Respiratory Management of COVID-19

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Company Statement

This white paper is shared with our health care colleagues to increase knowledge about respiratory management during the COVID-19 crisis. This paper reflects a literature review and clinical experience. Information in this document is provided only with regard to the COVID-19 pandemic, and not for routine care for patients outside of the anesthesia care setting or for periods longer than 24 hours. Vyaire Medical is not seeking to promote, endorse or advise the use of its products for patients failing supplemental oxygen therapy or in respiratory insufficiency or failure. However, we recognize the unusual and acute circumstances created by the COVID-19 pandemic and the needs of health care professionals to consider modifications to standard clinical practices in an effort to address the needs of patients in respiratory insufficiency or failure. The clinical care of patients with COVID-19 must first be reviewed and evaluated by each facility's medical and administrative staff before implementation.

Introduction

As the COVID-19 pandemic evolves worldwide, more insight is emerging into the pathophysiology and management of patients infected with SARS-CoV-2. As with any new pathogen or disease, staying up-to-date with new information and expert opinions is critical to adapt clinical management protocols. Initial descriptions of the clinical course of COVID-19 disease reported patients with acute respiratory distress syndrome (ARDS) suffering high morbidity and mortality on mechanical ventilation.[1,2] Investigations and clinician accounts of patient physiology have proposed this original opinion may not be entirely accurate and may contribute to worsening patient outcomes for those in the early stages of disease. This review provides an up-to-date account of current knowledge as of early June 2020, regarding the pathophysiology and management of patients presumed infected with SARS-CoV-2 throughout their clinical course and specifically discusses the role of non-invasive ventilation options in the treatment of patients presenting with early-stage COVID-19 disease.

Pathophysiology

Most patients who contract the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have asymptomatic or mild self-limiting disease requiring very little treatment. However, upwards of 14 percent of patients experience severe disease requiring hospitalization and 5 percent require critical care admission.[3]

Of those requiring hospitalization, new reports demonstrate that two broad phenotypes are seen: an early hypoxemic stage followed by a severe late-stage acute respiratory failure and high mortality.[4,5]

In the early stages of coronavirus disease (COVID-19), patients present hypoxic without hypercarbia, and in many cases without apparent respiratory distress. Clinicians call this "silent hypoxia," as the patient does not seem to notice their respiratory insufficiency and may not have the sensation of dyspnea or breathlessness despite increases in respiratory rate or minute ventilation (MV) or both.[6]

Patients can have normal or near-normal lung compliance and on computed tomography (CT) imaging, bilateral infiltrates are appreciated in a ground-glass pattern without significant alveolar airspace disruption.[7] When looking more closely at CT images, infiltrates may be located subpleurally and along lung fissures, which signifying edema in the interstitial space rather than alveolar.

SARS-CoV-2 enters the human host primarily via the upper respiratory tract and migrates to the lung, which supports the hypothesis that the initial infection leads to a modest local subpleural interstitial edema with disruption of normal regulation of pulmonary vascular tone.[8] The result is a loss of hypoxic pulmonary vasoconstriction leading to hypoxemia, without hypercarbia, from ventilation-perfusion mismatch (particularly shunt) typical in the differing West zones of the lung.[9]

This infection manifestation is exemplified by a nearly normal gas volume in the lung during the early stages of disease with little disruption in air spaces. This early "L-type" phase is characterized by low elastance (high compliance), low lung weight (as calculated on CT), and low response to positive end-expiratory pressure (PEEP), with low recruitability because alveoli are open.[10]

As the disease progresses, oxygenation declines and a resultant increase in MV occurs. Increased respiratory drive may intensify tidal strains and energy loads applied to vulnerable lung tissues.[11,12] Early interstitial edema causes localized changes in elastance in the diseased parts of lung resulting in an inhomogenous lung. With increased tidal volume (VT) breathing, "normal" lung tissue surrounding the non-expanding diseased tissues must carry the additional stress and strain of expansion, further disrupting lung parenchyma.[13]

This increased strain and expanding parenchymal damage leads to increased lung permeability from inflammation ultimately resulting in lung edema, described as "patient self-inflicted lung injury" (P-SILI), mirroring the pathophysiology of the well-established ventilator-induced lung injury (VILI) caused by mechanical ventilation.[14,15]

Over time, the increased edema increases lung weight and dependent atelectasis. Gas volumes begin to decline and VTs generated for a given inspiratory pressure decrease, leading to dyspnea and worsening P-SILI.[16]

