Inhalation of Heliox as a potential treatment for the ARDS caused by COVID-19

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Systematic Review

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Abstract

Corona virus disease 2019 (COVID-19) is currently a global pandemic It presents as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to COVID-19 infection. Despite the widespread use of symptomatic, antiviral, , and supportive treatment, the daily death toll from COVID-19 is still rising. The most common lethal complication is acute respiratory distress syndrome (ARDS). Mechanical ventilation is one of the necessary support methods of treating ARDS. Heliox (Helium-oxygen mixture) inhalation can reduce respiratory work of breathing, improve oxygenation, improve lung compliance, and effectively optimize the treatment of ARDS. Heliox also has potential anti-inflammatory, neuroprotective, and cardiac effects, and could reduce the inflammatory storm caused by SARS-CoV-2. This article reviews the properties of heliox, the therapeutic mechanism for ARDS, and the effects of heliox on inflammation, nerves, and the heart. *Conclusion* We suggests that heliox is a potential treatment for COVID-19.

1. Introduction

In December 2019, a group of pneumonia cases were reported in Wuhan, Hubei Province, China. Subsequently, COVID-19 was soon confirmed to be causefor SARS-CoV-2, which has caused a global pandemic. As of September 8, 2020, a total of 27,418,709 patients with COVID-19 and 894,770 deaths have been confirmed worldwide. SARS-CoV-2 infects the lungs by using angiotensin-converting enzyme 2 in type 2 alveolar epithelial cells as a gate. The inflammatory storm after SARS-CoV-2 infection can cause lung cell loss, pulmonary edema, and formation of hyaluronic acid, induces acute respiratory distress syndrome (ARDS), which leads to death. Autopsy report also showthat the pathological features in both lungs indicate findings similar to that of ARDS or SARS., and Middle East respiratory syndrome (MERS) [1,2]. ARDS is the most serious complication, accounting for 20.1% of COVID-19, with a mortality rate of 41.1%[3]. Mechanical ventilation is necessary for treating ARDS. Heliox is a helium–oxygen mixture gas. Helium has special physical properties. Heliox by mechanical ventilation can reduce the work of breathing, improve compliance, promote removal of carbon dioxide and improve oxygenation. Therefore, heliox could become a lung-protective ventilation strategy. Another potential benefit of heliox is its anti-inflammatory effect. This effect not only effectively reduces the inflammatory response to lung damage, but also inhibits overflow of inflammatory cytokines or chemokines, and reduces the occurrence of a systemic cytokine storm. Heliox also protects nerves and the heart during ischemia-reperfusion. Therefore, heliox is likely to have a therapeutic potential for ARDS caused by COVID-19.

2. Properties And Safety Of Helium

Helium is a colorless, odorless, and non-toxic inert monatomic gas, which does not react with other gases in the body and has no pharmacological activity. Helium is also the lightest noble gas and has the lowest melting and boiling points of all elements. Helium has a lower density (0.179 g/m) compared with oxygen (1.43 g/m) and nitrogen (1.25 g/m), and its absolute viscosity is 201.8 mp (oxygen: 211.4 mp; general air: 188.5 mp). Under the same conditions, helium flows 2.68 times faster than air. Because the size of the airflow depends on the density and viscosity of each component of the mixture, the physical

properties of helium reduce respiratory resistance and increase airflow through the lungs[4].Heliox (Helium-oxygen mixture) has a viscosity similar to, but a density nearly six times lowers than atmospheric air. Because of these unique properties, heliox has a potential application in respiratory medicine. Heliox gas mixtures are known to be nontoxic, noncarcinogenic, and have no lasting effects on any human organs. Due to its lower density, inhalation of heliox results in significantly lower turbulence, particularly in the more distal portions of the lung. This effect translates to a greater proportion of laminar flow and lower overall airway resistance. The decreased turbulence effect results in increased flow rates by up to 50% during heliox inhalation[5]. This decreased turbulence remained evident even when airflow was restricted, as in the case of obstructive lung disease. Heliox has been applied to various respiratory diseases in adults for more than 70 years with no adverse effectswith no sereous complications reported[6].A case report showed that the combination of helium and oxygen is safe during pregnancy[7]. A lower density of helium causes inaccurately high readings from flow meters that are calibrated for air and/or oxygen[8,9]. Therefore, the flow transducer within the ventilator needs adjustment to correctly measure flow to prevent discrepancy in exhaled tidal volumes and misinterpreted improvement in carbon dioxide (CO_2) clearance.

