Low-Flow ECCO$_2$R for Acute Exacerbation of COPD

ALung Technologies, Inc.

Chronic obstructive pulmonary disease (COPD) is an irreversible, progressive, lung disease caused by chronic bronchitis and emphysema, resulting in persistent expiratory airflow limitation.\(^1\) According to the World Health Organization, COPD is the fourth leading cause of death worldwide, and projected to increase by more than 30% over the next 10 years.\(^2\)

Acute exacerbations are a major cause of worsened morbidity and mortality in COPD patients and can be triggered by bacterial or viral infections, air pollutants, temperature change and allergies. Typically, exacerbations in mild to moderate COPD can be treated pharmacologically and with supplemental oxygen; however, exacerbations in patients with severe COPD are often associated with acute hypercapnic respiratory failure requiring hospitalization and ventilatory support.\(^3\)

For patients requiring intubation and mechanical ventilation (MV), in-hospital mortality in recent meta-analyses and observational studies has been reported to be as high as 25-39%.\(^4\)\(^-\)\(^7\) Furthermore, COPD patients requiring intubation and standard MV have a higher risk of prolonged weaning and failure to wean due to the underlying physiologic changes to the respiratory system caused by COPD.\(^8\)\(^-\)\(^10\)

Noninvasive Ventilation

Randomized trials conducted in the mid-1990s established noninvasive positive pressure ventilation (NIV) as an alternative method of lung support that has been shown to reduce mortality in COPD patients by 50%.\(^11\)\(^,\)\(^12\) As a result, the use of NIV has increased substantially over the last decade, and is now used as a first line of defense in more than 50% of patients who require ventilatory support for acute exacerbations of COPD.\(^4\)\(^,\)\(^13\) However, 15%-26% fail NIV support and require intubation and MV.\(^15\)\(^-\)\(^16\) The mortality for patients who require intubation and MV after failing NIV has been shown to be worse than for those who are treated at the outset with MV.\(^4\) The primary reason for failure of NIV is the inability to ventilate CO$_2$, resulting in increased hypercapnia, dyspnea and work of breathing.\(^17\)\(^,\)\(^18\)

What are the risks of intubation and mechanical ventilation?

Endotracheal intubation and MV are associated with a long list of acute and chronic complications. MV can cause additional injury to the already compromised lungs because of the pressures and tidal volumes needed to achieve respiratory support. Complications associated with ventilator-induced lung injury include pneumothorax, pneumomediastinum, and subcutaneous or pulmonary interstitial emphysema. Other complications result from injuries to the airway caused by the endotracheal tube. In one study of risk factors associated with endotracheal intubations, at least one severe complication occurred in 28% of ICU patients requiring intubation.\(^19\) The mortality rate in the patients who experienced a severe complication due to intubation was two times the rate of those patients who did not experience a severe complication.\(^19\)\(^,\)\(^20\)

The development of nosocomial respiratory infections resulting from long-term intubation and MV (longer than 48 hours) is one of the foremost risks of intubation and MV. The incidence of ventilator-associated pneumonia (VAP) ranges from 9%-27%,\(^21\)\(^-\)\(^25\) and is associated with prolonged duration of MV and ICU stay.\(^22\)\(^,\)\(^24\)\(^,\)\(^25\) The risk of ICU mortality was found to be significantly
increased in studies of COPD patients who developed VAP compared to patients without COPD. In these studies, ICU mortality for COPD patients on invasive MV who developed VAP ranged from 60–64%. Other complications of endotracheal intubation and MV include aspiration, bronchospasm, inadvertent esophageal or mainstem bronchus intubation, stress gastritis/ulcers, thromboembolic disorders, gastrointestinal motility dysfunction, diaphragmatic dysfunction, and impaired swallowing.

Avoidance of intubation and MV is also a heavily weighted, patient-centered outcome. Several studies have linked prolonged MV to depression, anxiety, and post-traumatic stress disorder. While intubated, patients are unable to communicate, mobilize, or receive oral nutrition, and often become malnourished and severely weakened. Most patients who are intubated require sedation or analgesics which are associated with their own complication risks.

