

## ARTICLE

# The Outcomes of Hyperbaric Oxygen Therapy to severe and critically ill patients with COVID-19 pneumonia.

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## Summary

**Background** Progressive hypoxemia is a characteristic manifestation in the clinical course of severe and critically ill patients with COVID-19 pneumonia. Oxygen therapy plays an important role in its systematic therapies. Hyperbaric oxygen therapy (HBOT) is the most powerful oxygen therapy known, and may be the best choice of oxygen therapy for severe or critically ill adult patients with COVID-19 pneumonia. Here we shared the outcome of additional HBOT to COVID-19 patients in General Hospital of the Yangtze River Shipping of Wuhan.

**Method** 5 patients, 24-69 (mean 47.6) years old, with progressive symptoms and diagnosed severe or moderate ARDS, were included. 3-8 (mean 4.6) treatments of HBOT additional to routine therapies were given. Data collection were emphasized in hypoxia rectification, and included the symptoms, finger pulse oxygen saturation (SpO<sub>2</sub>), arterial blood gas (ABG), blood cell count, coagulation functions, high-sense C-reaction protein, and chest CT. The data were analyzed with paired t test.

**Finding** The symptoms were obviously mitigated from first HBOT treatment. SpO<sub>2</sub> beside chamber before compression significantly elevated day by day (P<0.01). Means of daily SpO<sub>2</sub> restored to above 95% in 1-8 times HBOT treatments. SpO<sub>2</sub> after decompression of first and second HBOT treatment were higher than that before compression of the same HBOT (P<0.01). Before HBOT, ABG showed low PaO<sub>2</sub> 37-78mmHg (61.60±15.24mmHg) but normal PaCO<sub>2</sub> (31.48±3.40mmHg), and high lactate level. After HBOT, PaO<sub>2</sub> and SaO<sub>2</sub> were significantly increased (P<0.05), and lactate level was obviously declined. The amount of lymphocyte and LYM% of each patients were obviously elevated after HBOT treatments (P<0.05). Fibrinogen were significantly declined after HBOT treatment than that before (P<0.05), while as D-Dimer (D-D) obviously decrease too. Chest CT obtained during or after HBOT showed significantly improved imaging status of lung lesion in each patient.

**Interpretation** Our results suggested that HBOT can effectively correct systematic hypoxia, benefit to improve circulation and immune function. It is supposed that the progressive systemic hypoxia

injury plays an important role in the disease than the virus infection per se. our results highlight HBOT as a preferable oxygen therapy to COVID-19 pneumonia. Early HBOT treatment may improve the total efficiency of systemic support treatments, reduce the using of mechanic ventilation and even mortality of severe or critically ill patients with COVID-19.

## Introduction

COVID-19 has kill a lot of lives around the world. Symptomatic supportive treatment is still the main treatment for COVID-19 [1]. The latest results of pathological anatomy suggest that alveolar inflammation and mucilaginous secretion were main pathological changes of COVID-19[2]. Progressive hypoxemia were the typical manifestation of progressive COVID-19 pneumonia [2,3,4,5]. All methods of atmospheric oxygen therapy, including nasal oxygen breath, non-invasive/invasive mechanical ventilation, and even extracorporeal membrane oxygenation (ECMO), have been included in the WHO and Chinese official recommendation of COVID-19 treatment, except for hyperbaric oxygen therapy (HBOT). The later is the most powerful oxygen therapy known, and have been used as a routine oxygen therapy to acute and chronic hypoxemia for more than half a century. Here we share the detail of five cases with severe COVID-19 successfully treated by HBOT in General Hospital of the Yangtze River Shipping(Wuhan), including the clinical course, management of illness, and the clinical examination results of these 5 cases.

## History of cases

5 patients, 24-69 (mean 47.6) years old, were hospitalized in General Hospital of the Yangtze River Shipping. Their chest CT showed typical pulmonary imaging changes of COVID-19, and nucleic acid tests of SARS-CoV-2 were positive. HBOT treatment was started with informed consent and voluntary request after the routine treatments were failure to stop deterioration of condition. then the HBOT treatment was given once a day. Their brief histories in hospital were described as below:

*Patient 1#:* male, 69 years old, was admitted to the hospital with fever for one day. Past history had hypertension, coronary heart disease, acute myocardial infarction, and the coronary stent implantation. the symptomatic treatments were given as Methylprednisolone (2×40 mg/d for 5 days), Immunoglobulin (20g/d), Ceftriaxone (3 g/d), and Abidol (3×0.2 g/d). Oxygen therapy started with 5-day's nasal oxygen inhalation, and then followed 15-day's mask oxygen inhalation. Then patient's condition continued to deterioration. Chest CT indicated progress of lung lesions. The medical advice of non-invasive mechanical ventilation was rejected by the patient. HBOT treatments were introducing 21 days after admission.

