

## CLINICAL CASE REPORTS

## Hyperbaric oxygen therapy may be effective to improve hypoxemia in patients with severe COVID-2019 pneumonia: two case reports

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### ABSTRACT

**Objective:** To determine whether hyperbaric oxygen (HBO<sub>2</sub>) therapy be effective to improve hypoxemia for severe COVID-19 pneumonia patients.

**Method:** Two male patients ages 57 and 64 years old were treated. Each met at least one of the following criteria: shortness of breath; respiratory rate (RR)  $\geq 30$  breaths/minute; finger pulse oxygen saturation (SpO<sub>2</sub>)  $\leq 93\%$  at rest; and oxygen index (P/F ratio: PaO<sub>2</sub>/FiO<sub>2</sub>  $\leq 300$  mmHg). Each case excluded any combination with pneumothorax, pulmonary bullae or other absolute contraindications to HBO<sub>2</sub>. Patients were treated with 1.5 atmospheres absolute HBO<sub>2</sub> with an oxygen concentration of more than 95% for 60 minutes per treatment, once a day for one week. Patients' self-reported symptoms, daily mean SpO<sub>2</sub> (SO<sub>2</sub>), arterial blood gas analysis, d-dimer, lymphocyte, cholinesterase (che) and chest CT were conducted and measured.

**Results:** For both patients, dyspnea and shortness of breath were immediately alleviated after the first HBO<sub>2</sub> treatment and remarkably relieved after seven days of HBO<sub>2</sub> therapy. The RR also decreased daily. Neither patient became critically ill. The decreasing trend of SO<sub>2</sub> and P/F ratio was immediately reversed and increased day by day. The lymphocyte count and ratio corresponding to immune function gradually recovered. D-dimer corresponding to peripheral circulation disorders and serum cholinesterase, reflecting liver function had improved. Follow-up chest CT showed that the pulmonary inflammation had clearly subsided.

**Conclusions:** Our preliminary uncontrolled case reports suggest that HBO<sub>2</sub> therapy may promptly improve the progressive hypoxemia of patients with COVID-2019 pneumonia. However, the limited sample size and study design preclude a definitive statement about the potential effectiveness of HBO<sub>2</sub> therapy to COVID-2019 pneumonia. It requires evaluation in randomized clinical trials in future. ■

### INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) caused by the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed tremendous challenges to the world's public health systems [1].

Autopsy has revealed that the terminal bronchiole and alveolar tissue were directly damaged by SARS-CoV-2 [2,3]. Respiratory symptoms, such as fever, dry cough and fatigue, are the main clinical manifestations. Severe patients usually have dyspnea and/or hypoxemia one week after the onset. The conditions of some patients can quickly progress to acute respiratory distress syndrome (ARDS), septic shock, difficult-to-correct metabolic acidosis, coagulation dysfunction and multiple organ failure [4].

Because there is currently no vaccine or specific drug therapy, symptomatic supportive therapy is still the main treatment for COVID-19 pneumonia [5].

It is recommended by China's COVID-19 Diagnosis and Treatment Program (Trial Version 7) that a timely and effective oxygen therapy should be given, including: nasal cannula; mask inhalation; high-flow nasal cannula oxygen therapy; mixed oxygen and hydrogen inhalation (H<sub>2</sub>/O<sub>2</sub>: 66.6%/33.3%); non-invasive mechanical ventilation; invasive mechanical ventilation; and extracorporeal membrane oxygenation (ECMO) [6]. However, the thickened respiratory membranes and increased blood flow-ventilation ratio caused by pulmonary inflammation cause difficulty in overcoming the obstacles of gas exchange by inhaling oxygen at 1 atmosphere absolute, 1 ATA = 101.32kPa).

KEYWORDS: COVID-2019 pneumonia; hyperbaric oxygen therapy; hypoxemia

Hyperbaric oxygen (HBO<sub>2</sub>) is the inhalation of oxygen at a pressure greater than 1 ATA. HBO<sub>2</sub> therapy has been used in the treatment of decompression sickness, severe anemia (when suitable blood is not available or there is a religious objection to blood), soft-tissue infections, chronic wounds, arterial gas embolism, osteoradionecrosis, and various poisonings such as carbon monoxide (CO), cyanide (CN), hydrogen sulfide (H<sub>2</sub>S), carbon tetrachloride (CCl<sub>4</sub>), mushrooms, hydrocarbons, organophosphates and barbiturates [7]. The use of 100% oxygen at 2 to 3.5 times the atmospheric pressure at sea level can result in arterial oxygen tensions of greater than 1,200 mmHg [8]. Thus, HBO<sub>2</sub> can help overcome the damage to air-blood barrier caused by lung tissue inflammation by increasing the content of physically dissolved oxygen in the blood and oxygen diffusion distance in tissue.

