

Extracorporeal carbon dioxide removal in the treatment of hypercapnic respiratory failure due to acute exacerbation of chronic obstructive pulmonary disease: a prospective, randomized, controlled trial

A. Study Purpose and Rationale

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide, accounting for nearly 5% of deaths globally according to a recent analysis by the World Health Organization (1). In the United States, chronic lower respiratory diseases, of which COPD is the primary contributor, are the third leading cause of death (2).

In patients with COPD, acute exacerbations are a major cause of hospital and intensive care unit (ICU) admissions and contribute to nearly 85% of the total economic cost of the disease (3). Characterized by worsening dyspnea and increased production of sputum or increased sputum purulence, such exacerbations may lead to predominantly hypercapnic, as well as hypoxemic, respiratory failure and acidosis due to failure of the respiratory system to maintain adequate alveolar ventilation. These gas exchange abnormalities can lead to major clinical decompensation with the development of profound dyspnea, right ventricular failure, and encephalopathy (4,5).

Despite standard medical therapy (bronchodilators, steroids, antibiotics) in the management of acute exacerbations of COPD, respiratory failure may persist, and artificial ventilation may be necessary to improve gas exchange and reduce the workload of the respiratory system (3,5-7). In patients requiring artificial ventilation, endotracheal intubation and invasive mechanical ventilation (IMV) had traditionally been employed. However, IMV is associated with considerable adverse effects, including ventilator-associated pneumonia and ventilator-associated lung injury (7). In patients with COPD, IMV management is particularly challenging, as the combination of positive pressure and airway obstruction may result in air-trapping and dynamic hyperinflation of the lung, ultimately leading to worsening gas exchange, patient-ventilator dyssynchrony, hemodynamic instability, and increased risk of pneumothorax (7). Not surprisingly, prior analyses have cited in-hospital mortality for such patients near 30% (8-10). Over the past two decades, non-invasive ventilation (NIV) has become an established modality in the therapy of hypercapnic respiratory failure associated with exacerbations of COPD when combined with standard medical therapy. Prior studies have demonstrated that the addition of NIV can adequately improve gas exchange and result in improvements in hypercapnia and acidosis, prevent the need for IMV, and lead to reductions in hospital length of stay and in-hospital mortality (5,9,10). However, in some patients, hypercapnia, acidosis, and muscle fatigue persist despite NIV, with many patients still requiring IMV (8). In patients in whom hypercapnia is the persistent physiologic disturbance driving the need for IMV, additional methods of carbon dioxide (CO₂) removal beyond increasing alveolar ventilation through NIV may prevent further acidosis, respiratory decompensation, and the need for IMV. One such method is extracorporeal CO₂ removal (ECCO₂R), a form of extracorporeal life support in which blood is circulated outside the body through an oxygenator (where carbon dioxide is also removed), and is subsequently returned to the patient's circulation (12,13).

Similar to venovenous extracorporeal membrane oxygenation (VV-ECMO), which has been shown to successfully treat severe hypoxemic respiratory failure by using high blood flow rates (often up to 75% of cardiac output), ECCO₂R relies on lower blood flow rates (near 25% of cardiac output) to predominantly remove carbon dioxide (14). ECCO₂R has been used previously to provide "lung rest" during mechanical ventilation in patients with the acute respiratory distress syndrome (ARDS) (15). In ARDS, adhering to low-volume, low-pressure ventilation has been associated with reduced mortality. However, given the poor lung compliance of many patients with ARDS, low-pressure, low-tidal volume strategies may result in marked hypercapnia and acidosis. In such scenarios, ECCO₂R, by directly removing CO₂ from the blood, can assist in maintaining an acceptable pH, allowing for the maintenance of low-pressure, very low-tidal volume ventilation (15,16). In recent years, several pilot studies and retrospective analyses have investigated the use of ECCO₂R specifically for the management of hypercapnic respiratory failure, including in patients with acute exacerbations of COPD. Case reports and case series have demonstrated the ability of ECCO₂R to reduce minute ventilation, hypercapnia, and hyperinflation in mechanically ventilated patients with acute exacerbations of COPD, raising the possibility of ECCO₂R being used to facilitate earlier extubation and subsequent physical therapy in such patients (17,18). A pilot study conducted here at Columbia University Medical Center of 5 patients with acute exacerbations of COPD requiring IMV demonstrated that ECCO₂R could be used to facilitate early extubation, with a median time to extubation following initiation of ECCO₂R of 4 hours (19).