*Patient 2#:* male, 64 years old, was admitted to the hospital with cough and fever for 5 days. symptomatic treatment was given Methylprednisolone, Immunoglobulin, Ceftriaxone, Abidol, Ribavirin (0.5 g/d), and albumin (10 g/d). Oxygen therapy started with one-day's nasal inhalation, and then followed 6-day's mask. Additional HBOT was introduced 12 days after admission.

*Patient 3#:* male, 28 years old, was admitted to the hospital with cough and expectoration for 12 days, fever with pharyngalgia and pectoralgia for 10 days. The symptomatic treatment was given Methylprednisolone, Immunoglobulin, Ceftriaxone, Abidol, and Ribavirin. Oxygen therapy started with 2-day's nasal inhalation, and followed 12-day's mask. However, signs and symptoms of hypoxemia were aggravated. Chest CT images showed significant progress of lung lesions. Then the non-invasive mechanical ventilation was used for 2 days but failure to improve SpO<sub>2</sub>. Subsequently, additional HBOT was introduced 19 days after admission.

*Patient 4#:* male, 53 years old, was admitted to the hospital with cough one week and fever three days. The symptomatic treatments were given Methylprednisolone, Ceftriaxone, Abidol, Ribavirin, and Immunoglobulin. Oxygen therapy start with one-day nasal inhalation, and followed with 13 days' mask. Additional HBOT was introduced 18 days after admission.

*Patient 5#:* female, 24 years old, was admitted to the hospital with fever three days. The symptomatic treatments were given as Methylprednisolone, Ceftriaxone, Abidol, Ribavirin, and Immunoglobulin. Oxygen therapy was start with one-day nasal oxygen inhalation, and followed with 17 days mask oxygen inhalation. 14th day in hospital, the patient was transferred to ICU for complication of myocarditis. conditions were deteriorated. Then the HBOT treatment was started at the 19th day in hospital.

The oxygen therapy used were listed in Table 1. The main oxygen therapy in the ward before introducing HBOT was mask inhalation, and nasal oxygen breathing after first HBOT.

**Table 1 the usage of oxygen therapy for 5 cases in the hospital**

patient	sex	age	before HBOT treatment(d)			after first HBOT treatment(d)		HBOT(d) times
			Nasal	Mask	Mech	Mask	Nasal	
1#	M	69	2	14	-	3	15	8
2#	M	64	1	6	-	4	5	5
3#	M	28	2	12	2	0	2	4
4#	M	53	1	12	-	0	7	3
5#	F	24	1	16	-	0	9	3
mean		47.6	1	12	-	1.4	8	4.6

NOTE: nasal = nasal oxygen breathing with a flow of 3-5L/min; Mask = mask oxygen breathing with a flow of 5-8L/min; Mech = non-invasive mechanical ventilation

## Protocol of HBOT Treatments

HBOT once a day was carried out for every patient with a medical hyperbaric chamber (China Hongyuan Oxygen Industrial, GY2800D-A). Patients enter hyperbaric chamber through the exclusive path. Immediately entering the chamber, the patients breathed oxygen with the built-in breathing apparatus (BIBS) until the end of decompression without interval for the infectious disease control. The chamber was compressed to 2.0 ATA(absolute pressure, the same below) for

Patient 1# and 1.6ATA for the other patients with air in 15 min. The bottom time was 90min in first treatment and 60min in the followed. The decompression to atmospheric pressure was in 20 min.

Disease control and prevention was primary high concern. Above all, hyperbaric chamber and oxygen inhalation system are perfect gas management systems for disease control with properties of closed, one-way gas flow, all fresh air, and relatively independent gas lines for medical staff and patients, which suggested that the risk of medical staff infection in chamber would not be higher than that in the infection ward. HBOT had mature measurements of disease control and prevention originally. For the treatment of COVID-19 patients, the measurements of disease control outside the chamber were the same as infection wards, such as separate path for medical staff and patients, and infectious areas distinguished. Disinfection measures in chamber were further strengthened as that for infectious ward area. In the procedure of treatment, the patients respired with BIBS immediately entering the chamber. The chamber kept continuous ventilation with fresh air in a high volume. Medical staff were separately compressed readily in clean auxiliary chamber, and would exposure to a relative clean treatment chamber in minutes if needed. The exhausted oxygen and air from the outlet of chamber decompression system and BIBS were disinfectant. There was none of medical staff infected during more than 20 chambers treatments.