Here we share two cases of severe COVID-2019 pneumonia with hypoxemia treated by HBO<sub>2</sub> using a mobile monoplace chamber at Wuhan Huoshenshan Hospital in China. The aim is to explore whether HBO<sub>2</sub> therapy is effective in improving hypoxemia in patients with severe COVID-19 pneumonia.

## METHODS

This study was conducted at Huoshenshan Hospital, Wuhan, China, from March 15, 2020, to March 29, 2020. The study was approved by the ethics committees from Huoshenshan Hospital, and each patient gave written informed consent.

### Patients

Patients were diagnosed based on China's COVID-19 Diagnosis and Treatment Program (trial version 7) [6]:

1. real-time fluorescent reverse-transcription polymerase chain reaction detection of SARS-CoV-2 nucleic acid is positive;

- 2) viral gene sequencing is highly homologous with SARS-CoV-2.

In addition, they also met at least one of the following criteria: shortness of breath; respiratory rate (RR)  $\geq 30$  breaths/minute; finger pulse oxygen saturation (SpO<sub>2</sub>)  $\leq 93\%$  at rest state; and P/F ratio (PaO<sub>2</sub>/FiO<sub>2</sub>, where PaO<sub>2</sub> is the arterial oxygen partial pressure and FiO<sub>2</sub> is the percentage of inhaled oxygen concentration)  $\leq 300$  mmHg. Each case excluded any combination of pneumothorax, pulmonary bullae or other absolute contraindications to HBO<sub>2</sub>.

### Patient information

**Patient #1:** A male, 57 years old, was admitted to the hospital with cough, fever and fatigue for two days. Past history showed hypertension. Antiviral and symptomatic treatments were given as:

- methylprednisolone sodium succinate – 40 mg twice daily (Pfizer Manufacturing, Puurs-Sint-Amunds, Belgium NV);
- human immunoglobulin – 20 g daily (Zhejiang Haikang Biological Products Co., Ltd., Wenzhou City, China);
- lopinavir/ritonavir oral solution – 400 mg twice daily (AbbVie Inc., Shanghai, China);
- arbidol hydrochloride tablets – 200 mg three times daily (Jiangsu Wuzhong Pharmaceutical Group Corporation, Suzhou City, China; and
- Qingfei Paidu Decoction, traditional Chinese medicines – 1 package per day, take warm twice).

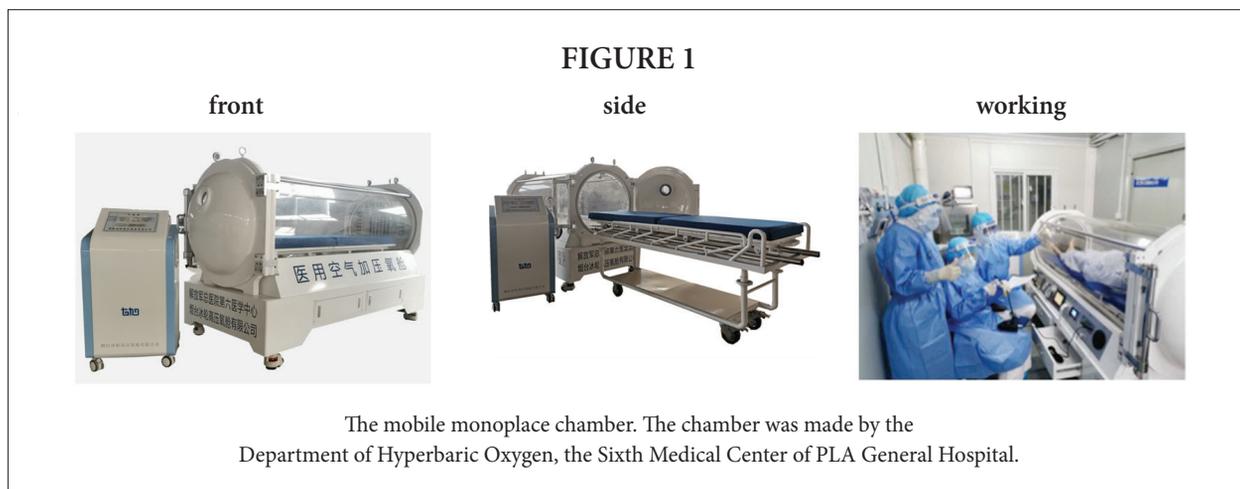
Oxygen therapy started with seven days of nasal oxygen inhalation, then followed by three days of mask oxygen inhalation. The patient then had shortness of breath and RR  $\geq 30$  breaths/minute. His SpO<sub>2</sub> (inhaled oxygen at 15 liters/minute flow) was lower than 93% at rest; PaO<sub>2</sub> values were 60 mmHg; and chest computed tomography (CT) indicated progress of lung lesions.

