Effects of Hyperbaric Oxygen Therapy in treatments of Severe Patients with COVID-19 Pneumonia.

Note: Been submitted to the Academic Journal of SMMU (ajsmmu-20200504) and under review.

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Abstract

Objective: COVID-19 pneumonia becomes a pandemic and with a high mortality of severe patients. Hypoxemia is the therapeutic difficulty in the treatment of severe patients. Hyperbaric oxygen therapy (HBOT) is the most powerful non-invasive oxygen therapy, and routinely used in the treatment of refractory hypoxia in various diseases. The clinical outcomes of severe patients treated with HBOT in the General Hospital of Yangtze River Shipping of Wuhan, were analyzed to explore the efficiency of HBOT.

Methods: Five patients, aged 24-69 years old, COVID-19 positive, accepted HBO treatment for progressive hypoxemia as PaO2 (61.60±15.24 mmHg) and SaO2 (73.20±6.43%) on normobaric oxygen supplement. Daily once HBO treatment's bottom pressures were 2.0 ATA or 1.6 ATA, bottom time was first 90 min and 60 min followed. Patients inhaled oxygen with the mask continuously without air interval under pressure. Treatment stopped 2 days after the mean of daily finger pulse oxygen saturation (SpO2) above 95%. Data collection included symptoms, respiratory rate (RR), SpO2, arterial blood gas analysis, blood cell count, coagulation function test, high-sensitivity C-reactive protein (CRP) and chest computed tomography (CT). The data were analyzed by paired t-test (two-tail).

Results: Symptomatic improvement occurred after the first HBO2 treatment in each case. The requirements of supplemental oxygen in the ward decreased after HBO2 treatments. Before HBO2 treatments, patients experienced high RR (27.20+/-5.40/min) and lactate (2.16±1.71mmol/L), but low PaO2 (61.60±15.24mmHg, 37-78mmHg) and SaO2 (73.20±6.43%), as well as SpO2 on mask oxygen inhalation. In the first and second HBO2 treatment, SpO2 alongside the chamber after decompression were significantly higher than that before compression($p<0.05$), the later increased daily($p<0.05$). Daily records of SpO2 in the ward improved after the first HBO2 treatment and generally showed progressive improvement with the course of HBO2 therapy. The mean value of daily SpO2 was increased to ≥ 95% on nasal oxygen inhalation after 1-5 times (mean 2.8) HBO2 treatments. After finishing HBO2 treatment, RR(20.80±2.28/min, $p<0.05$) decreased significantly than that before HBO2 introduced, while PaO2 (130.20±18.58mmHg) and SaO2 (98.40±-0.55%) were

significantly increased ($p<0.05$). There were significantly differences (all $p<0.05$) before and after HBO2 treatment course in the indices of Lym% (9.46±6.21% vs 20.78±7.42%, $p<0.05$), Neu% (83.62±10.39% vs 67.98±10.72%, $p<0.05$), lymphocyte count (0.61±0.35×10^9/L vs 1.09±0.24×10^9/L, $p<0.05$), FIB (4.45±0.94g/L vs 2.97±0.27g/L, $p<0.05$) , CRP (30.56±1.15mg/L vs 3.98±1.50mg/L, $p<0.05$). And obvious but insignificant changes showed in lactate (1.13±0.97mmol/L), APTT(23.25±2.93s vs 26.70±2.63s), D-D(1.84±1.29μg/L vs 0.42±0.13μg/L). There were obvious improvement in CT imaging of lung of each patient after HBO2 treatment.

Conclusions: Our results showed that severe patients with COVID-19 had a relatively normal pulmonary ventilation function but a poor alveolar gas-blood exchange with an inefficient oxygen uptake. HBOT, with providing the body an intermission of adequate aerobic metabolism by sufficient tissue oxygen supply, take advantage to reverse refractory hypoxemia of COVID-19, even it failed with mechanical ventilation. It also suggests the secondary effects of HBOT to improving tissue perfusion and oxygen supply, stress level, immune function. Early introducing HBOT along with routine systematic therapies may stop the patient's condition deterioration and reduce mortality.

keywords: COVID-19; Pneumonia; Hyperbaric oxygen therapy; Hypoxia; Hypoxemia.

Introduction

Coronavirus Disease 2019 (COVID-19) has kill more than 30 thousand people around the world before this paper writing(8th April), and become a pandemic. Symptomatic supportive treatment is still the standard of care for COVID-19[1]. Many recent clinical reports of COVID-19 pneumonia demonstrate a progressive hypoxia, lactic acidosis, adult respiratory distress syndrome (ARDS), and respiratory failure[2,3,4,5]. Autopsy specimens of COVID-19 infected patients demonstrate an intense inflammation with alveolar exudates, interstitial edema and leukocytosis, vasculitis, and airspace consolidation[5]. All methods of normobaric oxygen therapy, including nasal and mask oxygen breathing, non-invasive/invasive mechanical ventilation, and extracorporeal membrane oxygenation (ECMO), have been recommended by WHO[1] and the Chinese government health authority. However, the mortality of severe and critically ill patients remained high level, even have been claimed more than 60% in the clinical report[3]. There are two possibilities, either hypoxia is not the main cause of death, or treatment of hypoxia is not effective.