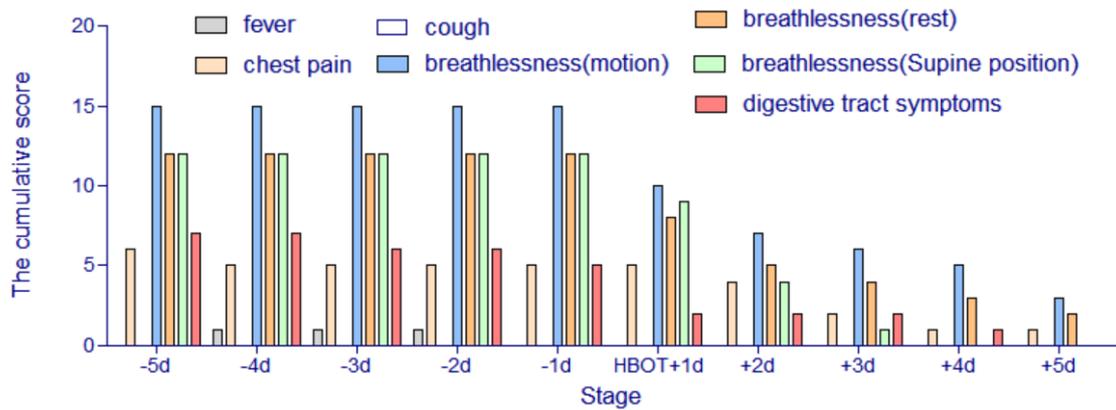
## **Data Collection and Statistical Analysis**

We reviewed clinical electronic medical records, nursing records, laboratory findings, and radiological examinations. The patients' symptoms, including fever, chest pain, breathlessness (motion), breathlessness (rest), breathlessness (supine position), and digestive tract symptoms, were divided into mild, moderate and severe, and the corresponding 1-3 score were assigned. Then the sum of 5 patients' score were calculated to evaluate the degree of changes. Daily SpO<sub>2</sub> in the ward were recorded every four hours. SpO<sub>2</sub> beside chamber before compression and after decompression were recorded every HBOT treatment. the other data were not regulation but divided into before and after HBOT introduction, such as measurement of the Arterial Blood Gases (ABG), complete blood count, coagulation function (6 parameters), blood high-sensitive C reaction protein(CRP), and chest CT. Obtained data was statistical analysis with paired t-test.

## **Results**

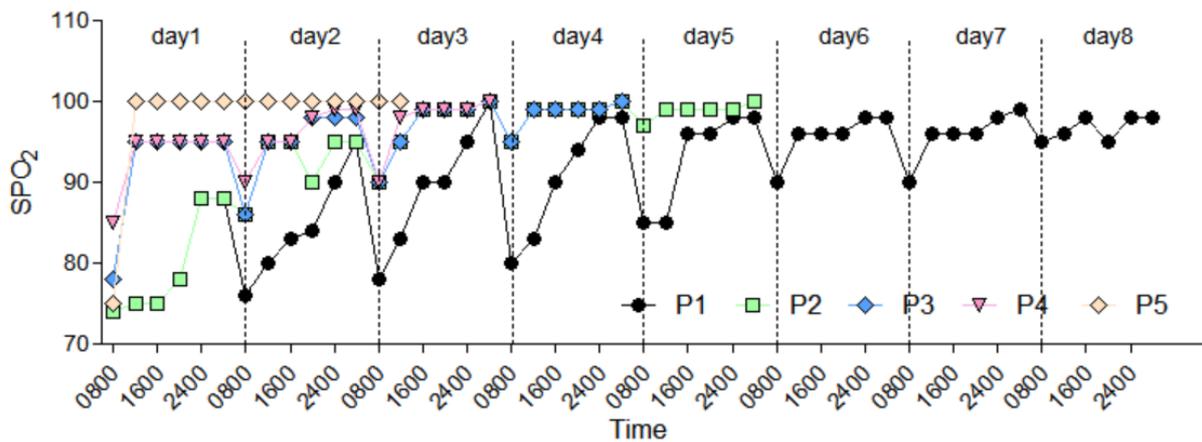
### **1. clinical manifestations**

The sum of 5 cases' symptoms score were display in Fig 1. Fever was not a persistent symptom, always released after one course of routine therapy. Cough was not prominent symptom in our cases. However, all of these 5 patients had severe breathlessness. Even 2-days non-invasive mechanical ventilation was failure to prevent the worsening of Patient 3#. It is interested that those symptoms of every case were obviously mitigated after first HBOT treatment. Breathlessness(supine position) disappeared three days later, and digestive tract symptoms five days later. All the symptoms were basically relieved except for mild breathlessness (motion) complained by every patient.