3. Principle Of Treatment Of Ards

Since the outbreak of SARS-CoV in 2002 and MERS-CoV in 2012, the emergence of SARS-CoV-2 marks the third introduction of a highly pathogenic and pandemic coronavirus into humans in the 21st century. SARS-CoV-2 is a beta coronavirus, and two other known beta CoVs are SARS and MERS. All these coronaviruses can lead to severe and potentially fatal respiratory infections, mainly caused by lung cell loss, pulmonary edema, and formation of hyaluronic acid. This then leads to ARDS causing death. Autopsy report showe confirm the lesions in both lungsas seen in ARDS [1,2]. Therefore, development of more effective mechanical strategies to reduce the mortality of ARDS is not only an urgent need in the current outbreak of novel coronavirus, but also a long-term need to reduce the mortality of viral pneumonia worldwide[3]. Heliox due to its unique properties may be an ideal gas in ARDS caused by SARS-COVID-2 in reuducing the work of breathing, improving compliance and inflammation and reducing morbidity and mortality[10]. During ventilation with heliox, lower driving pressures are necessary to distribute oxygen to the distal alveoli to improve oxygenation and CO_2 diffusion . This will result in better gas exchange in ARDS[11]. Therefore, Heliox is a better lung-protective ventilation strategy for ARDS.

3.1 Animal models

In a study of neonatal piglets where ARDS was induced by saline lavage[12], three types of aeration therapy were evaluated, including oxygen-enriched air and heliox (60% oxygen/40% helium and 40% oxygen/60% helium). The results showed that the partial pressure of carbon dioxide($PaCO_2$), in the two heliox groups decreased on an average of 10.5 and 20.3 mm Hg. A modest improvement in oxygenation was observed with the 40% helium mixture. These results indicated that heliox improved oxygenation and elimination of carbon dioxide. Similar results were found in other animal models of ventilation in ARDS.

Heliox significantly improved gas exchange, reduced the need for oxygen, and decreased PaCO2 compared with the pediatric swine ventilated with nitrogen[13,14].

3.2 Clinical study

Heliox has been clinically studied for more than 70 years to reduce airway resistance and improve ventilation. Two adult studies reported results in patients who were diagnosed to have bronchiolitis obliterans syndrome and acute respiratory failure following lung transplantation.and were treated with 60% heliox administered either via bi-level positive airway pressure(BiPAP) or high-frequency oscillatory ventilation (HFOV)[15]. This report showed that heliox ventilation increased pH and decreased PaCO2. In a randomized, controlled study of newborn respiratory distress syndrome[16], 51 newborns were randomly divided into two groups. Both groups received nasal continuous positive airway pressure (NCPAP). The first group received NCPAP plus Heliox21 while control group received NCPAP with standard medical air. The intervention group (n=27) received 80% heliox and the control group (n=24) received nasal continuous positive airway pressure with medical air. This study showed that NCPAP with heliox treatment significantly decreased the risk of intubation for mechanical ventilation (14.8% vs 45.8%; P=0.029, relative risk 0.32, 95% confidence interval 0.12–0.88) and decreased the requirement for surfactant (11.1% vs 43.5%; P=0.021, relative risk 0.26, 95% confidence interval 0.08–0.82). In clinical studies on the treatment of ARDS in adults and childrenit has been shown that a helium–oxygen mixture improves gas exchange, promotes elimination of CO2, and reduces the rate intubation r. Therefore, using a helium–oxygen mixture is a reasonable intervention for treating ARDS caused by COVID-19.