Hyperbaric oxygen therapy (HBOT) is the most powerful non-invasive oxygen therapy, and have been used as a routine therapy to deal with acute and chronic refractory hypoxia for more than half a century. After the first case of severe COVID-19 was successfully treated by HBO2 therapy in February 11th in General Hospital of the Yangtze River Shipping(Wuhan), the other 4 severe or critically ill patients with progressive hypoxia failed by non-invasive normobaric oxygen therapies in hospital were accepted HBOT after signing voluntary informed consent. All patients were discharged from hospital after full recovery. HBOT just provided intermittent sufficient oxygen. Oxygenation declined quickly after decompression. However, every patient accepted HBOT presented the very consistent clinical responses, especially whole condition improvement occurred

since the first HBOT in each patient. This phenomenon could not contribute to occasionality and fortuity under the background of high mortality of severe and critical illness. It prompted us to collect and analyze the cases data in order to explore the potential mechanism of the effectiveness.

Methods

1. Brief History of cases

Five SARS-CoV-2 positive patients, 24-69 (mean 47.6) years old, were hospitalized in the General Hospital of the Yangtze River Shipping. All patients' chest computed tomography (CT) showed typical imaging changes of COVID-19 infected patients.[4,5] HBOT were introduced after routine therapies failed to stop deterioration and presentation of progressive hypoxia. The brief clinical courses of each case were presented as following.

Patient 1#: a 69 years old male, 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. Medicine treatments were Methylprednisolone (40 mg twice/day), Immunoglobulin (20g/d), Ceftriaxone (3g/d), and Arbidol (0.2g three times/day) for 5 days. Oxygen therapy started with 5-day's nasal cannula oxygen inhalation (3-5 L/min, the same below), and then followed 15-day's mask oxygen inhalation (5-8 L/min, the same below). The symptoms of hypoxemia continued to deteriorate. The medical advice of non-invasive mechanical ventilation was rejected by the patient, and then HBOT began 21 days after admission.

Patient 2#: a 64 year old male, was admitted to the hospital with cough and fever for 5 days. Past medical history included hypertension, coronary heart disease, and diabetes. Medicine treatments were Methylprednisolone, Immunoglobulin, Ceftriaxone, Arbidol, Ribavirin (0.5 g/d), and albumin (10 g/d). Oxygen therapy began with nasal cannula for one day that was increased to mask oxygen for 6-days. The patient continued to deteriorate clinically and proposed treatment requirements of HBOT 12 days after admission.

Patient 3#: a 28 year old male, was admitted to the hospital with cough and expectoration for 12 days, and fever, sore throat, and chest pain for 10 days. Medicine treatments were Methylprednisolone, Immunoglobulin, Ceftriaxone, Arbidol, and Ribavirin. Oxygen therapy began with nasal cannula for 2 days and was increased to mask oxygen for 12 days. The patients' condition deteriorated with increased signs and symptoms of hypoxemia that were accompanied by significant worsening of lung lesions on Chest CT scan. The patient was advanced to non-invasive mechanical ventilation for 2 days but his SpO2 failed to improve. HBOT was initiated by the patient's requirement at this point 19 days after admission.

Patient 4#: a 53 year old male, was admitted to the hospital with cough for one week and fever for three days. Medicine treatments were Methylprednisolone, Ceftriaxone, Arbidol, Ribavirin, and Immunoglobulin. Oxygen therapy began with nasal cannula for one day and was increased to mask

oxygen for 13 days. The patient deteriorated clinically and was advanced to HBOT 18 days after admission.

Patient 5#: a 24 year old female, was admitted to the hospital with fever for three days. Medicine treatments were Methylprednisolone, Ceftriaxone, Arbidol, Ribavirin, and Immunoglobulin. Oxygen therapy began with nasal cannula for one day and was increased to mask oxygen for 17 days. The patient's condition deteriorated on the 14th hospital day with myocarditis, necessitating transfer to the Intensive Care Unit (ICU). HBOT began on the 19th hospital day.

The oxygen therapy used were listed in Table 1. Mask breathing oxygen was the mainly oxygen therapy before HBOT, except patient 3# had 2-days non-invasive mechanical ventilation just before HBO2 treatment. After first HBOT, 2 cases were still mask oxygen breathing several days in the ward, and the other 3 case were on nasal oxygen breathing for several days.