An alternative therapeutic use of ECCO₂R in hypercapnic respiratory failure in acute exacerbations of COPD that has recently been investigated is the initiation of ECCO₂R in addition to NIV to avoid IMV (20, 21). A retrospective analysis of 21 patients with hypercapnic respiratory failure (14 of which had underlying COPD) started on a variant of ECCO₂R plus NIV due to failure of NIV alone showed that 19 were able to avoid IMV (22). In this same analysis, those patients who had undergone ECCO₂R at the point of NIV failure had shorter lengths of hospital stay compared to a matched control group that had undergone IMV at the point of NIV failure (20). A recently published pilot study also demonstrated that in a group of 7 patients receiving NIV with a high-likelihood of requiring IMV, all were able to avoid IMV after the initiation of ECCO₂R, and for 2 patients who could not be weaned from NIV but who did not wish to undergo IMV, both were able to be weaned following the initiation of ECCO₂R (18).

Given the prior use of ECCO₂R in ARDS and its reported success in the avoidance of IMV in hypercapnic respiratory failure associated with acute exacerbations of COPD in the retrospective and small prospective pilot studies described above, a larger, prospective, randomized controlled trial is necessary to further evaluate the potential benefits of ECCO₂R in such patients. It is our belief that in patients with hypercapnic respiratory failure in the setting of an acute

exacerbation of COPD who fail NIV alone, there will be a reduction in in-hospital mortality for those who are treated with continuation of NIV plus ECCO2R compared to those who undergo endotracheal intubation and IMV.

B. Study Design and Statistical Analysis

Goal:

The aim of this study is to assess if at the point of failure of NIV for hypercapnic respiratory failure in patients with acute exacerbations of COPD, continuation of NIV plus ECCO2R will improve mortality compared to those patients who undergo IMV.

Hypothesis:

We hypothesize that in patients with hypercapnic respiratory failure in the setting of an acute exacerbation of COPD who fail NIV alone, there will be a reduction in in-hospital mortality for those who are treated with continuation of NIV plus ECCO2R compared to those who undergo endotracheal intubation and IMV.

Study Overview:

This will be a prospective, randomized control, interventional trial in which the best standard practice for persistent hypercapnic respiratory failure in the setting of an acute exacerbation of COPD (IMV), will be compared with a protocol that includes NIV plus ECCO2R.

Study Population:

Patients with an acute exacerbation of COPD admitted to the medical step-down unit (SDU) or medical ICU (MICU) with hypercapnic respiratory failure requiring, and subsequently failing, NIV. All subjects, regardless of randomized intervention, will be treated with standard medical therapy for acute exacerbations of COPD with bronchodilators, systemic steroids, and antibiotics. The choice of these specific therapies (such as steroid dosing, antibiotic agents) will be made at the discretion of the treating physician.

Inclusion/Exclusion Criteria at the time of study:

The subjects in the study will be based on the following criteria:

1) Inclusion Criteria

- a) Male and female subjects aged 40 to 90 years
- b) Exacerbation of COPD defined as acute onset in change of patient's baseline dyspnea, cough, and/or sputum production in a patient with underlying COPD (COPD diagnosis based on medical history, physical exam, and if available, prior pulmonary function testing results indicating airway obstruction)
- d) Hypercapnic respiratory failure with arterial blood gas at time of initiation of NIV with $\text{pH} \leq 7.35$ and $\text{PaCO}_2 \geq 50$ mmHg
- e) Treated with NIV for at least 1 hour with either $\text{PaCO}_2 > 55$ mmHg and $\text{pH} < 7.30$ or $\text{pH} < 7.35$ and $\text{PaCO}_2 > 55$, with < 5 mmHg PaCO_2 decrease from baseline prior to initiation of NIV
- f) Informed consent obtained from patient or surrogate

