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ADVANCES IN ADULT AND PEDIATRIC PULMONOLOGY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

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Adapting ECMO to Carbon Dioxide Removal in Patients with COPD Exacerbations

Some 15 million people in the United States have been diagnosed with chronic obstructive pulmonary disease (COPD) according to data from the Behavioral Risk Factor Surveillance System. Other data suggest that another 12 to 13 million have the disease but have gone undiagnosed. It is increasingly a disease of the middle-aged and not the elderly, and 70 percent of people with COPD are actively working in the workforce.

"We've clearly made progress over the course of the last decade in that there are many more treatment options to offer patients, and I believe it is fair to say that COPD, while it may not be curable, is almost always treatable," says Byron M. Thomashow, MD, Medical Director of the Lung Volume Reduction Program at NewYork-Presbyterian/Columbia University Medical Center.

But COPD is still the third leading cause of death in the country and the only major disease that continues to increase in mortality. For more than 35 years, Dr. Thomashow has been an active investigator in clinical trials and studies to improve treatment for COPD, particularly in its end stages. In addition to problems that can occur with oxygenation or hypoxemic respiratory failure, carbon dioxide retention – hypercapnic respiratory failure – can become a life-threatening issue for patients who have an exacerbation of their COPD.

"As COPD progresses, the lungs become increasingly incompetent in blowing out the bad air, increasing carbon dioxide levels," explains Dr. Thomashow. "Those with severe degrees of COPD who have an exacerbation, such as bronchitis, pneumonia, or even a bad cold, can

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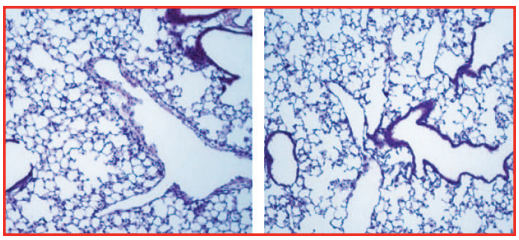
Discovery of a Unique Form of Asthma May Lead to Targeted Treatment

Researchers at NewYork-Presbyterian/Weill Cornell Medical Center, NewYork-Presbyterian/Columbia University Medical Center, and SUNY Downstate Medical Center have discovered the roots of a common type of childhood asthma, showing that it is very different from other asthma cases. Their report, published in *Science Translational Medicine* in July 2013, reveals how an overactive gene linked in 20 to 30 percent of patients with childhood asthma that interrupts the synthesis of sphingolipids causes asthma.

Although the researchers do not yet understand why asthma results from reduced production of sphingolipids, their experiments clearly show a link between loss of these lipids and bronchial hyperreactivity. What makes this pathway unique, they say, is that it is not related to allergens and, the investigators discovered, it has nothing to do with inflammation.



When assessing whether inflammation is associated with decreased SPT activity in the respiratory tract, no inflammatory changes were seen in lung sections of Sptlc2$^{+/-}$ mice (at left) or myriocin-treated mice (at right).*

**an inhibitor of sphingolipid biosynthesis*

"Usually asthma is thought to be an inflammatory disease or a reaction to an allergen," says the study's senior author Stefan Worgall, PhD, MD, Chief of Pediatric Pulmonology, Allergy and Immunology, NewYork-Presbyterian/Komansky Center for Children's Health. "Our model shows that asthma can result from having too little of a

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Adapting ECMO to CO_2 Removal *(continued from page 1)*

develop more inflammation in their lungs and more trouble clearing their carbon dioxide level. Often these people come into the ED almost in extremis. Studies show that even with the increasing use of noninvasive ventilation in managing acute exacerbations of COPD, a substantial number of patients fail this intervention and require invasive mechanical ventilation for hypercapnic respiratory failure."