表1 五例患者住院期间的氧疗情况

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

patient	sex	age	before HBO2 (d)			after first HBO2 (d)		HBO2
			Nasal	Mask	Mech	Mask	Nasal	times
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

2. **Protocol of HBO2 Treatments**

HBO2 treatment was administered once daily (about 9:00-10:30) in a medical hyperbaric chamber (China Hongyuan Oxygen Industrial, GY2800D-A). Patients entered the treatment chamber through a dedicated exclusive access and immediately breathed oxygen through the mask of built-in breathing apparatus (BIBS) without breaks of air breathing until leaving chamber. This is to let the exhaled gas of patients be eliminated through BIBS, minimize the pollution of the air in the chamber, so as to reduce the cross-infection risk of medical staff entering the chamber when necessary. During the whole treatment process, the pressurized chamber maintains continuous high flow ventilation to ensure the air in chamber is relatively clean. The chamber was compressed to 200kPa for Patient 1# and 160 kPa for the other patients in 15 min. Bottom time was 90min for the first treatment and 60min for subsequent treatments, and decompression was 20 min. Total

treatment time was 125 minutes for the first treatment and 95 minutes for all other treatments. Then, the patients were leaved department of HBO through the same exclusive access.

Although Infectious diseases prevention and control in HBOT to COVID-19 was highly concerned, there was not any technical problems needed scientific discussion. Because those detail measurements were not the topic of this article, here was presented in brief. First of all, according to Heating Ventilation and Air Conditioning (HVAC) requirements for the infectious disease control in an enclosure such as the ward, the hyperbaric chamber and its oxygen inhalation system (BIBS) are the perfect gas management system. Their structure and performance characteristics include a closed gas system, one-way gas flow control system, all fresh air ventilation system, relatively independent breathing gas pipeline system for medical staff and patients. These characteristics are superior to the infection ward. It suggests that the cross-infection risk of medical staff is not higher than that in infectious disease ward. The differences between the pressured chamber and the common wards can be regarded as that the wards on plain and plateau, just the difference of atmospheric pressure. In our practice, the measures outside the chamber in HBOT department were the same as that for the infectious disease department, while inside the chamber as those in the infection ward. Every hospital has its procedures of infectious diseases prevention and control for the infectious disease department and the wards, and the detail was not covered here. Disinfection measurements were added to the exhaust gas output of the BIBS and the chamber air system, and around area were prohibited approaching. For the special environmental pressure change process, the medical staff separately compressed in the clean auxiliary chamber. If necessary, the medical staff should balance the pressure of the main and auxiliary chamber and enter treatment chamber immediately. Nevertheless, all those patients didn't claim need for medical emergent treatment during HBOT, although medical staff had been waiting in the auxiliary chamber always. None of medical staff were infected after more than 20 times treatment.

3. **Data Collection and Statistical Analysis**

This paper was not a clinical trial but a retrospective report of case history. We reviewed clinical electronic medical records, nursing records, laboratory findings, and radiological examinations. The symptoms, including fever, chest pain, shortness of breath (at rest, with exertion, and supine), and digestive tract symptoms (Nausea, diarrhea and loss of appetite), were self-rated by the patient as mild (1 point), moderate (2 points) or severe (3 points), then scored 1 to 3 degree, and summed all patients's score at the date series of HBO2 (showed as figure 3) to present the changes of symptoms. SpO2 data included every four hours daily records in ward, and records alongside the hyperbaric chamber before and after every HBO2 treatment. The other data including Arterial Blood Gases (ABG), complete blood count, Prothrombin Time (PT), Activated Partial Thromboplastin Time(APTT), fibrinogen(FIB), Thrombin Time(TT), D-Dimer(D-D), Prothrombin Time-International Normalized (RatioPT-INR), high-sensitive C-reaction protein (CRP), were obtained before the first HBO2 and after the completed course of HBO2 for each patient. Data was analyzed by paired t-tests (two-tailed) with SPSS. $p < 0.05$ was considered significant.

Results

1. clinical manifestions

Mean individual symptom scores for the five patients from 5 days pre-HBO2 to 5 days post-HBO2 are shown in Figure 1. Fever was not a persistent symptom, always released after one course of routine therapy. Cough was not prominent symptom in any patients. Fever was the least intense symptom and resolved before HBO2 was administered. All 5 patients had breathlessness and increasing RR (27.20±5.40/min) before HBO2 therapy.

All symptoms of all cases were mitigated after the first HBO2 treatment. Supine shortness of breath disappeared on the 4th day after initiation of HBO2 therapy, and digestive tract symptoms after the 5th day. Only mild chest pain, shortness of breath, and dyspnea on exertion remained on the fifth day. The RR decreased to 20.80±2.28/min($p<0.05$) after HBO2.