**Patient #2:** A male, 64 years old, was admitted to the hospital with cough and fever for three days. Past history had diabetes and coronary heart disease. Antiviral and symptomatic treatments were given as:

- lianhua qingwen granules – 6 g three times daily (Beijing Yiling Pharmaceutical Co., Ltd., Beijing, China);
- human immunoglobulin – 20 g daily (Zhejiang Haikang Biological Products Co., Ltd., Wenzhou City, China);
- lopinavir/ritonavir oral solution – 400 mg twice daily (AbbVie Inc., Shanghai, China);
- arbidol hydrochloride tablets – 200 mg three times daily (Jiangsu Wuzhong Pharmaceutical Group Corporation, Suzhou City, China; and
- albumin prepared from human plasma – 10 g daily (Sinopharm Group Shanghai Blood Products Co., Ltd., Shanghai, China).

Oxygen therapy started with eight days of nasal oxygen inhalation, and then followed two days of mask oxygen inhalation. The patient's condition continued to deteriorate. SpO<sub>2</sub> (inhaled oxygen at 10 liters/minute flow) was lower than 93% at rest; PaO<sub>2</sub> values were 66 mmHg; chest CT indicated progress of lung lesions.

In addition to the above therapeutic schedule, both patients were started on treatment with HBO<sub>2</sub>.



### HBO<sub>2</sub> therapy

HBO<sub>2</sub> treatment was begun to help improve hypoxemia in patients with severe COVID-2019 pneumonia. A mobile monoplace chamber at Wuhan Huoshenshan Hospital in China was used (Figure 1). The basic technical parameters are as follows:

1. The maximum design pressure of chamber is 0.16 MPa (1.6 ATA) which is pressurized by an air compressor; the operating pressure can be controlled at 0.15 MPa (1.5ATA);
2. The chamber is made of transparent, high-strength plexiglass; the diameter and length are 800 mm and 2,000 mm respectively, and can accommodate one person at a time. It is easy to observe the vital signs of the patient, and communicate with the patient through a walkie-talkie at any time, which can help to avoid a patient's claustrophobia;
3. Through the hospital centralized gas supply and oxygen supply pipeline, the external oxygen supply terminal plug is connected to the chamber, while increasing the oxygen humidification function;
4. Patients use our own designed oxygen mask to inhale oxygen. The mask fits the Asian face well and ensures a good airtight fit. It is connected to the oxygen supply pipeline through an "oxygen storage bag" to ensure that the mask always maintains 100% concentration of oxygen.

Our test results have shown that this mask could provide an inspired oxygen concentration of over 95%. Therefore, the modality would provide inspired partial pressure of oxygen of over 0.14 MPa (1.42 ATA) inside our chamber at 0.15 MPa (1.5 ATA). In addition, the

oxygen concentration in the chamber can be controlled between 30% and 35% [5]. The chamber bed can be pushed out by pulleys as an external transfer vehicle for easy access for critical patients [6]. The operating system uses touchscreen control, with automatic decompression and oxygen inhalation procedures, which is easy for medical staff to operate [7]. It is equipped with ultraviolet lamps and ozone disinfection equipment.

The mobile monoplace chamber is equipped in the negative-pressure ward. The air in the chamber is automatically updated with the air in the ward, and is equipped with a disinfection device. The inner wall of the pressure chamber is irradiated with ultraviolet rays and wiped with alcohol to prevent cross infection in patients.

The treatment strategy is to pressurize the air to 1.5 ATA and allow the patients to inhale pure oxygen (>95% oxygen) with our own designed oxygen mask for 60 minutes per treatment, once a day for one week.

### Data collection

Self-reported symptoms and SpO<sub>2</sub> were recorded before each patient entered and exited the air pressurized chamber. Other clinical laboratory data was measured before or after HBO<sub>2</sub> therapy. This included the following: arterial blood gas analysis; lymphocyte count and lymphocyte ratio (the percentage of lymphocytes in white blood cells), D-dimer assessing peripheral circulation disorders and serum cholinesterase (ChE) reflecting liver function. A chest CT scan was conducted at the same time.