2) Exclusion criteria

- a) Hemodynamic instability (defined as systolic blood pressure < 90 mmHg or heart rate > 120 bpm)
- b) Acute coronary syndrome
- c) Uncontrolled arrhythmia
- d) Pneumothorax
- e) Excessive respiratory secretions
- f) Glasgow Coma Score < 8
- g) Recent gastric, laryngeal, or esophageal surgery
- h) Significant facial fracture
- i) Inability to cooperate with fitting and wearing NIV mask
- j) Known sensitivity to heparin or history of heparin-induced thrombocytopenia
- k) Recent major surgery
- l) Thrombocytopenia (platelet count $< 100,000$)
- m) Known bleeding diathesis
- n) Endotracheal intubation not in accordance with goals of care as per patient or their surrogate

Study Design:

Treating physicians will refer potential subjects by contacting the ICU triage service physician, in addition to a dedicated study coordinator screening the charts of patients admitted to the medical ICU (MICU) or medical step-down unit (SDU), who will then contact the treating physician.

All subjects will be treated with standard medical therapy as described above, as well as NIV (the settings of which will be at the discretion of the treating physician). At the time of failure of NIV (treated with NIV for at least 1 hour with either $\text{PaCO}_2 > 55$ mmHg and $\text{pH} < 7.3$ or $\text{pH} < 7.35$ and $\text{PaCO}_2 > 55$, with < 5 mmHg PaCO_2 decrease from baseline prior to initiation of NIV), subjects will be randomized in a 1:1 fashion to either continuation of NIV plus ECCO2R or to undergo endotracheal intubation and initiate IMV.

Randomization:

Subjects meeting the above inclusion criteria and without any exclusion criteria will be randomized (1:1) to either continuation of NIV plus ECCO2R or to undergo endotracheal intubation and initiate IMV. Randomization will be performed by a computer generated algorithm.

Masking:

It will not be possible to mask treating physicians, patients at the time of treatment delivery.

Statistical Analysis:

The assumed primary outcomes for the two treatment groups are extrapolated from published data. The study will be powered for mortality using data citing mortality rates for patients on IMV (in addition to standard medical therapy) for hypercapnic respiratory failure in setting of COPD exacerbation at 30%, with mortality rates for those treated with medical therapy plus NIV cited at 10% (8-10). Using the chi-square test for 80% power and significance at $p < 0.05$, the number needed in each group is 71 subjects. A total of 142 subjects will be needed for randomization.

Primary analysis will be by intention-to-treat, using the chi square test to evaluate the difference in in-hospital mortality.

C. Study Procedure.

Research Procedure

Treating physicians will refer potential subjects by contacting the ICU triage service physician, in addition to a dedicated study coordinator screening the charts of patients admitted to the medical ICU (MICU) or medical step-down unit (SDU), who will then contact the treating physician. Study personnel will then discuss with such patients and their surrogates after agreement from the treating physician. The primary research procedure will be the initiation of ECCO2R (plus NIV) for the management of hypercapnic respiratory failure.

Enrollment

After initial enrollment in the study, demographic (prior pulmonary function testing results, smoking history [current status and pack year history]) will be obtained as will clinical data (vital signs, chest x-ray, arterial blood gas results, time on NIV and NIV settings) from the medical record and the patient and/or surrogate.

All patients will be continued on medical therapy for management of an acute exacerbation of COPD as described above. Such treatments will be continued through to hospital discharge at the discretion of the treating physician.