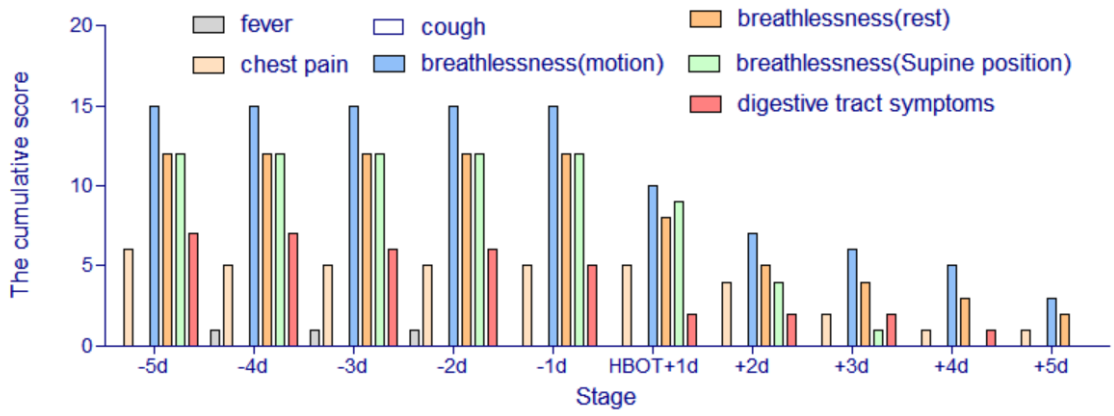

Figure 1 Total symptom scores of five patients before and after initiation of HBO2

2. Non-invasive measurement of blood oxygen saturation

The changes of daily SpO2 after beginning HBO2 therapy is shown for all patients in Figure 2. Daily SpO2 levels were the lowest in the mornings and maximal at midnight. All patients' daily SpO2s improved after the first HBO2 treatment and generally showed progressive improvement at the same times of the day through the course of HBO2 therapy. The mean value of daily SpO2 was increased to ≥ 95% on oxygen or room air after 1, 2, 3, 3, and 5 days (mean 2.8d). Patients 4# and 5# were only administrated 3 HBO2s due to recovery well. The following treatments kept the other three patients' daily SpO2 ≥ 95%. It is suggested that daily once HBO2 treatment could basically keep severe patient COVID-19 pneumonia from hypoxemia. Although patients obtained full oxygenation (SpO2, 99%) under hyperbaric oxygen inhalation in chamber, their SpO2 dropped after very short time beck to the ward, and beck to the prescribed procedure of daily changes. This phenomenon of The intermittent HBOT with prolonged effects was also in the routine HBOT to any other disease.

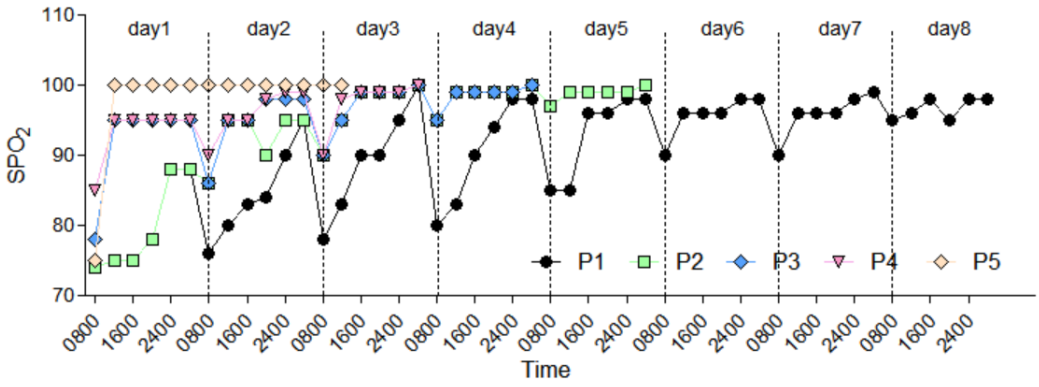

Figure 2 Records of daily SpO2 after beginning of HBO2 (Patients are P1-P5)

SpO2 alongside the hyperbaric chamber before and after every HBO2 treatment were shown in Figure 3. SpO2 before compressing was the data of patients transferred from ward to hyperbaric oxygen chamber. Non resting state could best reflect the true oxygen supply capacity and degree of hypoxemia of patients. SpO2 (73.20±6.42%) in 0900 before the first HBOT treatment was lower than that of 0800 (77.20 ± 4.66%) in the ward.

Although the SpO2 monitoring of the patients exposed to hyperbaric pressure during the treatment was 99%, the SpO2 immediately decreased to 93.60±0.07% after the first HBOT treatment. Although it was significantly higher than that before compression ($P < 0.05$), it also suggested that the systemic "oxygen debt" was not fully paid off for one HBOT in most patients. SpO2 increased significantly before HBOT compression for the second and third time ($P < 0.05$), and the difference between SpO2 and data after HBOT compression was smaller and smaller. There was no significant difference before and after HBOT compression for the third HBOT. It suggested that the accumulation of oxygen debt decreased day by day. Three times HBOT treatment can alleviate the systemic "oxygen debt" of most severe patients.