> **"Those with severe degrees of COPD who have an exacerbation...can develop more inflammation in their lungs and more trouble clearing their carbon dioxide level."**
>
> **— Dr. Byron M. Thomashow**

Over the course of the last two decades, the approach for patients who have acute respiratory failure superimposed upon their chronic obstructive lung disease is to use noninvasive ventilation or noninvasive positive pressure ventilation. This often includes bi-level positive airway pressure to vary both the inspiratory and expiratory pressure. In its earliest days, noninvasive ventilation in this population had failure rates in the 25 to 30 percent range, with patients then needing intubation and respirator support.

In 2012, a major study published in the *American Journal of Respiratory and Critical Care Medicine* reported on patterns and outcomes of noninvasive, positive-pressure ventilation (NIPPV) in patients hospitalized for acute exacerbations of COPD nationwide based on 1998-2008 data from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample. The results were encouraging and significantly better than what was seen 15 or 20 years ago. There was more than a four-fold increase in the use of noninvasive ventilation, and only five percent of patients who were supported by noninvasive ventilation required mechanical support and intubation.

"The study also showed, and this was a surprise, that those transitioning from noninvasive ventilation to mechanical support had a dramatically greater chance of dying than those who were treated directly with intubation," says Dr. Thomashow. "People with COPD who are intubated tend to do terribly whether or not we intubate them immediately on admission, with 20 percent mortality, or after they fail noninvasive ventilation, with 30 percent mortality. That's a lot of deaths."

However, Dr. Thomashow continues, noninvasive ventilation remains at this point the gold standard for treatment of these patients. "Only if they are failing noninvasive ventilation or, for one reason or another, are not a candidate for noninvasive ventilation, do we intubate these patients and put them on a ventilator."

A New Role for ECMO

Two years ago, NewYork-Presbyterian/Columbia established the Center for Acute Respiratory Failure co-directed by Daniel Brodie, MD, Director, Medical Intensive Care Units and Medical Critical Care Service, and Director, Medical ECMO Program, and thoracic surgeon Matthew Bacchetta, MD, Director, Adult ECMO Program. The Center cares for adult patients who rapidly develop respiratory failure and require advanced therapeutic interventions – the most advanced of which is Extracorporeal Membrane Oxygenation (ECMO).

"Over the years, ECMO technology has improved, and the equipment has gotten better, smaller, and safer to use," says critical care specialist Darryl Abrams, MD. "The newer devices enabled the use of lower levels of anticoagulation and easier cannula placement. Lower blood flow means smaller cannulas, which should result in lower complication rates.

"For some time we had wanted to determine the feasibility of using low flow ECMO focused on the removal of blood CO_2 in patients with exacerbations of COPD," adds Dr. Abrams. "In particular, the COPD patients we targeted were those who historically, and documented in the literature, have extremely high mortality rates once they fail conventional therapies."

"A typical patient is 68 years old with long-standing COPD," describes Dr. Bacchetta. "The patient was stable, but for some

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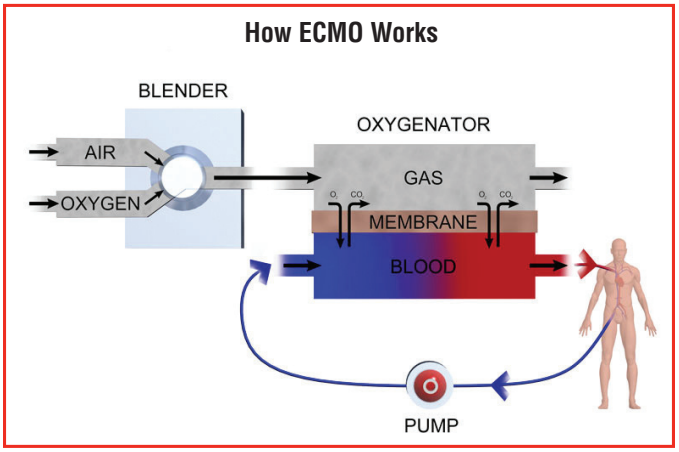
Outcomes After Extracorporeal Carbon Dioxide Removal Initiation

