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Perspective

Nocturnal oxygen therapy as an option for early COVID-19

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ABSTRACT

There is currently no effective antiviral therapy or immune-based treatment for coronavirus disease (COVID-19). The urgent challenge is to prevent the transition of COVID-19 from mild to severe infection. This paper discussed nocturnal oxygen therapy as a new option for people with COVID-19 under home quarantine. It suggested that nocturnal oxygen therapy in the early stages may be helpful in preventing disease progression by inhibiting the rapid replication of the virus and improving the body's antiviral ability.

Introduction

The coronavirus (COVID-19) has rapidly spread and swept across most countries worldwide since the first case was detected. There is currently no effective antiviral therapy or immune-based treatment for COVID-19, especially for asymptomatic or mild patients who are recommended to self-care under home quarantine. However, severe cases rapidly increase in their progression from mild cases one week after onset and can develop into respiratory failure and acute respiratory distress syndrome (ARDS) on the basis of pneumonia (Wang et al., 2020a). Therefore, there is an urgent challenge to prevent the transition of COVID-19 from mild to severe. Oxygen (O_2) therapy has been widely used and strongly recommended for patients in hospitals and cabin hospitals in China; however, asymptomatic or mild COVID-19 has not been given sufficient consideration in the present therapeutic guidelines. Through reviewing the relevant literature and combining the characteristics of COVID-19, this study proposed that nocturnal O_2 therapy could be administrated for patients diagnosed with COVID-19 regardless of hypoxia, and may be helpful in preventing disease progression by inhibiting rapid replication of the virus and improving the body's antiviral ability.

An oxygen-rich environment may disrupt virus replication

Viruses rely on the host cell's infrastructure and metabolism to complete their life cycle. Many viruses can re-programme host cellular metabolism for their replication. For instance, it has been shown that adenoviral, cytomegalovirus, vaccinia virus, and Kaposi's sarcoma-associated herpesvirus decrease oxidative phosphorylation and induce glycolysis, which provide a large carbon source for the synthesis of nucleotides and amino acids needed to replicate the virus (Thai et al., 2014; Yu et al., 2014; Mazzon et al., 2014; Cullen et al., 2014). The mechanisms of viral activation of glycolysis are sophisticated. Some investigations have found that hepatitis B virus, H1N1 virus, vaccinia virus, and human papillomavirus can stabilise hypoxia-inducible factor 1α (HIF-1α) from degradation under normoxic conditions (Mazzon et al., 2014; Ren et al., 2019; Guo et al., 2014; Moon et al., 2004). It is well-known that HIF-1α is a transcriptional activator of cellular metabolic state by hypoxia, and stabilising HIF-1α induces metabolic transformation from mitochondrial biogenesis to glycolysis. Furthermore, evidence has also revealed that hypoxia could enhance human B19 erythrovirus gene expression and hepatitis C virus replication (Pillet et al., 2004; Vassilaki et al., 2012). These results indicate that HIF-1α may play a pivotal role in promoting virus replication. From the analysis of clinical data, the development of COVID-19 is a process of gradual hypoxia, which is more conducive to virus replication. However, HIF-1α activity is suppressed by hydroxylate two proline residues within HIF-1α under sufficient O_2 conditions (Bracken et al., 2003). Although there is no direct evidence that O_2 supplementation could reduce HIF-1α expression in virus-infected cells, researchers have reported that HIF-1α expression in the kidney significantly

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decreased after exposure to high O_2 concentrations in vivo (Popescu et al., 2013). A recent study also showed that hyperoxic breathing of 60% O_2 markedly down-regulated HIF-1α expression in tumour cells and inhibited tumour growth compared with breathing 20% O_2 (Wang et al., 2019).

Thus, this study speculated that early and appropriate O_2 therapy for COVID-19 patients could disrupt virus replication by decreasing HIF-1α.