With progression of this vicious cycle, the pathophysiology of disease changes dramatically (Table 1). Extensive CT consolidations characterize the lung, including alveolar air spaces. Additionally, the disease manifests high elastance (low compliance) and high lung weight secondary to decreased gas volumes and increased edema, and high PEEP response and recruitability because of increased amount of non-aerated tissue.[17,18] This "H-type" phase certainly meets the severe ARDS criteria, with the resulting high morbidity and mortality to which early descriptions of COVID-19 referred.[19]

	Early	Late
Elastance	Low *(high compliance)*	High *(low compliance)*
Lung weight	Low *(minimal alveolar edema)*	High *(increased alveolar edema)*
PEEP	Low	High
Non-aerated tissue	Low	Increased
Recruitability of collapsed alveoli	Low	High

Table 1. Progression of COVID-19 Disease Pathophysiology

Management

With such divergent pathophysiologic features between early- and late-stage COVID-19 disease, it is appropriate that specific respiratory management goals may also differ.

In the early stages of disease, the key respiratory issue seems to be disrupted vasoregulation, in which normal hypoxic pulmonary vasoconstriction fails to occur secondary to endothelial viral assault. As a result, ventilation-perfusion mismatch occurs, causing profound hypoxemia.[20]

The first step in treatment, therefore, is reversing hypoxemia through an increase in inspired oxygen concentration (FiO_2). The goal in this early stage is the avoidance of further P-SILI from excessive inspiratory efforts associated with increased MV.

As the patient's intrathoracic negative pressure increases to accommodate larger VT, increased tissue stress and transvascular pressures ensue, resulting in increased vascular flows and fluid leakage into the lung.[21,22] For these reasons, therapy should focus on minimizing excessive inspiratory efforts in response to hypoxemia. If supplemental oxygen alone is insufficient, non-invasive ventilation (NIV) should be considered.

Three types of NIV are used today, continuous positive airway pressure (CPAP), high-flow nasal oxygen (HFNO), and high FiO_2/PEEP nasal positive airway pressure via the SuperNO_2VA nasal PAP ventilation device (SuperNO_2VA) (Table 2).[23] These therapies improve oxygenation and decrease work of breathing in patients with respiratory distress, thereby potentially halting further progression of P-SILI in early-stage COVID-19 disease.[24,25,26,27]

When using NIV, monitoring for increased respiratory effort is important to timely identify disease progression.[28] Measuring esophageal pressure swings as a surrogate for breathing work and strain is appropriate but may not be easy to employ. Central venous pressure swings or clinical detection of excessive inspiratory effort may suffice.

Many patients may stabilize at this phase while others deteriorate. When P-SILI inhibits spontaneous ventilation, endotracheal intubation and mechanical ventilation may be necessary. After intubation, perform an early evaluation of the patient's lung compliance to identify if the disease course more closely matches the early L-type phase or more severe H-type.

If compliance is good, the patient should be able to accept larger VT than those typically used for the treatment of patients with ARDS. With appropriate lung compliance, both driving and plateau pressures remain well below the currently accepted thresholds for VILI protection [15 and 30 centimeters of water (cmH_2O), respectively], whereby higher VT may help avoid resorption atelectasis and hypercapnia caused by hypoventilation with low VT.[29] Lower PEEP in these L-type patients may be appropriate

because increased PEEP will raise transpulmonary pressures and thereby redirect blood away from patent alveoli, accentuate stress on permeable microvessels and contribute to edema and compromise of carbon dioxide (CO_2) exchange without actually recruiting functional lung units.[30]

When lung edema increases and lung volume decreases, the clinical pathophysiology begins to mirror conventional ARDS. In this setting, it remains appropriate to treat patients with H-type disease as having ARDS with conventional management including higher PEEP, lower VT, and prone positioning as recruitment of functional lung units and prevention of further VILI is paramount.[31]

NIV

Slowing disease progression and avoiding mechanical ventilation are key to treating patients with COVID-19. Of the critically ill, 71 to 79 percent require mechanical ventilation and of those, mortality is upwards of 81 percent.[32,33,34]

The need for mechanical ventilation is high when ICU capacity in regional pandemic "hot-spots" is stressed, raising concern that supply of critical care beds and ventilators may not be sufficient for the number of patients. Better treatment of patients with early COVID-19 disease may decrease the number of those subsequently