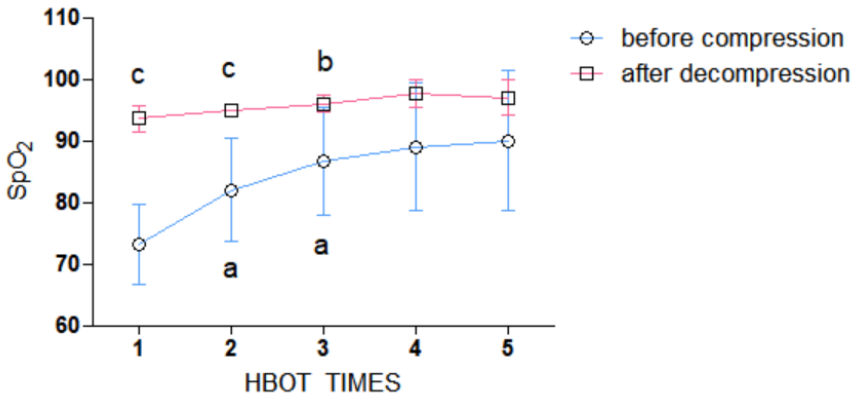

Figure 3 Mean SpO2 values alongside the chamber pre and post each HBOT. (a: p<0.05 vs first day before compression; b: p<0.05 vs first day after decompression; c: p<0.05 vs same day before compression.)

3. Measurement of ABG

Figure 4 showed the results of ABG including pH, part pressure of oxygen(PaO2), part pressure of carbon dioxide(PaCO2), hematocrit (Hct), saturation of oxygenation (SaO2), sodium (Na), potassium (K), glucose (Glu), and lactate (Lac) . The lowest PaO2 of 5 patients were separately 37mmHg, 65mmHg, 60mmHg, 78mmHg, and 68mmHg under mask oxygen breath (FiO2 about 0.4-0.6) before HBOT. However, PCO2 were not elevated but slightly lower than normal range(31.48±3.40mmHg, normal range 35-40mmHg). It was suggested that patients had been in a condition similar to over-ventilation. Patients had a relative normal pulmonary ventilation but a terrible gas exchange function. Low PaO2 companied elevated level of lactate before HBO2 treatments (2.16±1.71mmol/L) was suggested systemic anaerobic metabolism due to progressive hypoxia.

PO2 were significantly increased after HBO2 treatments(61.60±15.24mmHg to 130.20±18.58mmHg, P<0.05), and SaO2 too(73.20±6.43% to 98.40±-0.55%, p<0.05),but not PCO2 (34.86±3.66mmHg). Blood level of lactate declined obviously to 1.13±0.09mmol/L after HBO2. These meant hypoxemia was corrected.

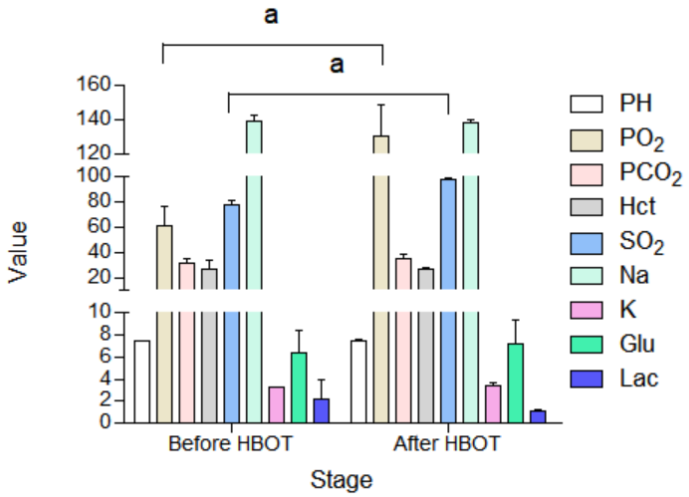

Figure 4 Changes of ABG parameters before and after HBO2. (a: p< 0.05)

4. Laboratory examination

The results of WBC count was showed in Figure 5. As recent report of COVID-19 [2], the lymphocyte count were significantly decreased in non-survivors (0·62±0·37×10^9/L). The Lym# were obviously elevated before HBO2(0.61±0.35×10^9/L), which was the same degree as this report. All the 5 patients recovery quickly, and the Lym# was significantly increased after HBO2 treatments(1.09±0.24×10^9/L, p<0.05) while as Lym% (from 9.46±6.21% to 20.78±7.42%, p<0.05), which suggested that addition HBO2 treatments might reduced mortality. There were

significant differences Neu% (from 83.62±10.39% to 67.98±10.72%, p<0.05) but not obvious changes in Neu#, which might be the sequence of increasing of lymphocyte.