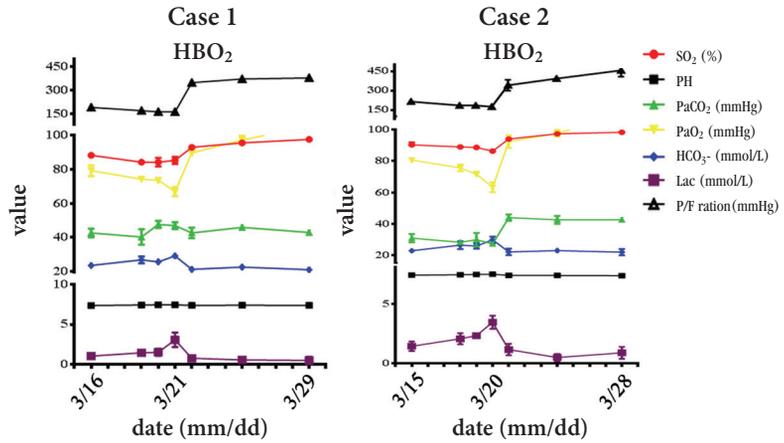
Before HBO<sub>2</sub> therapy both patients were given antiviral and symptomatic treatments, and inhaled oxygen with oxygen mask at a flow rate of 10–15 L/min. However, with each patient their condition continued to deteriorate, manifesting as shortness of breath, RR ≥30 beats/min, SpO<sub>2</sub> values less than 93%, and progress of lung lesions as shown in chest CT. After the first HBO<sub>2</sub> session SpO<sub>2</sub> values were higher than 93% in both patients. The decreasing trend of SO<sub>2</sub> and P/F ratio was immediately reversed and increased significantly day by day. From the third day after HBO<sub>2</sub> therapy, their SO<sub>2</sub> values reached more than 95%, and their arterial blood gas indices (PaO<sub>2</sub>, P/F ratio, HCO<sub>3</sub><sup>-</sup>, and Lac) improved substantially.

Before HBO<sub>2</sub> therapy lymphocyte count and ratio were reduced. After seven days of HBO<sub>2</sub> therapy, lymphocyte count and ratio were recovered.

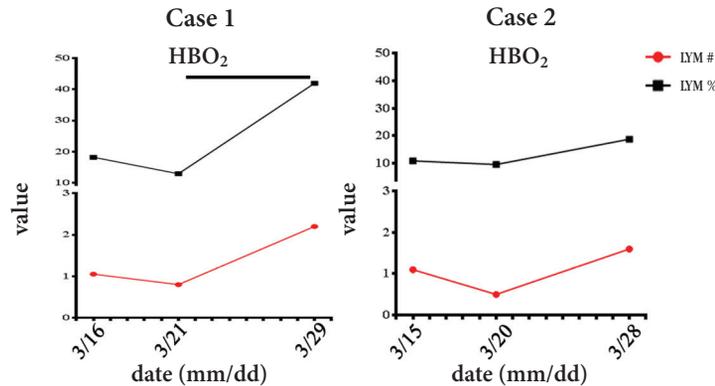
**Abbreviations**

SpO<sub>2</sub>, finger pulse oxygen saturation; SO<sub>2</sub> daily mean SpO<sub>2</sub>; HBO<sub>2</sub> hyperbaric oxygen therapy; Lac lactic acid; P/F ratio, oxygen index; LYM, lymphate; ChE, cholinesterase.

**FIGURE 2**



**FIGURE 3**



**RESULTS**

For these two patients, dyspnea and shortness of breath were immediately alleviated after the first HBO<sub>2</sub> treatment and remarkably relieved after seven days of HBO<sub>2</sub> therapy. The RR also decreased daily. Neither patient became critically ill, but they were slow in recovering from shortness of breath after performing an activity, suggesting that they need continuous lung rehabilitation.