**Figure 1 changes of patients' breathlessness symptom**

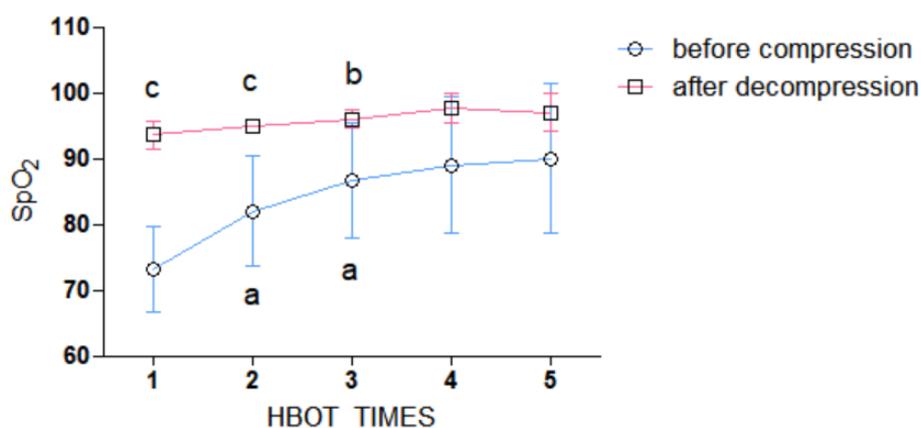
## 2. Non-invasive measurement of blood oxygen saturation



**Figure 2 changes of daily SpO2 after beginning of HBOT**

Shown as figure 2, The level of daily SpO2 decreased to the lowest in the morning and then increased to the maximum at the stage of midnight. But all patients' daily SpO2 in the ward improved from the first treatment of HBOT. Each patient's value of the same time obviously increased day by day. The mean value of daily SpO2 of Patient 1# was restored 95% after 5 days, while 2# and 3# after 3 days, 4# after 2 days, and 5# after 1 day.

After the patients were transferred from the ward to the chamber without oxygen breathing, their SpO2 beside chamber before compression were lower than that in the ward, and reflects the true degree of hypoxemia under nature breathing state. Studies of sports medicine have found that people with pre-existing pulmonary disease is likely to induce hypoxemia when exposure to a certain intensity of exercise load[6]. This phenomenon suggests that pathological changes in the lungs lead to a severe imbalance between oxygen demand and oxygen supply in patients with COVID-19 pneumonia. Shown as Fig 3, SpO2 beside chamber before compression was significantly increased day by day after HBOT introducing ( $P < 0.05$ ), which reflected significant effect of HBOT treatment.



**Figure 3 Changes of SpO2 beside the chamber before compression and after decompression**

(a: P<0.05 vs first day before compression; b: P<0.05 vs first day after decompression; c: P<0.05 vs same day before compression.)

After the first treatment, SpO2 increased significantly than before (from 73.20±6.43% to 93.60±2.07%, P<0.05). Although it dropped about 2h later (1200 in the ward, showed as Fig 1), the elevated SpO2 beside chamber after treatment suggested that even once treatment had basically repaid the body’s “oxygen debt”[6,7] accumulated in the previous continuous condition of hypoxemia. It is suggested that even once a day, HBOT provided the body an intermission of adequate aerobic metabolism, which just an interval of continuous vigorous exercise. There was also significant difference between SpO2 before and after the second treatment(P<0.05) , but not the third one, because of elevated value before treatment. It was supposed that two HBOT treatments were enough for correcting hypoxia of most patients with sever COVID-19.

Two patients (4# and 5#) had only three treatments because of recovering well. Although the data later were not compared, there is a clear trend towards improvement too. It is suggested that daily HBOT could basically avoid hypoxemia of COVID-19 pneumonia patient with SpO2 lower than 70% in the follow-up daily treatment.