Subject	Duration of $ECCO_2R$ (hours)	Time from $ECCO_2R$ Initiation to Extubation (hours)	Time from $ECCO_2R$ Initiation to Mobilization (hours)	Maximal Ambulation on $ECCO_2R$ (feet)	ICU Length of Stay (days)	Hospital Length of Stay (days)
1	91	2.0	18.5	150	7	8
2	140	21.5	26.5	450	8	10
3	280	1.5	45.0	70	12*	30**
4	240	5.0	40.0	240	12	15
5	214	4.0	17.0	600	12	15

* Medical ICU length of stay before lung transplantation **Total hospital length of stay, including posttransplant course



In ECMO, a pump delivers venous blood to the oxygenator, which is made up of two chambers divided by a semipermeable membrane. Venous blood travels along the blood side of the membrane, while fresh gas is delivered to the gas side. Gas exchange – oxygen uptake and CO_2 elimination – takes place across the membrane. The oxygenated blood is then reinfused into the patient's venous system.

Illustration used with permission by www.coachsurgery.com.

reason developed bronchitis or viral pneumonia. This was enough to affect the patient's breathing to the point that a hospital admission was necessary. The patient continues to worsen and now has to go into the ICU and be put on a ventilator. The patient who does not show any signs of improvement from medical interventions and, in fact, is getting worse, is the one for whom we can intervene with this newer technology and hopefully make a significant difference in the outcome."

"The COPD patients we targeted were those who historically, and documented in the literature, have extremely high mortality rates once they fail conventional therapies."
— Dr. Darryl Abrams

"This is a subset of patients with COPD who are at tremendous risk," adds Dr. Thomashow. "They are very marginal to begin with and when you put them on a ventilator with limited nutrition and no exercise at all, you can only imagine what the sequelae may be if they survive the acute event. That brings us to what we attempted to do with the study."

The Columbia physicians and others in the field believed that applying extracorporeal technology would help keep patients with hypercapnic failure due to a COPD exacerbation from either getting intubated or, if they did need intubation, help get them off the ventilator. "The real work was always done up front," says Dr. Bacchetta. "We tailored the way that we ran our devices to the patient. For these types of patients, you do not have to provide a lot of support in the more traditional sense. Most people think that you have to run everybody at 100 miles an hour; you don't. Some patients just need a little assistance with the device."

In their study, the investigators wanted to isolate patients with hypercapnic failure and determine if by implementing a version of ECMO called extracorporeal carbon dioxide removal ($ECCO_2R$), they could eliminate the ventilator entirely, allow for extubation, and facilitate ambulation, early rehabilitation, and better delivery of medications to promote better outcomes.

"In addition to the high mortality rates that we see in this particular subset of COPD patients, there are severe complications that come with ventilator use," says Dr. Abrams. "If these patients fail noninvasive ventilation and end up on the ventilator, they can get ventilator-associated pneumonia, ventilator-associated lung injury, and deconditioning that is not resolved with ventilator management. Our goal wasn't just to have the patients extubated, but also to get them rehabbed very early on, resolve their deconditioning, and have them discharged directly home. That was the whole concept: to replace the ventilator with $ECCO_2R$ to facilitate mobilization and rehabilitation and to get them discharged from the hospital sooner and with fewer complications. However, we first had to prove that we could do this."

"We believed that applying extracorporeal technology would help keep patients with hypercapnic failure due to a COPD exacerbation from either getting intubated or, if they did need intubation, help get them off the ventilator."
— Dr. Matthew Bacchetta

To study this further, the physicians initiated a pilot study focused on five patients with exacerbations of COPD with uncompensated hypercapnia requiring invasive mechanical ventilation. The prospective trial used a protocol of low blood flow $ECCO_2R$, extubation and physical rehabilitation with a goal of extubation within 72 hours of starting $ECCO_2R$. The selected patients were intubated and stabilized on the respirator. "Rather than keeping them sedated on the respirator, not eating, and not moving for days," says Dr. Bacchetta, "we inserted a catheter and began the $ECCO_2R$ approach to remove their carbon dioxide."