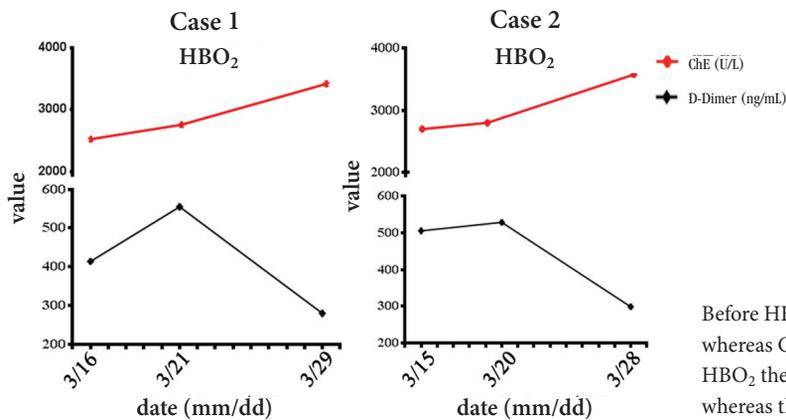
After the first HBO<sub>2</sub> session (patients exited chamber) the patients' SpO<sub>2</sub> values were higher than 93%. The decreasing trend of SO<sub>2</sub> and P/F ratio immediately reversed and increased significantly day by day. From the third day after HBO<sub>2</sub> therapy, their SO<sub>2</sub> values reached more than 95%, and their arterial blood gas indices (PaO<sub>2</sub>, P/F ratio, HCO<sub>3</sub><sup>-</sup>, and lactic acid) improved substantially, suggesting their hypoxemia had improved (Figure 2).

In addition to the improvement in SO<sub>2</sub> and arterial blood gas indices, the patients' lymphocyte count and ratio corresponding to immune function had gradually recovered (Figure 3). D-dimer corresponding to peripheral circulation disorders and cholinesterase (ChE) reflecting liver function had improved (Figure 4). Follow-up chest CTs showed that their pulmonary inflammation had clearly subsided (Figure 5)

**DISCUSSION**

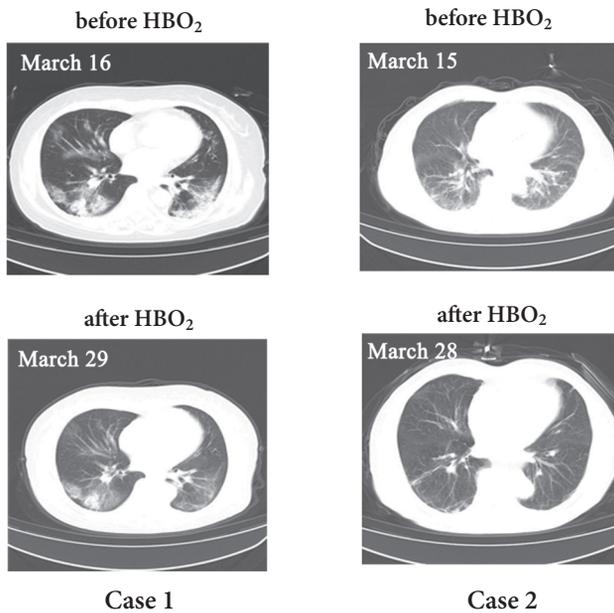
Most patients with severe COVID-2019 pneumonia experience dyspnea and hypoxemia a week after the disease onset. Some of them rapidly progress to acute respiratory distress syndrome, septic shock, difficult-to-correct metabolic acidosis, coagulation disorders, and multiple organ failure due to the exudative injury of pulmonary inflam-

FIGURE 4



Before HBO<sub>2</sub> therapy D-dimer was high, whereas ChE was low. After seven days of HBO<sub>2</sub> therapy, the former decreased, whereas the latter increased.

FIGURE 5



Before HBO<sub>2</sub> therapy chest CT of the two patients showed diffuse lesions of the lungs dominated by consolidation shadows combined with ground-glass shadows, multiple cord shadows, and bronchial inflation signs. After seven days of HBO<sub>2</sub> therapy, follow-up observations of chest CT showed that pulmonary inflammation was clearly resolved.

Abbreviations

SpO<sub>2</sub>, finger pulse oxygen saturation; SO<sub>2</sub> daily mean SpO<sub>2</sub>; HBO<sub>2</sub> hyperbaric oxygen therapy; Lac lactic acid; P/F ratio, oxygen index; LYM, lymphate; ChE, cholinesterase.

mation, formation of hyaline membranes, clogging of airways with large amounts of secretions, and progressive hypoxemia [2,9].