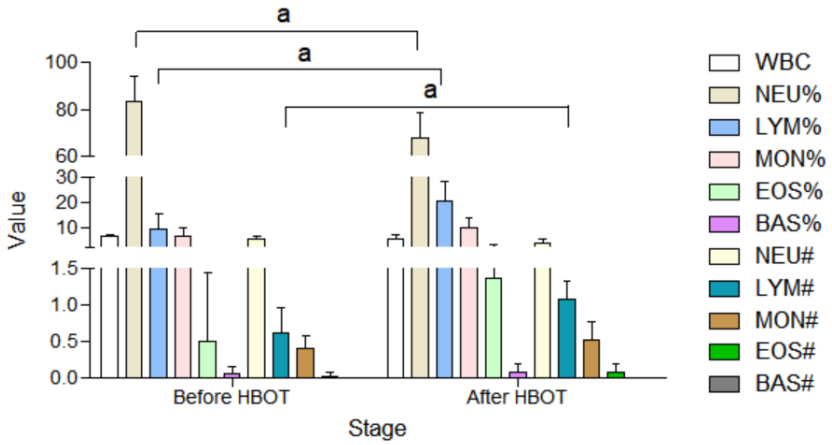

Figure 5 Changes of WBC count(WBC=white blood cell count, NEU=Neutrophils, LYM=Lymphocytes, MON=Monocytes, EOS=Eosinophils, BAS=Basophils, #=count)

The results of coagulation function (Figure 6) showed that the blood level of FIB (4.45±0.94g/L) and D-D(1.84±1.29μg/L) was elevated, and APTT(23.25±2.93s) declined before HBO2, which suggested peripheral hemodynamic changes as a hyper-coagulable state and microcirculatory dysfunction. FIB was significantly declined after HBO2 treatment(2.97±0.27g/L, p<0.05), while obviously but insignificantly declined in D-D (0.42±0.13μg/L). APTT was obviously increased but not significantly (23.25±2.93s to 26.70±2.63s). Changes of coagulation index suggested that HBO2 therapy was able to overcome the peripheral perfusion and diffusion disorders in severe patients with COVID-19 pneumonia. Those results suggested a secondary benefit to the improvement in systemic immune function.

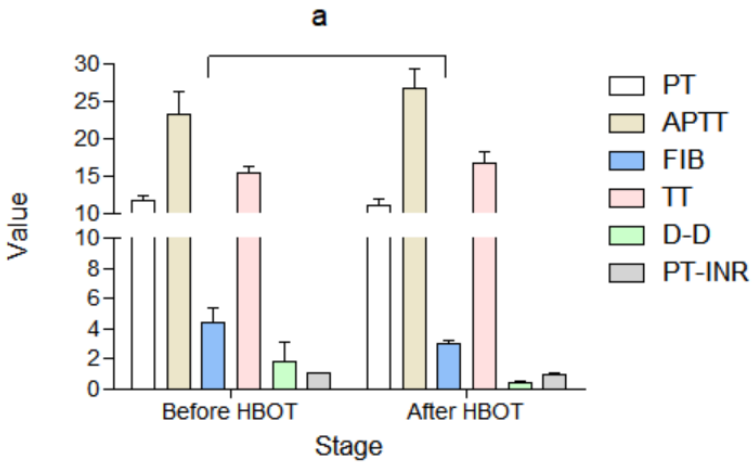

Figure 6 Changes of coagulation function

There were significantly differences before and after HBO2 therapy course in the blood level of CRP (30.56±1.15mg/L vs 3.98±1.50mg/L, $p<0.05$, Figure 7), which was one of the biomarks of cytokine storm in severe patient with COVID-19 pneumonia[2,3]. Although the other cytokines, such as IL-6, were not examined in our cases, the change of CRP provided impressive was supposed to lower the stress and secondary to stop cytokine storm.

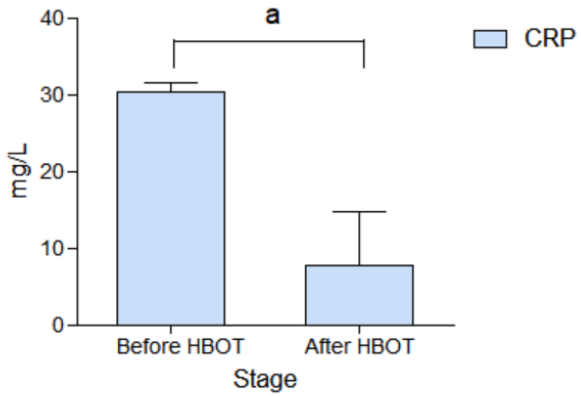

Figure 7 Changes of hs-CRP levels before and after HBO2

5. chest CT

CT of the lungs performed pre-HBO2 showed bilateral high density infiltrates in all subjects (Figure 8). After HBO2 there was significant visual improvement of the lungs in all patients.