Oxygen supplementation can improve antiviral immune response

The median time from the initial symptoms to dyspnoea is 5.0 days (Wang et al., 2020b), which may be associated with cytokine storm and result in multiorgan damage or failure. Early robust virus replication disrupts the immune response and contributes to the subsequent inflammatory storm; however, the mechanism has not been fully elucidated. For virus infection, host factors initiate an immune response against the virus. A major component of innate immunity is the type I interferon (IFN-I) response. IFN-I can activate transcription factors and induce expression of IFN-stimulated genes (Kindler and Thiel, 2016), thus promoting host cells to fight against the virus infection. However, SARS-CoV, which is similar to SARS-CoV-2, has been proven to inhibit the production of IFN-I in cell and animal models (Roberts et al., 2007). Therefore, it is imperative to understand the mechanism of the virus to overcome the interferon response and in order to take appropriate measures. Researchers recently demonstrated that lactate derived from glycolysis is the first metabolite directly combined with mitochondrial antiviral-signalling, and the lactate aggregation due to glycolysis or by increased lactate dehydrogenase (LDH) may be a potential mechanism for the virus to inhibit IFN-I production (Zhang et al., 2019). It is worth noting that clinical studies have shown that elevated LDH or lactate levels have been detected in some patients with viral infection, especially those with poor prognosis (Hunt et al., 2015; Chen et al., 2013). According to clinical data from patients infected with SARS-CoV-2 in Wuhan, China, LDH increased in 29 of 40 participants (73%), of which 12 of 13 (92%) were in ICU and 17 of 27 (63%) were not in ICU (Huang et al., 2020). Thus, inhibiting glycolysis and reducing lactate production are expected to activate antiviral immunity in the early stages of virus infection. As previously mentioned, O_2 can affect the activation of HIF-1α and reduce glycolysis. In addition, O_2 could reduce the accumulation of lactate by accelerating its degradation. Therefore, early and appropriate O_2 therapy for COVID-19 patients could be beneficial to release interferons and activate the antiviral immune response.

Immune cells such as CD8+effector T cells and natural killer cells (NK) are believed to play a crucial role in antiviral immunity. However, the proportion of immune cells in the blood of most patients infected with SARS-CoV-2 is decreased. Recently, researchers detected the peripheral blood lymphocyte subsets in patients with COVID-19 and found that the reduction in rates of CD4 + T, CD8 + T and NK cells were 60.16%, 68.3% and 36.59%, respectively (Wan et al., 2020), which greatly weaken the body's resistance to the virus.

Until now, no specific strategy has been recommended to improve the body's immunity to deal with early COVID-19. Concurrently, the therapeutic effect of O_2 therapy in severe cases has prompted investigation into the impact of O_2 on the immune system. Functional T-cell exhaustion has been demonstrated in patients with COVID-19, especially in severe cases, which is associated with higher levels of PD-1 (Diao et al., 2020). PD-1 is considered as a marker of T-cell exhaustion and previous studies have confirmed that blocking PD-1 / PD-L1 can restore T-cell function and accelerate virus clearance (Schönrich and Raftery, 2019). Recently, researchers have found that PD-L1 expression can be controlled by HIF-1α both in mouse myeloid-derived suppressor cells and in the sepsis model. Silencing HIF-1a has been shown to reduce the expression of PD-L1 in monocytes and restore T-cell proliferation (Avendaño-Ortiz et al., 2018; Noman et al., 2014). It is noteworthy that a previous analysis suggested that sufficient O_2 could reduce HIF-1α expression, and respiratory hyperoxia was also proven to reverse immunosuppression by decreasing PD-L1 expression levels in a cancer mouse model (Qian et al., 2019). Moreover, Atkuri et al. reported that T-cell proliferation was significantly higher at atmospheric O_2 levels (20% oxygen) than at physiological O_2 levels (5% or 10% oxygen) when lymphocytes were cultured in vitro in response to external stimuli (Atkuri et al., 2005a). A recent study revealed that breathing 60% O_2 increased activities of T and NK cells, and decreased immunosuppressive molecules in a murine lung cancer model (Hatfield et al., 2015). Some researchers have also demonstrated that lymphocytes have higher proliferation efficiency in conditions of rich O_2 compared with hypoxia (Waskowska et al., 2017; Atkuri et al., 2005b). Accordingly, it is tempting to speculate that sufficient O_2 may improve the antiviral ability of patients with early COVID-19 by increasing the abundance and activities of immune cells.

Early oxygen intervention may reduce the up-regulated expression of ACE2 caused by hypoxia

