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SHORT COMMUNICATION

Implication of inhaled nitric oxide for the treatment of critically ill COVID-19 patients with pulmonary hypertension

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Abstract

Aims This study aims to analyse whether inhaled nitric oxide (iNO) was beneficial in the treatment of coronavirus disease 2019 (COVID-19) patients with pulmonary hypertension.

Methods and results Five critically ill COVID-19 patients with pulmonary hypertension designated Cases 1–5 were retrospectively included. Clinical data before and after iNO treatment were serially collected and compared between patients with or without iNO treatment. The five cases experienced pulmonary artery systolic pressure (PASP) elevation (≥50 mmHg) at 30, 24, 33, 23, and 24 days after illness onset (d.a.o), respectively. Cases 1–3 received iNO treatment on the 24th, 13th, and 1st day after the first elevation of PASP, with concentrations varied from 10 to 20 ppm based on the changes of PASP and blood pressure for 10, 9, and 5 days, respectively. Upon iNO treatment, PASP of Cases 1 and 2 returned to normal on the 10th day and 1st day, and maintained between 50 and 58 mmHg in Case 3. $Pa0_2/Fi0_2$ increased from 88 to 124, 51 to 118, and 146 to 244, respectively. SPO_2 increased from 91% to 97% for Case 1 and maintained a high level above 97% for Case 2. Cardiac function remained normal in the three patients after treatment. Moreover, Cases 1 and 3 survived from severe acute respiratory syndrome coronavirus 2 infection, while Case 2 finally died on the 36th day after the first elevation of PASP due to severe complications. Both cases who did not receive iNO treatment experienced a sudden decrease of PASP and $Pa0_2/Fi0_2$ due to right heart failure and then died.

Conclusions Inhaled nitric oxide treatment was beneficial in reducing and stabilizing the PASP and might also reduce the risk of right heart failure in COVID-19 with pulmonary hypertension.

Keywords SARS-CoV-2; COVID-19; Inhaled nitric oxide (iNO); Pulmonary hypertension; Heart failure

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Background

The ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has resulted in tens of thousands deaths (https://covid19.who.int/). Acute respiratory syndrome (ARDS), which is characterized by pulmonary hypertension and increased intrapulmonary shunting of blood through hypoventilated regions, was one of the most frequent complications in severe and critically ill COVID-19 patients.[1,2] Nitric oxide (NO) can induce the relaxation of smooth muscle cells in the vasculature and has the unique ability to induce pulmonary vasodilatation specifically in the portions of the lung with adequate ventilation, thereby improving oxygenation of blood and decreasing intrapulmonary right to left shunting.[3] Recently, more and more studies have shown the benefits of inhaled NO (iNO) in the treatment of ARDS, and it is commonly used off-label as a pulmonary vasodilator for treatment of pulmonary hypertension in adults.[4] Moreover, it has also been proved that iNO treatment was beneficial for SARS-CoV-infected patients.[5]

Table 1 Baseline characteristics of the five critically ill coronavirus disease 2019 patients included in this study

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	69	65	69	66	63
Sex	Male	Male	Male	Male	Male
BMI	25.46	25.16	27.76	26.78	31.35
Underlying diseases					
Chronic heart disease	No	No	No	No	No
Chronic lung disease	Yes	No	No	No	Yes
Chronic renal disease	No	No	No	No	No
Chronic liver disease	No	No	No	No	No
Hypertension	No	Yes	Yes	Yes	No
Diabetes	Yes	Yes	No	No	No
Cancer	No	No	No	No	No
Bacterial coinfections					
Complications					
Pneumonia	Yes	Yes	Yes	Yes	Yes
ARDS	Yes	Yes	Yes	Yes	Yes
Severe ARDS	Yes	Yes	Yes	Yes	Yes
Respiratory failure	Yes	Yes	Yes	Yes	Yes
Hepatic insufficiency	Yes	Yes	No	Yes	No
Renal insufficiency	Yes	Yes	No	Yes	No
Cardiac failure	No	No	No	Yes	Yes
Shock	Yes	Yes	Yes	Yes	Yes
Treatment					
Antiviral agents	Lopinavir, Interferon, Favipiravir	Lopinavir, Interferon	Lopinavir, Ribavirin, Arbidol, Favipiravir	Ribavir, Lopinavir, Interferon	Lopinavir, Ribavirin, Arbidol, Favipiravir
Corticosteroid	Yes	Yes	Yes	Yes	Yes
Mechanical ventilation	Yes	Yes	Yes	Yes	Yes
Invasive mechanical ventilation	Yes	Yes	Yes	Yes	Yes
Immunoglobulin	No	No	No	No	No
ECMO	Yes	Yes	Yes	Yes	Yes
iNO	Yes	Yes	Yes	No	No
Intervals (days)					
Onset to admission	4	8	4	8	2
Onset to PASP elevation	30	24	33	23	24
PASP elevation to iNO treatment (days)	25	11	0	-	-
Laboratory findings					
CRP	74.11	49.37	265.67	120.67	79.54
IL-6	43.48	1,234	381.4	7.79	29.59
PCT	1.52	1.33	3.46	0.462	3.80
BNP	6.16	2,120	1,160	249	1,140
Echocardiography before PASP elevation					
Right heart	RA larger, Right ventricular wall thickening	Right ventricular wall thickening	Right ventricular wall thickening	Normal	Normal
Left heart	IVSd thickening	IVSd thickening	IVSd thickening	Interventricular septal thickening	Interventricular septal thickening
Outcome	Survival	Died	Survival	Died	Died