For patients with severe COVID-2019 pneumonia, although mechanical ventilation can increase P/F ratio, the degree of increase has a “ceiling,” and prolonged ventilator treatment may cause difficulty in sputum discharge, lung oxidative damage, and ventilator-associated pneumonia; although ECMO has surpassed the venti-

lation and gas exchange functions of the lungs and can completely saturate hemoglobin, it is invasive and thus can cause considerable damage to patients. Therefore, the above-mentioned respiratory support methods cannot completely prevent or reverse the progressive hypoxemia and hypoxic damage to organ and tissues in patients with severe COVID-2019 pneumonia, thereby resulting in a cycle of hypoxia – insufficient cellular energy supply – inflammatory attack – further hypoxia [10].

Oxygen that physically dissolved in the blood is the “treasure” of tissue oxygen supply. According to Henry’s law, the most effective way to improve hypoxemia is to increase the partial pressure of oxygen in the alveoli and tissues. Instead of inhaling oxygen at 1 ATA, patients can calmly inhale high partial pressure oxygen by using HBO<sub>2</sub> and thus can overcome gas exchange disorders caused by thickened respiratory membranes and increased blood flow-ventilation ratios; consequently, oxygen can diffuse further in the tissues [11]. Therefore, HBO<sub>2</sub> therapy is an effective modality to improve hypoxia induced by COVID-2019 pneumonia and provide aerobic metabolism windows for hypoxic organs and tissues. Moreover, HBO<sub>2</sub> has anti-inflammatory and anti-immune effects and can delay and block cytokine storms [12].

Zhong, et al. from China published two case reports about the application of HBO<sub>2</sub> therapy in patients with COVID-19 pneumonia [13,14]. They found that HBO<sub>2</sub> (0.2MPa and 95 minutes’ total treatment time) could reverse the progressive hypoxemia of patients with severe and critically ill COVID-2019 pneumonia. However, their HBO<sub>2</sub> therapy sessions were conducted in multiplace chambers. Regardless of strict cleaning and disinfection procedures of breathing masks or oxygen hoods implemented in all hyperbaric medical facilities, an accumulation of several patients in the confined space creates the risk of cross-infection when concerning highly infectious germs, including coronavirus. Therefore, the monoplace hyperbaric oxygen chamber may be a better choice.

Since March 2020 HBO<sub>2</sub> therapy has been employed to treat patients with severe COVID-2019 pneumonia by using a mobile monoplace chamber at Wuhan Huoshenshan Hospital in China. According to our experience, 1.5 ATA of HBO<sub>2</sub> therapy can promptly improve the progressive hypoxemia of patients with COVID-2019 pneumonia. It is conceivable that low-pressure HBO<sub>2</sub> (<2.0 ATA) may exert an anti-inflammatory effect on the lung, although oxygen delivered at high partial pressures can also be toxic, with proinflammatory effects [15]. In addition, the use of a mobile monoplace chamber in the ICU is convenient for the bedside treatment of patients with severe COVID-2019 pneumonia and does not pose a safety risk in monoplace chambers or cross infection in large-scale hyperbaric oxygen chambers.

## LIMITATIONS

This study has several limitations. First, this is just a two-case report study, the sample size is too small and do not contain controls. Given the number of COVID-19 pneumonia patients decreasing in China, an exploration of this therapy might provide needed help the physicians in other countries. Second, the data presented does not necessarily mean, or support that they improved because of being subjected to pressures at 1.5 ATA while breathing supplemental oxygen. They could have simply improved over time without HBO<sub>2</sub> therapy, as most patients with COVID-19 do. We recently registered a study on the efficacy and safety of HBO<sub>2</sub> on COVID-2019 pneumonia on [www.chictr.org.cn](http://www.chictr.org.cn) the Chinese Clinical Trial Registry. We hope to further study the therapeutic effects of HBO<sub>2</sub> on COVID-2019 pneumonia.

## CONCLUSION

Our preliminary uncontrolled case reports suggest that HBO<sub>2</sub> therapy may promptly improve the progressive hypoxemia of patients with COVID-2019 pneumonia. While no conclusions can be drawn regarding efficacy of HBO<sub>2</sub> from this small case series of two patients with COVID-19 pneumonia, administration of seven daily hyperbaric oxygen treatments at 1.5 ATA for 60 minutes provides limited reassurance regarding safety. However, the limited sample size and study design preclude a definitive statement about the potential effectiveness and mechanisms of HBO<sub>2</sub> on COVID-2019 pneumonia. It requires evaluation in randomized clinical trials in future studies. ■

### *Availability of data and materials*

*The data that support the findings of this study are publicly available from the website of National Health Commission of the People’s Republic of China.*

### *Conflict of interest statement*

*The authors declares that no competing interests exist with this submission.*

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