**ECCO\textsubscript{2}R as an alternative to mechanical ventilation when noninvasive ventilation fails**

Low-flow extracorporeal CO\textsubscript{2} removal (ECCO\textsubscript{2}R) is a minimally invasive alternative to intubation and MV, when NIV alone is not able to adequately ventilate CO\textsubscript{2}. The approach of low-flow, or partial, extracorporeal CO\textsubscript{2} removal (ECCO\textsubscript{2}R) was first explored by Gattinoni et al., and published in 1986. This was an important study which showed that if extracorporeal support was used to provide removal of only 33% of estimated basal CO\textsubscript{2} production in patients maintained with NIV, normalization of arterial CO\textsubscript{2} levels and significant reduction in minute ventilation could be achieved.

Low-flow ECCO\textsubscript{2}R, by nature, is less invasive than extracorporeal membrane oxygenation, or ECMO. ECMO is used to provide cardiopulmonary life support, and must meet the full oxygenation and CO\textsubscript{2} removal requirements of a patient. In so doing, ECMO requires the use of large-bore catheters to enable high blood flows of 3–6 liters per minute, and is often used in a venous-to-arterial cannulation configuration to offload the heart. In contrast, low-flow ECCO\textsubscript{2}R provides partial CO\textsubscript{2} removal at dialysis-like blood flows, which can be achieved through a single, dual-lumen, venous catheter.

The risks of low-flow ECCO\textsubscript{2}R are most similar to those associated with continuous renal replacement therapy (CRRT), which is also used in the critical care setting and operates at similar blood flows and with similar sized catheters. Like CRRT, the risks of low-flow ECCO\textsubscript{2}R are associated with central venous cannulation, a commonly performed procedure for a variety of indications, and the need for anticoagulation. However, unlike CRRT, low-flow ECCO\textsubscript{2}R does not put the patient at risk for electrolyte depletion or excessive volume removal, since the only molecule being removed from the blood is CO\textsubscript{2}.

**Clinical evidence for using low-flow ECCO\textsubscript{2}R for acute exacerbations of COPD**

There have been no randomized, controlled trials evaluating the efficacy of ECCO\textsubscript{2}R in patients experiencing an acute exacerbation of COPD. However, there have been several recent studies and case reports which support use of partial ECCO\textsubscript{2}R in this patient population.

In 2013, Burki et al. reported on the results of a clinical feasibility study of the Hemolung Respiratory Assist System (RAS) in patients with COPD. In addition, case reports of patients from this study were described in detail in articles by Mani et al. and Bonin et al. The Hemolung RAS (Pittsburgh, PA, USA) is a minimally invasive, low-flow, ECCO\textsubscript{2}R device which utilizes a 15.5 Fr single, dual-lumen, venous catheter to provide CO\textsubscript{2} removal using blood flows of 350–550
mL/min. The Hemolung feasibility study included eight evaluable patients who were experiencing a COPD exacerbation and were failing support with NIV. All eight of these patients successfully avoided intubation with Hemolung therapy. Bonin et al. describes one of the eight patients who experienced an acute exacerbation of COPD while awaiting a lung transplant. For this patient in particular, avoidance of intubation and MV was paramount to maintaining the patient’s status on the lung transplant list. Use of the Hemolung was effective in achieving avoidance of intubation, and ultimately, the patient was successfully transplanted and discharged.

In a separate study reported by Kluge et al. in 2012, partial $\text{ECCO}_2\text{R}$ with the Novalung interventional lung assist (iLA) device was used to treat 21 patients suffering from acute hypercapnic respiratory failure who were failing support with NIV. The Novalung iLA (Heilbronn, Germany) is a pumpless extracorporeal therapy that utilizes arterial pressure to drive blood flow through a hollow fiber membrane cartridge at blood flows between 1-2 L/min via femoral artery to femoral vein cannulation. The outcomes of these patients were compared retrospectively with patients treated with MV after failing support with NIV. Fourteen of the 21 patients had an underlying diagnosis of COPD. The results of this study showed that 90% of the patients treated with the Novalung iLA avoided intubation and MV. While there was a trend for reduced hospital length-of-stay using partial $\text{ECCO}_2\text{R}$, the study was not powered to evaluate differences in mortality, and the matched control group was found to have statistically less severe hypercapnia compared to the group treated with $\text{ECCO}_2\text{R}$. An interesting pilot study was recently reported by Abrams et al. in which $\text{ECCO}_2\text{R}$ with the Maquet Cardiohelp (Hirrlingen, Germany) was used in 5 patients experiencing an acute exacerbation of COPD who required intubation and invasive MV after failing support with NIV. In this study it was shown that $\text{ECCO}_2\text{R}$ could be used soon after intubation to facilitate rapid extubation. All 5 patients were extubated within 24 hours of $\text{ECCO}_2\text{R}$ initiation, were successfully mobilized, and all were discharged from the hospital. These encouraging results support further exploration of using partial $\text{ECCO}_2\text{R}$ in patients experiencing an acute exacerbation of COPD early after the need for intubation and MV, in addition to the use of partial $\text{ECCO}_2\text{R}$ to avoid intubation when timing permits.