ARDS, acute respiratory distress syndrome; BMI, body mass index; CRP, c-reactive protein; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; IVSd, interventricular septum end diastolic; PASP, pulmonary artery systolic pressure; PCT, procalcitonin.
Severe ARDS: $PaO_2/FiO_2 < 100$. Right atrium larger: the inner diameter of the right atrium ≥ 40 mm. Interventricular septal thickening: ≥12 mm. IVSd thickness: ≥12 mm. Right ventricular wall thickening: ≥5 mm.

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Objective

This study aims to analyse whether iNO was beneficial in the treatment of COVID-19 patients with pulmonary hypertension.

Methods

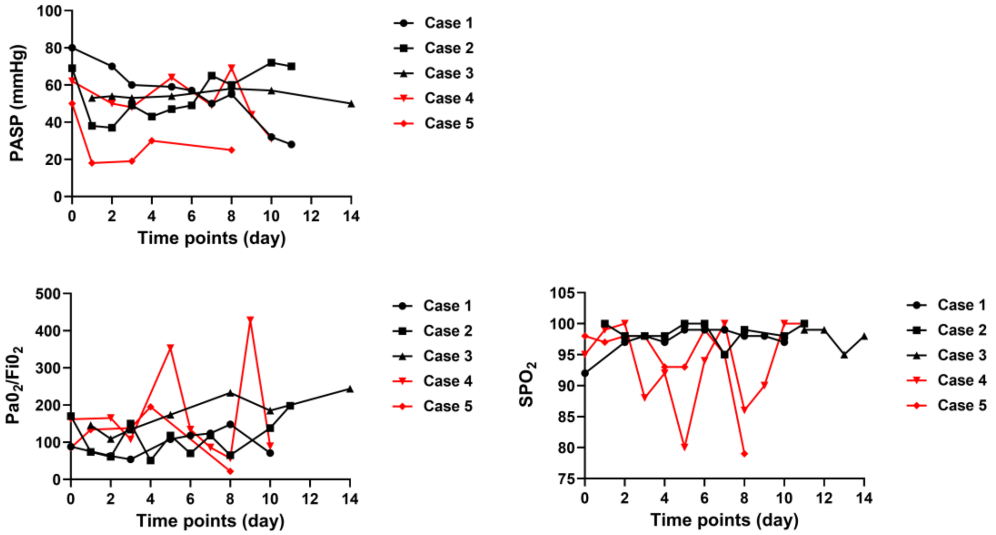
Five critically ill COVID-19 patients were retrospectively included in our study with the following inclusion criteria: (1) elevation of pulmonary artery systolic pressure (PASP) (≥50 mmHg); (2) acute respiratory failure or shock requiring mechanical ventilation, with or without cardiac dysfunction; and (3) heart diseases such as right ventricular outflow tract and pulmonary valve stenosis was excluded by echocardiography, and pulmonary arterial systolic blood pressure was <30 mmHg upon admission. The five cases were designated Cases 1–5, and Cases 1–3 were treated with iNO. Clinical data, PASP, cardiac function, oxygenation index ($Pa0_2/Fi0_2$), and oxygen saturation (SPO_2) before and after iNO treatment were serially collected and compared between patients with or without iNO treatment.

Results

The baseline characteristics of the included five critically ill COVID-19 patients were shown in *Table 1*. All the five patients were men and aged from 63 to 69 years old. All of them had at least one underlying disease, including chronic lung disease, hypertension, and diabetes, while no chronic heart diseases were found. Severe complications including severe ARDS, respiratory failure, and shock were found in all the five patients. All of them received antiviral, corticosteroid, mechanical ventilation, and extracorporeal membrane oxygenation treatment (*Table 1*). Thickened right ventricular wall and interventricular septum end diastolic were found in Cases 1–3, and larger right atrium was also found in Case 1. The echocardiography of the right heart for Cases 4 and 5 was normal, while interventricular septal thickening was found. However, heart function of all the five cases was normal before PASP elevation. The five cases experienced PASP elevation (≥50 mmHg) at 30, 24, 33, 23, and 24 days after illness onset (d.a.o) (*Table 1*).