### 3. Measurement of ABG

PaO2 of 5 patients before HBOT were separately 37mmHg, 65mmHg, 60mmHg, 78mmHg, and 68mmHg under mask oxygen breathing (FiO2 about 0.45). Accordingly, Patient 1# primary oxygenation index (OI) was below 100mmHg and severe ARDS, while the others had moderate ARDS. Figure 4 showed that PaO2 and SaO2 were significantly increased after HBOT treatments(P<0.05).

Although the increasing of PaCO<sub>2</sub> after HBOT treatments was not significant (before 31.48 +/-3.40mmHg VS after 34.86 +/-3.66mmHg), it was suggested that patients had a trend of over-ventilation with an inefficient oxygen uptake before HBOT introducing. It was consisted with the pathological finding as other clinical reports[2-5]. An obviously increasing lactate before HBOT (before 2.16 +/-1.71 mmol/L vs. after 1.13 +/-0.09 mmol/L) was supposed to a systemic anaerobic metabolism due to progressive hypoxia of patients.

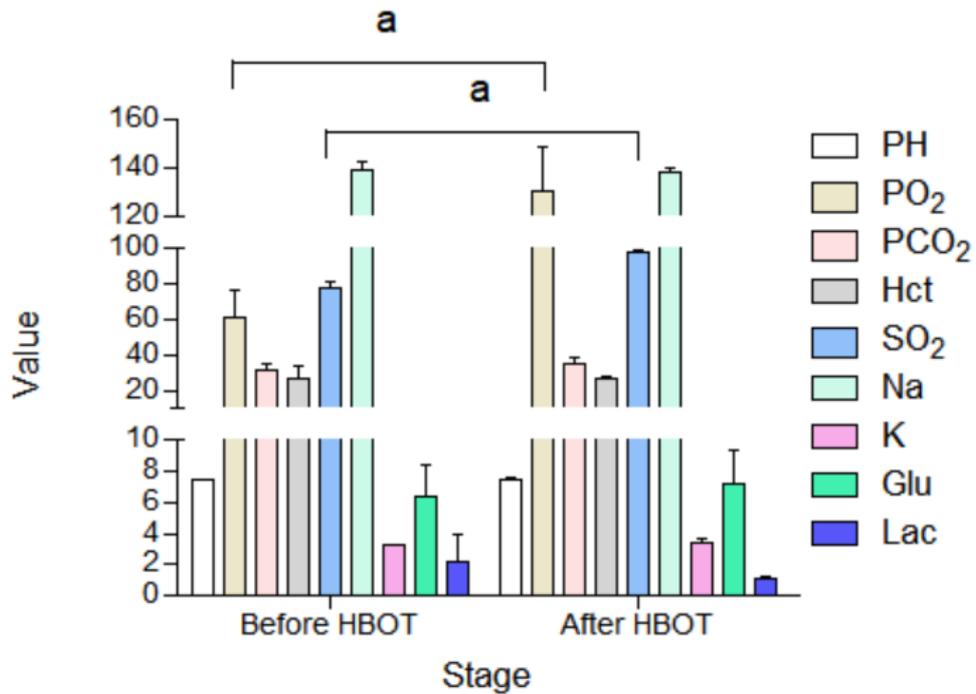


Figure 4 changes of ABG parameters before and after HBOT

#### 4. results of laboratory examination

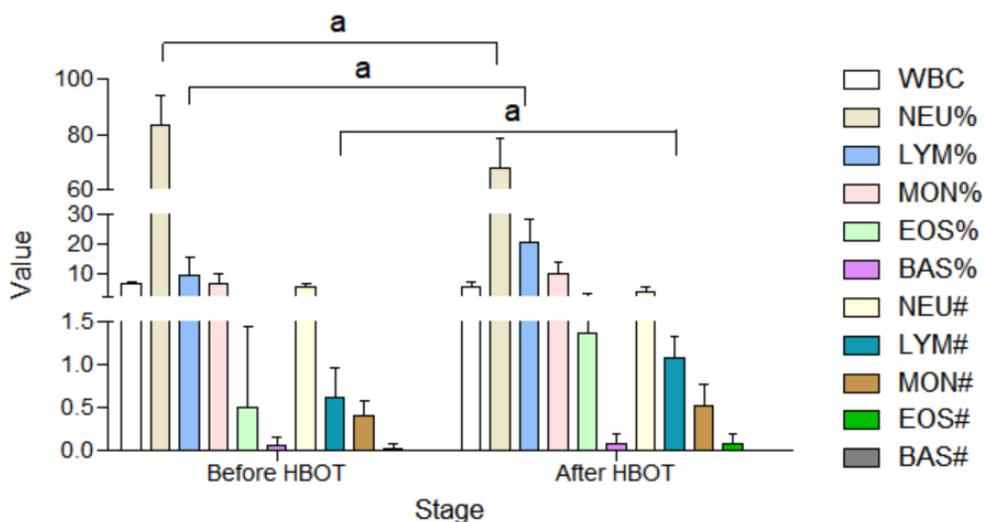
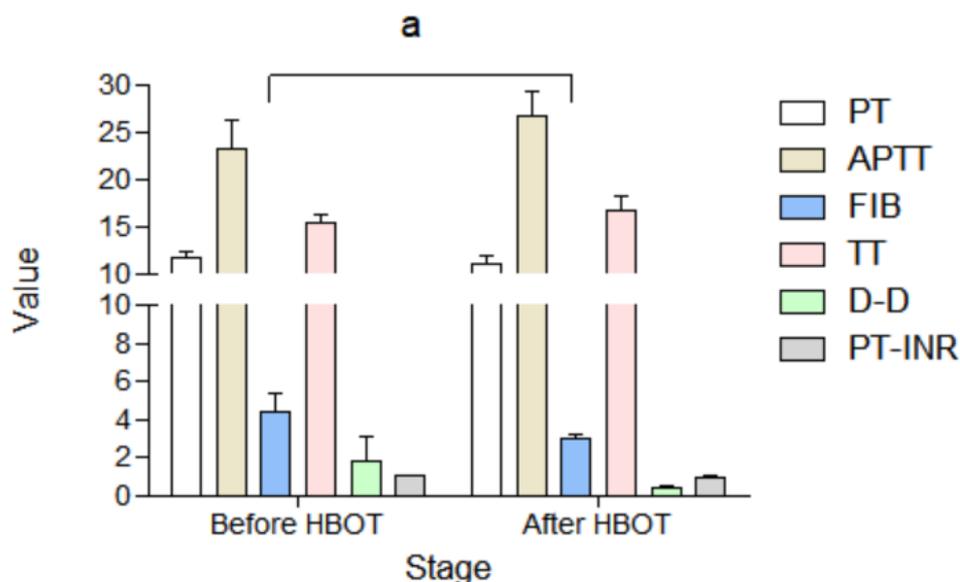


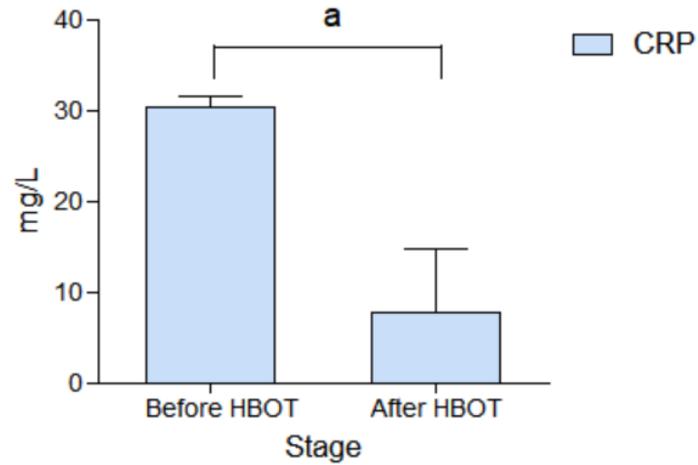
Figure 5 Changes of WBC count

As reported in recent paper of COVID-19[2], the lymphocyte count were significantly decreased in non-survivors ( $0.62 \pm 0.37 \times 10^9/L$ ). the amount of lymphocyte and LYM% of each patients were obviously elevated after HBOT treatments(  $0.61 \pm 0.35 \times 10^9/L$  before vs.  $1.09 \pm 0.24 \times 10^9/L$  after,  $P < 0.05$ ). The lymphocyte count before HBOT introducing was almost the same level of those report, which was supported that routine systematic supportive therapies additional daily HBOT would reduce mortality.