ECCO2R and IMV

After randomization, patients admitted to the SDU will be transferred to the MICU, and those admitted to MICU will remain in the unit. In those patients assigned to continue NIV plus ECCO2R, a bicaval dual-lumen catheter will be placed in the internal jugular vein. This will be done percutaneously using fluoroscopic and/or transesophageal echocardiography (TEE) guidance at the bedside. A loading dose of intravenous heparin will be administered prior to catheter insertion and a heparin drip will be continued to maintain a target activated partial thromboplastin time (aPTT) between 40-60 seconds. Packed red blood cells will be transfused only for a hemoglobin concentration less than 7 grams per deciliter or less than 10 grams per deciliter in patients with known coronary artery disease. Once the catheter has been confirmed in place, the catheter and ECCO2R circuit will be connected by the perfusionist. Blood flow through the ECCO2R circuit will be dictated by the catheter size. ECCO2R gas flow (sweep) will initially be set between 1 to 10 liters per minute and will be adjusted to maintain a target pH between 7.35 and 7.45 with the PaCO₂ not decreased by greater than 20 mmHg per hour. If the baseline PaCO₂ of the patient is known, the target PaCO₂ on ECCO2R will be this value ± 10 mmHg. The PEEP and pressure support settings of the NIV device will be titrated to avoid tachypnea and maintain oxygen saturation greater than 87% and greater than 94% for patients with known coronary artery disease. The sweep gas flow of the ECCO2R device will be reduced in a stepwise fashion until a minimal sweep gas flow (less than 1 liter per minute) is achieved and the respiratory status of the patient has improved as judged by the treating ICU physician. If there is no increase in work of breathing nor evidence of worsening respiratory acidosis on arterial blood gas analysis obtained 1 hour after on minimal sweep gas flow, ECCO2R will be discontinued and the subject will undergo bedside catheter removal. Notably, patients randomized to NIV + ECCO2R will be considered for endotracheal intubation and IMV if there is a worsening in acidosis or hypercapnia (pH < 7.30 or increase in PaCO₂ > 10 mm Hg) after 2 hours of treatment, or worsening respiratory status, worsening neurological status, intolerance of face or nasal mask, inability to clear secretions, or significant hemodynamic instability. The final decision to proceed to IMV in such cases will be made by the treating ICU physician. If, after 7 days, the patient remains on both continuous NIV plus ECCO2R, and the patient is observed to have no reasonable chance of breathing on their own without such support, a decision will be made regarding the removal of IMV and this will be discussed with the patient or their surrogate.

For patients assigned to undergo endotracheal intubation and IMV, initial ventilator settings will be assist control-volume control with a respiratory rate set at 8-12 breaths per minute, tidal volume 6-8 ml/kg predicted body weight, and a positive end-expiratory pressure of 5 centimeters of water. These settings will be adjusted to address the needs of individual patients at the discretion of the treating ICU physician. Subjects in the IMV arm will be treated with the best standard critical care management, including transfusion strategies described above in the ECCO2R group, daily breaks in sedation and assessment for readiness for a spontaneous breathing trial and extubation. Subjects in the IMV arm will not be able to cross over to receive ECCO2R.

Clinical and Laboratory Data Collection

For all subjects, baseline venous blood samples will be collected prior to ECCO2R and IMV initiation for monitoring of hematologic parameters, electrolytes and renal function, liver function. Arterial blood gases will also be drawn as mentioned above. Serial venous blood and arterial blood gas samples will be drawn throughout the period of investigation as well. While enrolled in the study, demographic and clinical data will continue to be collected regarding subjects in each study arm (vital signs, chest x-ray, NIV settings, IMV settings) and subjects will be followed until hospital discharge or death.

D. Study Drugs

No experimental drugs will be utilized in this investigation.

E. Medical Device

There will be three medical devices used in this study. First, an FDA-approved bicaval dual-lumen catheter will be used to provide simultaneous drainage of deoxygenated blood and reinfusion of oxygenated blood from the membrane oxygenator. The catheter is inserted into the internal jugular vein with the tip resting in the inferior vena cava and removes blood from both the inferior and superior vena cava and subsequently returns it to the right atrium.

The next device to be used will be an FDA-approved membrane oxygenator. This is an artificial device that takes the place of the lungs and facilitates gas exchange and temperature regulation of the blood removed using the catheter described above. This device efficiently performs oxygenation and CO₂ transfer. Notably, in the population to be studied, since hypercapnia is often the primary blood gas disturbance, the oxygenator will likely require much smaller blood volumes (given the solubility and diffusion properties of CO₂ that favor its removal) compared to the volumes required to address profound hypoxemia.