Their theory was substantiated by what the team clearly demonstrated clinically in this formal, well-designed, and well-executed study. "We had been developing our protocols over many years," notes Dr. Bacchetta. "We refined our technique, as well as our approach to who we selected, how we managed the machine, and how we managed the patients, including involving them in physical therapy. The study showed that if we could avoid the damage that the ventilator causes to their lungs, and then be able to exercise them while they're on the ECMO machine, we could maintain their physical conditioning and nutrition. That should make a significant difference in their outcomes."

"Getting many of our critically ill patients out of bed has become routine in our ICUs and the benefits have been significant," says Dr. Brodie. "We can often get patients intubated for respiratory failure, in the setting of COPD exacerbation, out of bed and walk them around. However, they are so short of breath that they can't get very far. CO_2 removal, without the ventilator, virtually eliminates the shortness of

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The Mobile ECMO Transport Team for the Center for Acute Respiratory Failure – shown here in a practice drill – is deployed when needed for the transfer of patients who would traditionally be considered too unstable for transfer between hospitals. The team includes paramedics who are specially trained in advanced airway and ventilator management and the transport of patients on ECMO. The team's ambulance is able to be equipped with a portable ECMO machine to provide the safest possible transport.

breath in these patients and allows them to do much more extensive rehab even while they are still critically ill. This, along with avoiding ventilator-associated complications, is what's so powerful about this potential paradigm change."

"The critical issue is that once patients are intubated their prognosis is guarded at best and often very poor," says Dr. Thomashow. "We are looking at this approach as a potentially better option for these very sick patients. Rigorous, multicenter, clinical trials are now needed to corroborate these results and to investigate the effect on long-term outcomes and cost effectiveness over conventional management."

The study's findings were published in the August 2013 issue of the *Annals of the American Thoracic Society*. "I think what we learned is laying the groundwork for the future of therapeutic interventions for these patients," says Dr. Bacchetta. "Although small, this was an important feasibility and pilot study demonstrating the efficacy of this type of technology."

Reference Article

Abrams DC, Brenner K, Burkart KM, Agerstrand CL, Thomashow BM, Bacchetta M, Brodie D. Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. *Annals of the American Thoracic Society*. 2013 Aug;10(4):307-14.

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Dr. Byron M. Thomashow

Dr. Byron Thomashow Receives 2013 ATS Public Advisory Roundtable Excellence Award

The American Thoracic Society has awarded Byron M. Thomashow, MD, the prestigious 2013 Public Advisory Roundtable (PAR) Excellence Award. Presented by persons affected by pulmonary disease, the award honors an individual who has improved the lives of patients. A decade ago, Dr. Thomashow helped found – and now chairs – the COPD Foundation, a non-profit organization that undertakes initiatives to expand services for individuals with COPD and enable them to have a greater quality of life. "The PAR Excellence Award is very precious to me because it is about patient care," says Dr. Thomashow. "And while the award is a fantastic individual honor, I believe it is as much a recognition of the COPD Foundation for what we have accomplished and what we hope to accomplish."

Discovery of a Unique Form of Asthma May Lead to Targeted Treatment (continued from page 1)

type of sphingolipid. This is a completely new pathway for asthma pathogenesis. Our findings are not only valuable in understanding the pathogenesis of this complex disease, but also provide a basis to develop novel therapies, especially asthma agents based on a patient's genotype."

Precision Medicine for Asthma

"While it has become increasingly evident that asthma takes several forms, treatment of the disorder is uniform," notes Dr. Worgall. "Most therapies are designed to reduce inflammation, but they do not help all sufferers."

The belief that asthma has different forms gained attention after several genome-wide association studies found variation in a gene, later identified as ORMDL3, in up to 30 percent of asthma cases. In 2007, over-production of the gene's protein was connected to childhood asthma, and this gene has been the most consistent genetic factor identified so far for asthma.