	Advantages	Disadvantages	Special Considerations
SuperNO$_2$VA	• High FiO_2 • Low flow rates equivalent to supplemental oxygen • Airtight mask seal • Allows for talking, eating, drinking, oral hygiene, etc. • Titratable PEEP • Can place surgical mask over mouth • Inexpensive and readily available • Single patient use	• Minimal inspiratory support *(may be advantage to limit stretch/P-SILI).*	• Does not need special equipment • Can be deployed anywhere a standard oxygen source exists *(wall or tank)*
CPAP	• High FiO_2 • Decreased work of breathing (L/Her) • Heated/humidified for prolonged use. • Positive inspiratory and expiratory pressure	• Leak-prone mask seal • Requires capital equipment • Expensive • Requires high-flow rates • Difficult to cover with surgical mask	• Increased VT may lead to P-SILI from increased inspiratory pressures *(Frat x 2).*[11]
HFNO	• High FiO_2 • Tolerated well by patients • Decreased work of breathing[1] • Heated/humidified for prolonged use • Can cover with surgical mask • Allows for talking, eating, drinking, oral hygiene, etc.	• Loose interface seal • Requires capital equipment • Expensive • Requires high-flow rates	• Limited positive pressure delivery

Table 2. Advantages and Disadvantages of SuperNO$_2$VA, CPAP and HFNO

requiring mechanical ventilation, thereby presenting potential opportunities to decrease morbidity and mortality while preserving scarce resources.

To address this goal, NIV may offer a reasonable middle-ground between supplemental oxygen and mechanical ventilation, and if used properly, may slow or halt disease progression in patients with mild to moderate COVID-19 disease.

The use of NIV has limitations to consider. Transmission of SARS-CoV-2 is primarily by virions contained in respiratory droplets, rather than airborne, although the World Health Organization (WHO) recognizes the significant risk of aerosol transmission to healthcare providers (HCPs) and patients during certain procedures or settings.[35] Therefore, delivery of treatment options for patients with COVID-19 should not increase transmission risk to others.

WHO defines NIV as an aerosol-generating procedure as a result of previous evaluation of air and particle dispersion using different NIV modalities.[36,37,38,39,40]

Whether aerosols from NIV modalities can transmit SARS-CoV-2 has not been validated yet and may not pose as large a threat as previously imagined. For other coronaviruses, previous evaluations of NIV use by HCPs have not identified significant infection transmission risks. When HCPs used proper Personal Protective Equipment (PPE), no significant association occurred between the use of NIV or HFNO and increased transmission of severe acute respiratory syndrome (SARS) virus during the outbreak of the early 2000s, although such risk did increase with endotracheal intubations.[41]

Similar results during the SARS outbreak describe no documented infections of 105 HCPs with the use of NIV, although their clinical management included avoiding endotracheal intubation in this 70 percent of the patient population, a treatment decision that also led to shorter length of stay and suggested a positive clinical advantage to NIV use.[42] These data are encouraging but require further validation in the setting of COVID-19.

Regardless, all would agree that appropriate PPE for HCPs is required, including N95 respirator masks, gowns, gloves, eye protection, and aprons.[43] Ideally patients requiring hospitalizations for treatment of COVID-19 would be placed in a negative pressure room with frequent air turnover to minimize the risk of aerosolized viral particles infecting others. Aerosolization studies also confirm that a loose fitting NIV interface increases exhaled air dispersion as well as use of increased flow rate and/or pressures.[44,45,46]

When using NIV, close patient monitoring is critical. NIV failure has long been associated with increased mortality and clinicians should have a low threshold to initiate mechanical ventilation early if NIV does not improve patient status.[47]

"...NIV may offer a reasonable middle-ground between supplemental oxygen and mechanical ventilation, and if used properly, may slow or halt disease progression in patients with mild to moderate COVID-19 disease."

In the treatment of ARDS, NIV failure occurred most when used on patients with already moderate to severe disease and was associated with high mortality. When reserved for patients with mild disease, NIV failure remains low, mortality rate is much improved, and avoidance of endotracheal intubation is possible.[48,49,50]

In the setting of COVID-19, therefore, it is sensible to favor the use of NIV during the early L-type stages of disease in an attempt to limit disease progression and avoid mechanical ventilation, but simultaneously have a low threshold for endotracheal intubation if patient physiology worsens or more closely mimics H-type disease.

For similar reasons, NIV also should be considered when weaning patients with COVID-19 from mechanical ventilation when their clinical course improves. Post-extubation management of oxygenation and ventilation in high-risk patients have successfully used CPAP, HFNO and SuperNO_2VA PAP, and they may assist with weaning while limiting extubation failure.[51,52]

Recommendations: Ensure adequate fit of any NIV interface and to limit flow and pressure to the lowest possible setting required to improve oxygenation and reduce the risk of P-SILI. Have caution using conventional CPAP or HFNO because of the high fresh gas flows required, whereas SuperNO_2VA PAP uses flows consistent with supplemental oxygen. Where possible, connect to a bacterial/viral filter, a surgical mask placed over the device, mouth, and nose may further reduce spread of aerosolized viral particles during NIV use.

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