The final device to be used will be an FDA-approved centrifugal pump that propels blood forward through the ECCO₂R circuit. This is one of the most modern pump systems that are less traumatizing to red blood cells leading to lower rates of hemolysis and allowing for lower systemic anticoagulation.

F. Study Questionnaires

No questionnaires will be used in this investigation.

G. Study Subjects

Please see above in study design.

H. Recruitment of Subjects

Potential study subjects admitted at the Milstein Hospital will be referred by their treating physician for enrollment in the study by contacting the principal investigator. If the patient or surrogate agrees with proceeding, study personnel will discuss with such patients and their surrogates involvement in the study. Informed consent will be obtained from patients or their surrogates before proceeding with the study procedures.

I. Confidentiality of Study Data

Patient data will be kept confidential throughout the time of investigation on a locked, password-protective computer database accessible to only the study investigators. No names or identifying data will be contained in this database as all data associated with study subjects will be de-identified and all subjects will be assigned identification numbers.

J. Potential Conflict of Interest

None of the investigators have a proprietary interest in a drug, device or procedure under investigation and none will benefit financially in any other way from the results of the investigation.

K. Location of the Study

The study will be conducted at the Milstein Hospital at Columbia University Medical Center, specifically the medical intensive care unit.

L. Potential Risks

The potential risks of ECMO have been reported previously in patients undergoing ECMO for the more traditional indications (to provide oxygenation and lung rest in profound hypoxemia in ARDS). The adverse effects specific to ECCO₂R, as reported in prior pilot studies have been consistent with those reported with traditional use of ECMO, but are not entirely clear in patients with hypercapnic respiratory failure in the setting of an acute exacerbation of COPD who will be managed without IMV.

The mechanical complications of ECMO/ECCO₂R include: mechanical circuit complications (with serious complications including rupture of the circuit being rare), which using Columbia's revised protocol occur in less than 5% of cases. Other ECMO-specific complications include hemorrhage associated with placement of the catheter and pneumothorax have been reported in 32% and 12% of cases, however more recently, using Columbia's revised ECMO protocol, these last complications have occurred in less than 5% of cases. Other reported adverse effects associated with the use of ECMO for profound hypoxemic respiratory failure include: gastrointestinal hemorrhage (5%) pulmonary hemorrhage (11%), hypoglycemia (2%), cardiopulmonary arrest (11%), and stroke or central nervous system hemorrhage (5%). It should be noted that using the centrifugal pump described above, less red blood cell trauma has been observed (with less risk of hemolysis), thus allowing for lower systemic anticoagulation and lower bleeding risk, though there may be a higher risk of thrombus formation and clotting.

Lastly, given that catheter placement is done under fluoroscopic guidance, exposure to radiation is also a risk.

Given the novelty of this investigation, a formal data monitoring and safety committee will be established to monitor the safety and welfare of subjects and will have the power to stop the study for safety reasons.

M. Potential Benefits

As mentioned above, it is our hypothesis that in patients with hypercapnic respiratory failure in the setting of an acute exacerbation of COPD who fail NIV alone, there will be a reduction in in-hospital mortality for those who are treated with

continuation of NIV plus ECCO2R compared to those who undergo endotracheal intubation and IMV. The benefits are largely tied to the avoidance of IMV and the corresponding deleterious effects (VAP, VALI, dynamic hyperinflation and other forms of barotrauma, negative hemodynamic effects). Also, by avoiding IMV and the sedation and analgesic agents needed, earlier physical therapy may be possible leading to reduced deconditioning.

N. Alternative Therapies

The alternative therapeutic intervention in this study is the standard treatment for acute respiratory failure of IMV.

O. Compensation to Subjects

Subjects in this study will not be compensated.

P. Costs to Subjects

Subjects will not incur any additional costs as a result of participating in this investigation.

Q. Minors as Research Subjects

No minors will participate in this investigation.

R. Radiation or Radioactive Substances

Please see above under potential risks.

S. References

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