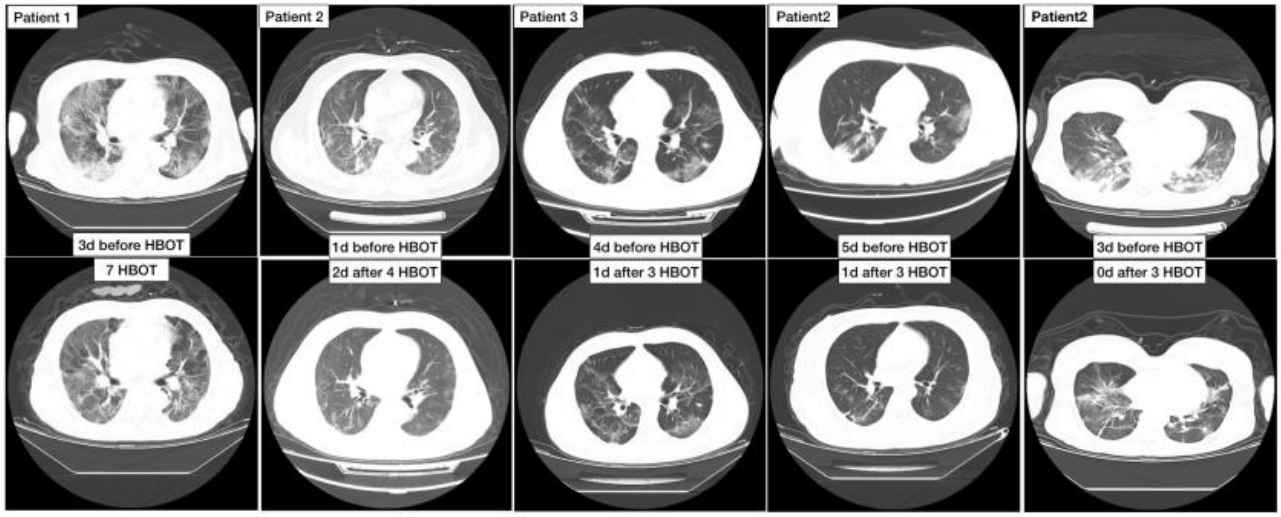

Figure 8 Chest CT imaging of 5 patients before and after HBO2

Discussion

Although clinical HBO2 therapy recommendation[7,8] have a long list of indications in the name of disease, hypoxia is the only indication of HBOT, as well as other oxygen therapy. The high part-pressure oxygen is the only reason of HBOT therapeutic effects working on local or systemic, acute or chronic, inflammatory or ischemic hypoxia in various diseases. Except for the special indication

of bubble embolism disease, pressure plays a more important role. Otherwise it is better to name recompression therapy than oxygen therapy. 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 or obstacles along this path would disturb the amount of oxygen presenting in distal tissue. Breathing pure oxygen in high-pressure environment can greatly improve the partial pressure of inhaled oxygen, the diffusion distance, diffusion rate of oxygen and the amount of physical dissolution in body fluid [10]. Compared with atmospheric oxygen therapy, it has obvious advantages in overcoming the dysfunction of various links, and also has the experience of successful treatment in ARDS and chest lung injury [11, 12]. Therefore, HBOT may be the best oxygen therapy for severe patients with COVID-19 pneumonia. Although there are only 5 cases in this paper, HBOT treatment is only started under the condition of progressive hypoxemia which can not be controlled by atmospheric oxygen supply. In particular, 5 cases, without exception, after the first treatment, not only the hypoxemia began to reverse, the condition also improved day by day. Such a consistent clinical effect cannot be explained by chance. Once a day HBOT, high pressure oxygen is a short time, and will not store a lot of oxygen in the body. The results also showed that SpO2 decreased after decompression and lower late. Whether the above natural advantages of HBOT can be responsible for the overall efficacy of patients is worth further exploration.

Recent articles [2-5] all show that the main pathological change of COVID-19 pneumonia is the alveolar inflammation. The latter means that the dysfunction of alveolar gas exchange is prominent, but not that of pulmonary ventilation. Our results also verify this point of view. Before HBOT, PaO2 and SaO2 decreased severely with low PaCO2. It is reasonable to speculate that only increasing ventilation function, such as mechanical ventilation, will not work, and even further increase the degree of respiratory alkalosis. Timothy's review mentioned that the mortality rate of mechanical ventilation in patients with acute respiratory failure was as high as 40% ~ 90%, among which mechanical ventilation played a role in respiratory tract injury and secondary infection [14]. There was no obvious respiratory injury and interference in HBOT patients with a nature ventilation. The increase of HBOT diffusion distance and diffusion rate overcomes the problem of thickening of gas-blood barrier induced by virus infection of alveoli. The first HBOT elevated SpO2 above 90% confirmed the superiority. Especially in Patient 3#, two-day non-invasive mechanical ventilation did not work, but deteriorating SpO2 was reversed since the first HBOT.