Cases 1–3 received iNO treatment on the 24th, 13th, and 1st day after the first elevation of PASP, with concentrations varied from 10 to 20 ppm based on the changes of PASP and blood pressure for 10, 9, and 5 days, respectively. PASP of Cases 1 and 2 returned to normal on Days 10 and 1 upon iNO treatment. Meanwhile, $Pa0_2/Fi0_2$ increased from 88 to 124, and SPO_2 increased from 91% to 97% for Case 1. For Case 2, $Pa0_2/Fi0_2$ increased from 51 to 118 and SPO_2 maintained a high level above 97% (*Figure 1*). Case 3 was treated with iNO on the first day the PASP elevated. After treatment, although pulmonary artery pressure continued to fluctuate between 50 and 58 mmHg, no significant increase was observed again during the observation period (*Figure 1*). In addition, $Pa0_2/Fi0_2$ continued to increase from 146 to 244. Notably, cardiac function remained normal in the three patients after treatment. Cases 1 and 3 survived from severe acute respiratory syndrome coronavirus 2 infection, while Case 2 finally died on the 36th day after the first elevation

Figure 1 Comparison of PASP, PaO_2/FiO_2, and SPO_2 change in the five critically ill coronavirus disease 2019 patients. Day 0 for Cases 1–3 was defined as the day before inhaled nitric oxide (iNO) treatment was given, and Day 1 was the day iNO treatment started, while Day 0 for Cases 4 and 5 was defined as the first day of PASP elevation. The two non-survival patients (Cases 4 and 5) were marked in red. PASP, pulmonary artery systolic pressure.



of PASP due to severe complications including multiple organ failure and active thoracic haemorrhage. Cases 4 and 5 did not receive iNO treatment. Both cases experienced right heart failure (RHF) and also a sudden decrease of PASP and $Pa0_2/Fi0_2$ (*Figure 1*), and then both patients died.

Discussion

Conventional vasodilators such as nifedipine or sildenafil can reduce pulmonary artery pressure, while they also dilate the pulmonary vessels in the consolidation and immobility areas of the lung, which may exacerbate the breath perfusion mismatch and thus hypoxaemia.[6] However, unlike these conventional vasodilators, the NO inhaled through the respiratory tract only dilates the pulmonary arteries in well-ventilated lung tissue and has no impact on breath perfusion,[3,7] as NO is rapidly scavenged by oxyhaemoglobin in red blood cells.[3] This reduces intrapulmonary shunt and may improve arterial oxygenation throughout the body. Current clinical studies suggest that NO, milrinone, and epoprostenol can improve pulmonary circulation through inhalation, but only iNO significantly improved oxygenation when compared with milrinone and epoprostenol.[8] Consistent with this study, we also observed the significant improvement of oxygenation in Cases 1–3 based on the change of SPO_2 and PaO_2/FiO_2.

Pulmonary hypertension serves as the most common cause of RHF, which is the leading cause of death for pulmonary arterial hypertension.[9] Systolic function of the right ventricle is sensitive to changes in afterload, and small increases in pulmonary artery pressure can result in large reductions in stroke volume (SV). Therefore, reducing afterload of the right ventricle is the cornerstone of prevention and management of RVF due to pulmonary hypertension.[9] In our study, RHF occurred in both cases without iNO treatment, while not the three cases with iNO treatment, indicating that iNO treatment might reduce the risk of developing RHF in COVID-19 patients as previously reported for the treatment of fat embolization syndrome.[10]

Based on our study, we found that treatment with iNO was beneficial in reducing and stabilizing the PASP in the critically ill COVID-19 patients with pulmonary hypertension, especially in the early stage of pulmonary hypertension. Moreover, treatment with iNO might also reduce the risk of RHF in COVID-19-related ARDS patients, as pulmonary hypertension has been shown to be associated with right ventricular dysfunction and heart failure.[5] To our knowledge, this is the first report on the implication of iNO treatment for the critically ill COVID-19 patients with pulmonary hypertension. However, we also acknowledge the observational nature of our study, which makes it challenging to directly access the effects of iNO treatment. Currently, as very few treatment options are available for the treatment of critically ill COVID-19 patients, iNO could therefore be considered as a therapeutic option for such patients.

Compliance with ethical standards

The study protocol was approved by the Ethics Committees of Shenzhen Third People's Hospital. Verbal informed consents were obtained from all patients or patients' family members due to the special circumstances that pens and papers were not allowed to be brought into containment facilities.

Conflict of interest

None declared.

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