4. Potential Anti-inflammatory Factors

Although the exact pathophysiological mechanism of progression of SARS-CoV-2 infection to ARDS is not fully understood, inflammatory storms are an important cause of ARDS. SARS-CoV-2 infects other cells in the body, especially alveolar macrophages. Inflammatory responses are triggered when infected cells die by apoptosis or necrosis[17]. The initial response of an organism to harmful stimuli is acute inflammation and this is characterized by increasing blood flow. This enables plasma and leukocytes to reach extra-vascular sites of injury, elevating local temperature and causing pain. An acute inflammatory response is also marked by activation of pro-inflammatory cytokines or chemokines. These pro-inflammatory cytokines or chemokines can lead to recruitment of inflammatory cells[18,19]. For severe inflammation associated with a cytokine storm, more serious pathological changes are observed, such as diffuse alveolar damage, hyaline membrane formation, fibrin exudates, and fibrotic healing. Therefore, ARDS develops and the patient eventually succumb to the infection. These observations are confirmed in autopsy reports where both lungs were affected consistent with the presence of ARDS caused by COVID-19, similar to SARS-CoV and MERS-CoV(20). Management of ARDS was investigated with the use of heliox in an experimental models. The lungs of two groups of rats were dissected after inhalation. This study histopathologically showed the effectiveness of heliox in decreasing infiltration of neutrophils, interstitial/intra-alveolar edema, perivascular and/or intra-alveolar hemorrhage, and HM formation in ARDS[20]. Similar results were found during continuous positive airway pressure ventilation using a

neonatal pig model in which ARDS was induced by oleic acid[21]. In the lung tissue of pigs that were ventilated for 4 h, interleukin-8 and myeloperoxidase levels, which are indicators of neutrophil activation, were lower in pigs that were ventilated with heliox compared with those ventilated with nitrogen.

5. Protection Of Nerves And The Heart

Recent studies of cells, isolated tissues, animals, and humans have shown that helium has profound biological effects as follows. When helium is applied before, during, or after an ischemic event, it reduces cellular damage, known as “organ conditioning”. Helium also exerts cellular effects in vitro and in vivo. Helium reduces ischemia-reperfusion damage in cardiac and neuronal tissue[22-26].

Helium induced changes in circulating caveolin in mice suggest a novel mechanism of cardiac protection[27]. In a rat model of resuscitation, one study examined the effects of helium pre- and post-conditioning on the brain and heart[28]. This study showed that helium treatment resulted in significantly less apoptosis. Therefore, according to the above-mentioned animal experiments, heliox has a protective effect on important organs of nerves and the heart. After SARS-CoV-2 infection, the body shows an inflammatory storm, resulting in formation of ARDS, often with multiple organ damage, such as the heart and nervous system. The use of heliox inhalation therapy without mechanical ventilation especially in early cases of COVID 19 chest infection as a protective mechanism to avoid the needs for invasive ventilation is a novel concept and requires further investigation. Use of heliox not only protects the lungs, but also has an important biological role in protecting the heart and nerves as shown in animal experiments.

6. Discussion And Prospects

There are still some questions to be considered in determining the use of a helium–oxygen mixture in treating patients with COVID-19 with ARDS. For ventilation of severely anoxic patients with ARDS, the percentage of oxygen in the helium–oxygen mixture needs to be determined. The time to use the helium–oxygen mixture also needs to be determined. Furthermore, there is the issue of whether clinical outcomes are consistent with animal models. Additionally, possible long-term complications associated with the use of helium–oxygen mixtures need to be addressed. More large-scale, randomized, well-designed, prospective studies are required to address these issues. The global COVID-19 pandemic is accelerating. In the absence of specific treatment, inhaling helium–oxygen mixtures on mechanical ventilation has great potential, although its efficacy is controversial.

Generally, pre-clinical and clinical studies on treatment of ARDS with a helium–oxygen mixture have shown encouraging positive effects, including improved ventilation, improved lung compliance, reduced inflammation, and protection of vital organs. However, data on clinical outcomes are limited, and we expect more well-designed prospective studies in the future.

7. Declarations

Author contributions Ma Juan, the first author,wrote the paper. Liu Hui-min, the corresponding author, designed and modifid the Manuscript. Yuan Shi drafted the work. Qing Mao approved the version to be published.

Compliance with Ethical Statements

Conflict of Interest The authors declare that they have no conflict of interest.

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Ethical approval The study protocol was approved by the Ethics Committee of Southwest Hospital (document No.KY201989) and was carried out in accordance with the principles of the Declaration of Helsinki, 1964.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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