**Paradigm for use of low-flow $\text{ECCO}_2\text{R}$**

Results of the studies reported by Burki et al. and Kluge et al. are evidence that low-flow $\text{ECCO}_2\text{R}$ can be used to avoid intubation in patients experiencing an acute exacerbation of COPD for whom:

- Support with NIV is failing after 1-2 hours of use, and
- Endotracheal intubation has a high risk of secondary complications associated with prolonged invasive MV.

Figure 1 represents a treatment algorithm for using low-flow $\text{ECCO}_2\text{R}$ which is based on the indications of NIV failure utilized in these studies.

**Conclusions**

Mounting clinical evidence supports the use of low-flow, partial $\text{ECCO}_2\text{R}$ for patients experiencing an acute exacerbation of COPD who are failing support with NIV, as indicated by increased or refractory hypercapnia, respiratory acidosis, dyspnea and/or work of breathing. Low-flow $\text{ECCO}_2\text{R}$ is a minimally invasive alternative to intubation and MV when the risks associated with MV are undesirable. The risks of low-flow $\text{ECCO}_2\text{R}$ are similar to the cannulation and anticoagulation risks of CRRT, a common therapy in the critical care setting.
Figure 1: Algorithm for use of low-flow ECCO$_2$R in acute exacerbation of COPD failing NIV

Hospital Admission for AE-COPD

Standard initial treatment according to international guidelines¹
[O$_2$, bronchodilators, corticosteroids, antibiotics as needed]

Requirement for respiratory support?

YES

Evaluate for signs of NIV failure (after minimum of 2 hours):
- pH < 7.25 and PaCO$_2$ > 55 mmHg
- pH < 7.3, PaCO$_2$ > 55 mmHg and less than 5 mmHg decrease in PaCO$_2$ from baseline³⁹
- Worsening respiratory acidosis
- Increasing respiratory rate
- Clinical signs of respiratory muscle fatigue or increased work of breathing

NO

Sign(s) of NIV failure?

YES

Immediate intubation required?

NO

Initiate Hemolung therapy

Patient improvement?

NO

Continue NIV + Hemolung

Indications of NIV + Hemolung failure?

YES

NO

Treat per Standard of Care

Abbreviations:
AE-COPD: Acute exacerbation of chronic obstructive pulmonary disease
IMV: Invasive mechanical ventilation
NIV: Noninvasive ventilation
About the Hemolung RAS
The Hemolung RAS from ALung Technologies provides Respiratory Dialysis®, a simple, minimally-invasive form of extracorporeal carbon dioxide removal (ECCO₂R). The system utilizes patented technology to provide highly efficient CO₂ removal at dialysis-like blood flow rates which are achieved through a single 15.5 Fr venous catheter. For more information, please visit http://www.alung.com.

Other Notes
Hemolung RAS Intended Use
The Hemolung RAS is intended to be used for partial extracorporeal respiratory support in the treatment of acute hypercapnic respiratory failure. Oxygen is supplied and carbon dioxide is removed from blood circulated through the Hemolung RAS. The utilization period of this device has been validated for up to 7 days.

Hemolung RAS Indications for Use (EU)
The Hemolung Respiratory Assist System is indicated for severe COPD patients failing non-invasive ventilation where no alternative established therapy is available.
The Hemolung Respiratory Assist System is indicated for the application of lung protective ventilation strategies for patients who are invasively mechanically ventilated.
The Hemolung Respiratory Assist System is not indicated for patients needing assistance in weaning from invasive mechanical ventilation, patients with severe asthma, and patients preparing for and following lung transplantation.

Caution: Federal law (USA) restricts this device for sale by or on the order of a physician. Not for sale in the USA.
References