ACE2 is a cell membrane-associated enzyme belonging to the renin-angiotensin system and is expressed more in the kidneys and heart than that in the lungs (https://www.ncbi.nlm.nih.gov/gene/59272). It has been confirmed that SARS-CoV-2 uses ACE2, the same cell entry receptor of SARS-CoV, to enter the target cell (Zhou et al., 2020). Thus, previous research on SARS-CoV may be helpful to understand COVID-19. One study showed that the SARS-CoV genome was found in the heart of 35% of the patients (7 of 20), demonstrating that a heart attack was associated with earlier death (Oudit et al., 2009). A study on renal function of patients with SARS-CoV also indicated that acute renal impairment caused by SARS-CoV was related to high mortality (Reddy et al., 2019). Moreover, according to the recent clinical data, the rate of renal impairment is remarkably higher in patients with COVID-19 compared with SARS-CoV (Li et al., 2020). These multiple lines of evidence indicate that COVID-19 can infect the heart and renal system by ACE2 and cause serious damage in patients. Therefore, reducing the expression of ACE2 in organs in the early stages of COVID-19 infection could inhibit virus invasion. Research shows that hypoxia could increase the transcription of ACE2 by increasing SIRT1 expression on Huh7 cells (Clarke et al., 2014) and up-regulate the expression of ACE2 in an HIF-1α-dependent manner on CD 34^+ cells (Joshi et al., 2019). In pulmonary vascular smooth muscle cells, hypoxia has also been shown to up-regulate ACE2 expression (Zhang et al., 2009). Researchers (Hu et al., 2012) have also found that the SARS-CoV infection significantly enhanced the expression of hypoxia upregulated 1gene as early as 6 hours, and patients with novel coronavirus pneumonia have already appeared anoxia in the early stages. However, the symptoms of dyspnoea do not appear until late in the disease course, which is probably due to hypoxia with accompanying hypocapnia (Ottestad et al., 2020). Thus, management of hypoxia in the early stages should delay the progression of COVID-19. Oxygen supplementation could increase the partial pressure of O_2 in arterial blood by driving pressure for O_2 and improve tissue oxygenation (Manning, 2002), which has been proven to improve function in the ischaemic myocardium (Kelly et al., 1995). Oxygen therapy has also been reported to reduce renal vascular resistance and increase blood flow in patients with hypoxaemia (Baudouin et al., 1992). Therefore, early appropriate O_2 therapy for COVID-19 patients may reduce the invasion of virus by increasing O_2 content of blood against the up-regulated expression of ACE2 in tissues and organs caused by hypoxia.

Nocturnal oxygen therapy may delay the progression of COVID-19

Since cytokine storm is currently considered to be the primary cause of acute exacerbation of COVID-19, early intervention should be taken to inhibit or reduce the excessive production of inflammatory cytokines. The production of cytokines in human whole blood shows diurnal rhythmicity. The production of pro-inflammatory cytokines – including IFN-γ, TNF-a, IL-1 and IL-12 – peaks at night and early morning when plasma cortisol is lowest (Petrovsky and Harrison, 1998). Evidence has shown that whole blood stimulation with lipopolysaccharide (LPS) in vitro at night and early in the morning displayed increased cytokine and chemokine levels in samples from healthy volunteers compared with during daylight (Petrovsky et al., 1998); a subsequent study in humans in vivo has also confirmed this (Alamili et al., 2014). Furthermore, in a vesicular stomatitis virus murine encephalitis model where mice infection occurring at the start of the rest period showed higher mortality than infection at the start of the active period was associated with increased numbers of inflammatory cells (Gagnidze et al., 2016). Therefore, a reduction of nocturnal pathogen exposure or replication is expected to inhibit the production of inflammatory factors. However, the rate of virus replication in the host may accelerate in the resting phase, according to Edgar et al., who showed that mice infected with murid herpesvirus at the start of the rest phase exhibited 10-fold higher viral loads than mice infected just before their active phase (Edgar et al., 2016). However, most studies have focused on the time of primary encounter with the antigen. It still needs to be investigated whether virus replication is related to time of day, especially after a virus infects the host. Moreover, a recent study reported that SARS-CoV-2 from the nasal cavity is likely to be aspirated into the deep lung via gastro-oesophageal reflex-associated aspiration, which may be an important route to lung infection and usually occurs at night (Hou et al., 2020). Therefore, limiting virus replication at night would be a valid therapeutic strategy. Combined with a previous analysis, it is speculated that nocturnal O_2 therapy could delay the progression of COVID-19 by inhibiting nocturnal virus replication.

Conclusion

The number of severe COVID-19 patients continues to increase, leading to an extremely increased demand on medical resources and requiring comprehensive treatment. Therefore, effective and safe interventions are urgently needed to prevent COVID-19 from developing from mild to severe. Based on the clinical data and literature analysis, it was proposed that O_2 therapy could inhibit virus replication, regulate autoimmunity and decrease ACE2 expression in tissues. Since the virus may speed up invasion at night and increase over-production of inflammatory cytokines, combined with the fact that patients with lung diseases are prone to have hypoxia during sleep (Trask and Cree, 1962), it is recommend that nocturnal O_2 therapy be given as a therapeutic option for patients under home quarantine. Since nocturnal O_2 therapy is not a new concept and has been widely used in COPD patients, it is safe and easy to use in clinical practice (a home O_2 concentrator is enough for a patient).

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Author contributions

All authors have read and approved the final manuscript. CXS carried out the main study and drafted the manuscript. XFY and JWW participated in collecting and sorting out relevant information. CMS and WBL revised the manuscript and supervised the whole work.

Ethical Approval

No ethical approval was required to conduct this work.

Competing interests

The authors declare no conflict of interest.

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