**Figure 6 Changes of coagulation function**

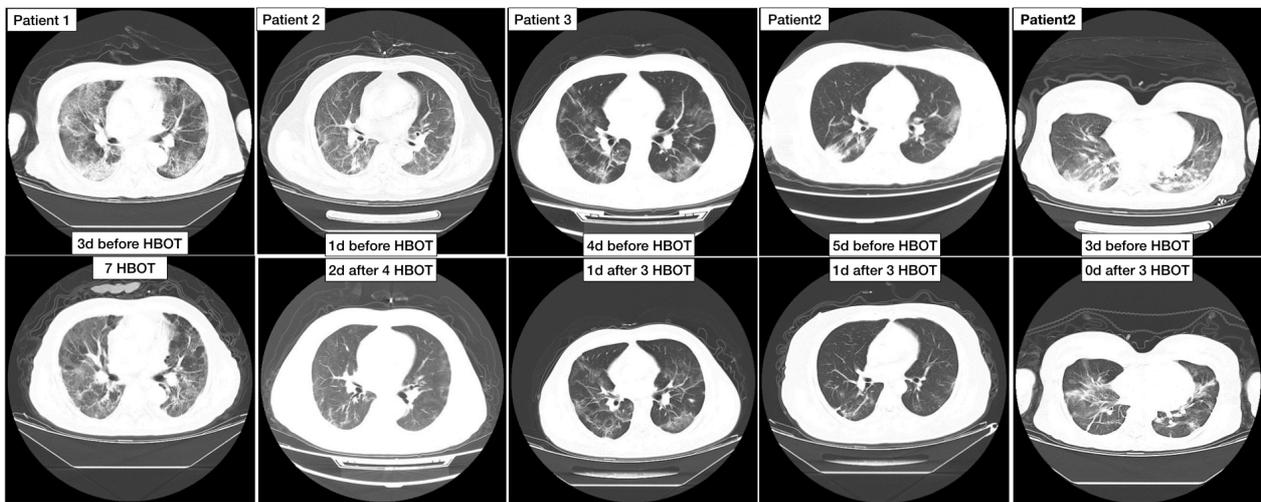
Fibrinogen(FIB) were increased before HBOT, and significantly declined after HBOT treatment( $P < 0.05$ ), while as D-Dimer(D-D). Activated partial thromboplastin time (APTT) was increased obviously after treatment. the changes of coagulation index before HBOT was suggested that there were peripheral hemodynamic changes and perfusion disorders in severe patients with COVID-19 pneumonia. Obviously restoring of those index suggested the role of HBOT in improving tissue perfusion and oxygen supply.



**Figure 7 Changes of hs-CRP levels before and after HBOT**

**5. chest CT**

Interval time of chest CT obtained showed as Fig 8. All of cases had previous imaging of mass shadows of high density in both lungs. and all Chest CT obtained during or after HBOT showed significantly improved status.



**Figure 8 Chest CT imaging of 5 patients before and after HBOT**

## Discussion

Although clinical HBOT recommendation[8,9] have a long list of indications in the name of disease, hypoxia is the only indication of oxygen therapy, as well as HBOT, the one under hyperbaric surrounding. As a symptomatic therapy, HBOT is the preferable oxygen therapy to refractory hypoxemia in severe patients of COVID-19. Oxygen is transferred from atmosphere environment to tissues and cells via several stages, including pulmonary ventilation function, alveolar gas exchange function, plasma carrying capacity and hemoperfusion, microcirculation and gas diffusing in tissue. Any dysfunction along this path would disturb the amount of oxygen presenting in distal tissue. Breathing pure oxygen under high pressure environment greatly increases the partial pressure of oxygen inhaled[8]. HBOT works on every stage by elevating diffusion rate, diffusion distance, and solubility based on the principles of physics Dalton's law and Henry's law. Compared with atmospheric oxygen therapy, it has native advantages in oxygen delivery efficiency[10]. Although only 5 cases were included, but all of these cases were accepted HBOT treatments after routine treatments as well as atmospheric oxygen therapy failure to stop exacerbation of hypoxemia and condition. SpO<sub>2</sub> of 5 patients responded very consistently to HBOT treatment, as well as breathlessness and other symptoms. Our results of these 5 cases confirmed the significant effects of HBOT treatments to hypoxemia of severe and critically ill patients of COVID-19.

