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. PaO2/FiO2 increased from 88 to 124, 51 to 118, and 146 to 244, respectively. SPO2 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 PaO2/FiO2 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

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

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| 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     | Yes    | No     | No     | No     |
| Hypertension                    | No     | Yes    | No     | Yes    | No     |
| Diabetes                        | Yes    | Yes    | No     | No     | No     |
| Cancer                          | No     | No     | No     | No     | No     |
| **Bacterial coinfections**      |        |        |        |        |        |
| 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           | No     | No     | Yes    | Yes    | No     |
| Renal insufficiency             | Yes    | No     | No     | No     | No     |
| Cardiac failure                 | No     | Yes    | Yes    | No     | No     |
| Shock                           | Yes    | Yes    | Yes    | Yes    | Yes    |
| **Treatment**                   |        |        |        |        |        |
| Antiviral agents                | Lopinavir, Interferon, Favipiravir | Lopinavir, Interferon | Lopinavir, Ribavirin, Arbidol, Ribavirin, Favipiravir | Lopinavir, 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    | Yes    | Yes    |
| **Intervals (days)**            |        |        |        |        |        |
| Onset to admission              | 4      | 8      | 4      | 8      | 2      |
| Onset to PASP elevation         | 30     | 24     | 33     | 23     | 24     |
| PASP elevation to iNO25         | 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**|        |        |        |        |        |
| Right heart                     | RA larger, Right ventricular wall thickening | Right ventricular wall thickening | Right ventricular wall thickening | Normal | Normal |
| Left heart                      | 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: PaO2/FiO2 < 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.
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 (PaO₂/FiO₂), and oxygen saturation (SPO₂) 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, PaO₂/FiO₂ increased from 88 to 124, and SPO₂ increased from 91% to 97% for Case 1. For Case 2, PaO₂/FiO₂ increased from 51 to 118 and SPO₂ 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, PaO₂/FiO₂ 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.
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 PaO$_2$/FiO$_2$ (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. 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, as NO is rapidly scavenged by oxyhaemoglobin in red blood cells. 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. 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. 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. 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.

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. 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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