In 2010, a study in yeast found that ORMDL3 protein inhibits sphingolipid de novo synthesis, prompting investigations as to whether sphingolipid production is connected to asthma. Using mouse models, researchers found that inhibition of an enzyme, serine palmitoyl-CoA transferase (SPT), which is critical to sphingolipid synthesis, produced asthma in mice and in human airways, as it did in mice with a genetic defect in SPT. The airway hyperactivity seen in the mice was not linked to increased inflammation, and the scientists saw a decreased response of the lung and airways to magnesium – which is often used to relieve chest tightness of patients with asthma attacks.

"In our mouse models, we found that small airways with defective sphingolipid production respond differently to magnesium, suggesting the same would be true for humans whose asthma is linked to ORMDL3," says Tilla S. Worgall, MD, an assistant professor in the Department of Pathology and Cell Biology and a member of the Institute of Human Nutrition at Columbia University Medical Center. "The association of decreased de novo sphingolipid synthesis with alterations in cellular magnesium homeostasis provides a clue into the mechanism of asthma. Therefore, therapies that circumvent the effect of the ORMDL3 genotype may be effective treatments for asthma sufferers. We are now working towards developing these new therapies."

The research of Dr. Worgall and his colleagues was highlighted recently in an editorial in *The New England Journal of Medicine.* "Although the study by Worgall et al. represents an important discovery for asthma research, there are still questions that have yet to be addressed," says Bruce D. Levy, MD, PhD, associate professor of medicine, Harvard Medical School, and author of the *NEJM* editorial. "…the important work of this team of investigators and the foundational discoveries of asthma functional genomics researchers are pointing the way toward an improved understanding of asthma pathobiology and new potential therapeutic targets."

Reference Articles

Worgall TS, Veerappan A, Sung B, Kim BI, Weiner E, Bholah R, Silver RB, Jiang XC, Worgall S. Impaired sphingolipid synthesis in the respiratory tract induces airway hyperreactivity. *Science Translational Medicine.* 2013 May 22;5(186):186ra67.

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For More Information

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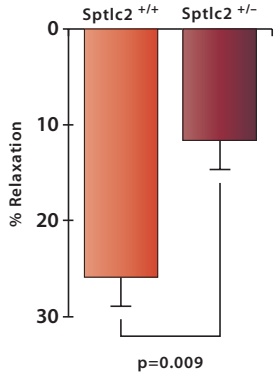
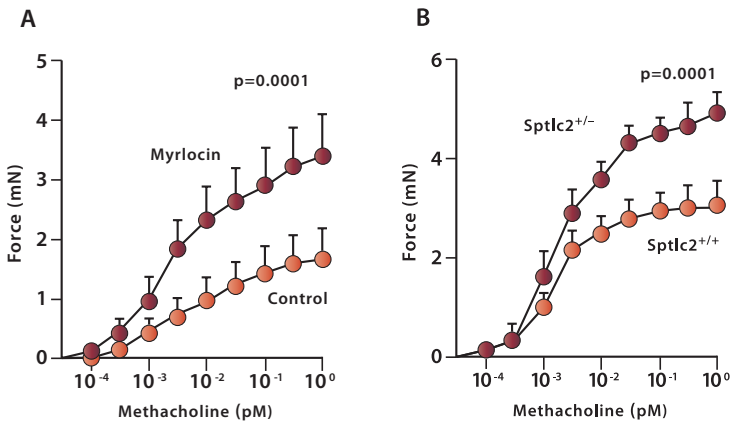


Small airways from mice that have defective sphingolipid synthesis respond differently to magnesium, which is used to relax small airways.



Small airways isolated from human lungs treated with myriocin, a drug that inhibits production of sphingolipids, constrict more in response to methacholine, a drug to test for asthma (A). Also small airways from mice that have a defect in the production of sphingolipids ($Sptlc2^{+/-}$) constrict more compared to small airways from normal mice ($Sptlc2^{+/+}$).

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AMAZING THINGS ARE HAPPENING HERE

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