Chest CT imaging suggested that the main pathological changes of COVID-19 pneumonia was inflammation of alveoli, which mean that those patients had a loss of the lung gas exchange function larger than that of ventilatory function. More gas exchange dysfunction with relatively normal ventilatory function will presents as decreased PaO<sub>2</sub> companied with decreased or normal PaCO<sub>2</sub> in ABG, the same as the data of these cases showed in Fig 4. It is reasonably supposed that only increasing of ventilation would not work, and even further increase the possibility of respiratory alkalosis. HBOT with higher diffusion rate of oxygen can overcome the increased diffusion distance of inflammatory alveolar blood-air barrier with virus infection. This may explain excellent effects of HBOT in these cases, especially the case of patient 3, to whom 2-days non-invasive mechanical ventilation had no effects, but once HBOT treatment reverses SpO<sub>2</sub>. According to Timothy's review, the mortality rate of mechanical ventilation in the care of patients with acute respiratory failure ranges from 40% to 90% of documented cases[11]. Oxygenation Index (OI), equal to PaO<sub>2</sub>/FiO<sub>2</sub>(atmospheric pressure/760)ratio, is used as a good index to evaluate the effects of mechanical ventilation. FiO<sub>2</sub> must be corrected with ratio of actual atmospheric pressure to sea level atmospheric pressure (760mmHg), which is the conception of ATA, the measurement unit of surround absolute atmospheric pressure in hyperbaric medicine. This equation could be transform as PaO<sub>2</sub> = OI×FiO<sub>2</sub>×ATA. mechanical ventilation improves PaO<sub>2</sub> by elevating OI, while HBOT by elevating ATA. ATA can be elevated in HBOT to the maximum 2.8 times of that under common atmospheric pressure. It means that, assume the same of pure oxygen breathing(FiO<sub>2</sub>=1), HBOT can have an efficiency equal to OI elevated 2.8 times by oxygen therapy of mechanical ventilation. Even further, patients breathe naturally in HBOT, avoiding all side effects of severe respiratory intervention with mechanical ventilation. This hypothesis could be enough to explain the unsatisfactory effect of mechanical ventilation oxygen therapy in early critical care treatment to

COVID-19 pneumonia. The recent clinical report shows that non-survivors were more likely to receive mechanical ventilation than survivors [2] .

These cases also suggested that additional HBOT treatment may be a foundation for other supportive therapies in the systemic treatment of severe patients with COVID-19 pneumonia. The other reports also support that additional HBOT is a decisive treatment improving cardio-respiratory function of patients with ARDS[12]. Increased plasma CRP concentrations have been reported as an observed clinical feature of COVID-19[3,4,5]. Previous review of H1N1 infectious pneumonia also found significantly elevated CRP in more severe presentations [13]. Elevated CRP levels are also significantly higher in patients with simple hypoxia problem, such as obstructive sleep apnea (OSA) and high altitude pulmonary edema (HAPE). CRP and interleukin-6 (IL-6) levels were significantly higher in patients with OSA compared to obese control subjects [14]. The levels of CRP of these 5 cases were decreased after introducing HBOT treatment, and along with clinical compliance released. Their CT imaging shows that lung infectious lesions have been reduced but still existed. The decline of CRP level could not be completely explained by pulmonary inflammations. Liu et al found that blood CRP levels of 161 patients with acute HAPE were elevated in acute stage and restored in recovery period, associated with similar changes of WBC counts[15]. This change in association of CRP and WBC count is also seen in the results of these 5 cases. Blood CRP levels were higher before HBOT ( $30.56 \pm 1.15 \text{ mg/L}$ ) and decreased after ( $3.98 \pm 1.50 \text{ mg/L}$ ), which were along with WBC count changes (before:  $6.78 \pm 0.39 \times 10^9/\text{L}$ , after:  $5.64 \pm 1.40 \times 10^9/\text{L}$ ). It is supposed that systemic inflammation is induced by combined effects of hypoxia and virus infection rather than by virus infection per se. If systemic hypoxia is not effectively corrected, the effects of other symptomatic treatments would be weakened.

## Conclusion

Our results showed that severe and critically ill patients with COVID-19 had a relatively normal pulmonary ventilation function and an inefficient oxygen uptake before HBOT introducing. There was an imbalance between oxygen demand and oxygen supply inducing a systemic anaerobic metabolism due to progressive hypoxia, which could play an important role in systematic hypoxia injury and circulatory disturbance.

It is suggested that HBOT provided the body an intermission of adequate aerobic metabolism. Two HBOT treatments might be enough for correcting hypoxia of most patients with severe COVID-19. The following daily HBOT treatment could basically avoid hypoxemia of COVID-19 pneumonia patient with SpO<sub>2</sub> lower than 70%. It supports the effects of HBOT to improve systematic tissue perfusion and oxygen supply, immune function, and lung lesion.

HBOT is a decisive treatment to the severe and critically ill patients with COVID-19 pneumonia. We suggest that early additional HBOT may stop the patient's condition deterioration when mask oxygen breathing could not prevent the SpO<sub>2</sub> decreasing. The routine systematic supportive therapies adding daily HBOT would reduce mortality.

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