The gold index to evaluate the oxygen delivery efficiency of mechanical ventilation, the oxygenation index (OI) is equal to PaO2 / FiO2. FiO2 is corrected by times "ambient pressure / 760" which is the absolute pressure (ATA) in high pressure medicine, standard atmospheric pressure is 1 ATA. As PaO2 is the target of oxygen therapy, the formula transport to PaO2 = IO × FiO2 × absolute pressure (ATA). The mechanical ventilation improves PaO2 by increasing OI, normobaric oxygen therapies by elevating FiO2, as well as HBOT by elevating absolute pressure (ATA). According to the different exposure pressure of HBOT, the absolute pressure varies from 1.6 to 2.8 ATA. It means that HBOT will obtain the 1.6 to 2.8 times improvement of PaO2 , as that effect of OI elevated 1.6-2.8 times by mechanical ventilation when the oxygen percentage of inhaled air is the same. Therefore, if mechanical ventilation cannot elevate OI to 1.5 times of natural respiration,

addition HBOT is also helpful to improve oxygen delivery efficiency. This derivation may explain the internal mechanism of the poor effect of mechanical ventilation on severe patients with covid-19 [2,3], and the significant effect of HBOT on hypoxia correction in our cases.

However, once a day HBOT short-term treatment, seems to be unable to explain the prolonged improvement of the overall condition. According to the literature of sports medicine, individuals with precordial cardiopulmonary disease are more likely to accumulate "oxygen debt" due to exercise [14]. The decrease of SpO2 before compression compared with that previous in the ward showed that, the slight activity transported from the ward to the hyperbaric chamber significantly increased the degree of decompensation of cardiopulmonary function. There is a huge gap between the low oxygen supply caused by the patients' severe impairment of cardiopulmonary function and the high oxygen consumption caused by the high metabolism in the state of disease. The body is in the state of continuous systemic "oxygen debt" accumulation dominated by the whole anaerobic metabolism. This may be an important problem of COVID-19. SpO2 data after decompression showed that one HBOT did not fully pay off the "oxygen debt" in most patients. However, decreasing SpO2 differences between before compression and after decompression suggested that the accumulation of "oxygen debt" was decreasing day by day. This may be similar to high intensity interval training in sports medicine, which can effectively improve anaerobic exercise tolerance [16]. Continuous hypoxemia in severe patients with COVID-19 pneumonia results in a continuous anaerobic metabolism state in which oxygen supply and oxygen demand are relatively unbalanced. HBOT provides sufficient aerobic metabolism intermittence, which makes the body obtain better tolerance to continuous anaerobic metabolism.

Our results also suggested that HBO2 treatment may be a foundation for other supportive therapies in the systemic treatment of severe patients with COVID-19 pneumonia. Increased plasma CRP concentrations have been reported as a clinical feature of COVID-19[3]. Previous review of H1N1 infectious pneumonia also found significantly elevated CRP in severe patients [17]. 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 [18]. Liu found that blood CRP levels of 161 patients with acute HAPE were elevated in acute stage and restored in recovery period, companied changes of WBC counts[19]. This synchronous variations of CRP and WBC count is similar to our results. High levels of blood CRP before HBOT were declined after HBO2 treatments, along with lymphocyte count changes. Decreasing Lymphocyte count as well as elevated level of D-dimer and CRP is presented and claimed as a mark of bad outcome in previous report [2,3,4,5]. CT imaging of these 5 cases shows that lung infectious lesions has improved but still existed after HBOT course. The decreases of CRP and D-dimer could not be completely explained by virus infection and pulmonary inflammations. HAPE is a typical hypoxia disease. It is supposed that systemic inflammation of COVID-19 patients is induced by both 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 patients with COVID-19 had a relatively normal pulmonary ventilation function but a poor alveolar gas-blood exchange with an inefficient oxygen uptake. HBOT, with providing the body an intermission of adequate aerobic metabolism by sufficient tissue oxygen supply, take advantage to reverse refractory hypoxemia of COVID-19, even it failed with mechanical ventilation. Our results suggested that three HBOTs should be enough to correcting hypoxia of majority patients with severe COVID-19 pneumonia. The following daily HBOT could keep them away from hypoxemia. It also suggests the secondary effects of HBOT to improving tissue perfusion and oxygen supply, stress level, immune function. The oxygen therapy is a decisive treatment to the severe patients with COVID-19 pneumonia. We suggest that early addition HBOT may stop the patient's condition deterioration when normobaric oxygen breathing could not prevent the SpO2 decreasing. The routine systematic supportive therapies adding daily HBO2 would reduce mortality.

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acknowledgement

We sincerely thank 5 patients involved in the study. We thank General Hospital of the Yangtze River Shipping of Wuhan and all its medical staff for their help in carrying out HBO2 treatment. We thank Dr. Jiguang Meng (The respiratory department of the Sixth medical center of general hospital of PLA, China) for his professional advices of respiratory disease treatment. We thank Professor Shuanghong Chen and Weipeng Li (both Naval Medical Center, Naval Medical University, Shanghai China), Dr. Lian Tian (CDC of Shanghai China) for their professional advices of infectious disease control. We thank Paul G. Harch(Hyperbaric Medicine Department, Louisiana State University Health Sciences Center, New Orleans, LA, USA) reviews this paper and help of English grammar.