was slightly reduced. PVR and mPAP were elevated indicating pulmonary artery hypertension. However, none of the patients suffered from a cor pulmonale.

An alleviated ventilation perfusion ratio is likely the mechanism whereby iNO improved arterial oxygenation. Albeit not significant, we did observe pulmonary vasodilation and in the five patients with severe ARDS PVR decreased by a median of 15.6% (interquartile range 9.9-20.3%; $P = .125$). Considering the proposed L- and H-phenotypes of COVID-19 ARDS, one could assume that iNO therapy should ideally be started in the early transition between the two types as there is increased shunting but still recruitability. However, as improved oxygenation was not only explainable with decreased pulmonary shunting, other modes of iNO action including the regulation of angiotensin II receptors, inhibition of platelet aggregation, surfactant function, antiviral properties[9] and alterations of the immune response[10] are likely to contribute to the improved arterial oxygenation. Hence, we cannot decipher whether the effects of iNO are limited to or superior in one of the proposed subphenotypes.

We only investigated a small number of patients and our study was not designed to examine any of these mechanisms nor a prolonged use of iNO. Furthermore, we cannot delineate survival benefits and it remains to be determined if an improved arterial oxygenation translates into an improved outcome. Nevertheless, our data indicate that the utilization of iNO is useful in COVID-19–induced moderate to severe ARDS. Inhaled NO could provide immediate help and delay deterioration if advanced resources, such as extracorporeal membrane oxygenation are not available. Further investigations such as the randomized multicenter NoCovid trial (NCT04305457) will depict if the use of iNO stalls disease progression and leads to an improved outcome in COVID-19–induced ARDS.

CONFLICTS OF INTEREST

All authors have disclosed that they do not have any conflicts of interest.

AUTHORS' CONTRIBUTIONS

CR, RMM and CL conceived the study and its design, had full access to the data, and take responsibility for the integrity of the data and accuracy of the analysis. MK and JS, organized and entered data. PM, PK, HM, IT, CBR and PL contributed to data interpretation and writing of the manuscript.

FUNDING INFORMATION

None of the authors received funding for the current study.

ETHICS APPROVAL

The institutional ethic board of the University of Wurzburg approved the study and waived the need for informed consent from individual patients due to the context of sole retrospective chart review within standard care.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

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

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