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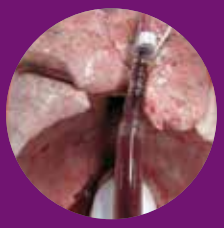

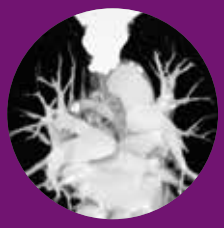

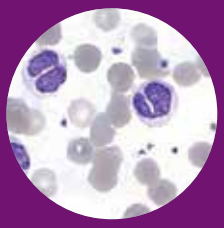

Cleveland Clinic

RespiratoryExchange

Research and News for Physicians from Cleveland Clinic's Respiratory Institute

Winter | 2017

FEATURE

Pathobiological Links Discovered Between Asthma and Metabolism

p. 3

Dear Colleagues:

Welcome to this issue of *Respiratory Exchange*, which highlights the latest discoveries and innovations of our pulmonary, critical care, allergy and clinical immunology staff within Cleveland Clinic's Respiratory Institute.

This issue is particularly representative of the wide range of interests and expertise of the staff in our institute. In these pages, you'll find:

- Details about the discovery of pathobiological links between asthma and metabolism, and key facts about our Asthma Center (pp. 3-5)
- New insights into the mechanosensing pathway involved in idiopathic pulmonary fibrosis (pp. 6-7)
- Highlights of ex vivo lung perfusion and its impact on lung transplantation (pp. 8-10)
- Surprising findings regarding cumulative radiation exposure in the MICU (pp. 11-12)
- A summary of ongoing progress in our Alpha-1 Antitrypsin Center (pp. 13-14)
- A glimpse into our standardization of respiratory therapy across the entire Cleveland Clinic health system (p. 15)
- An overview of the difficult procedure of pulmonary thromboendarterectomy and its success rates in CTEPH (pp. 16-17)
- An introduction to innovative obstructive sleep apnea treatment through hypoglossal nerve stimulation (pp. 18-20)
- A rubric for teaching mechanical ventilation to trainees (pp. 21-22)
- A case highlighting the work of our Adult Immunodeficiency Clinic (pp. 23-24)

We hope you enjoy the articles in this issue of *Respiratory Exchange* and find something useful for your patients, practice, trainees or research. Inside, you'll also find a listing of our actively enrolling clinical trials as well as a comprehensive directory of our staff and their specialty areas. Visit clevelandclinic.org/pulmonary to learn more about our clinical research activities.

If you have questions or would like to refer a patient, call our toll-free number for physicians, 866.CCF.LUNG. We welcome your thoughts, feedback and questions.

Sincerely,

Herbert P. Wiedemann, MD, MBA
CHAIRMAN | CLEVELAND CLINIC RESPIRATORY INSTITUTE

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Pathobiological Links Discovered Between Asthma and Metabolism

Asthma: an arginine-driven metabolic disorder

By Weiling Xu, MD, and Serpil Erzurum, MD

Clinicians and researchers have long observed a relationship between asthma and obesity, but the nature of the association has been poorly understood. Our recent research sheds light on this perplexing and important relationship and helps define the role of metabolism in the pathobiology of asthma.

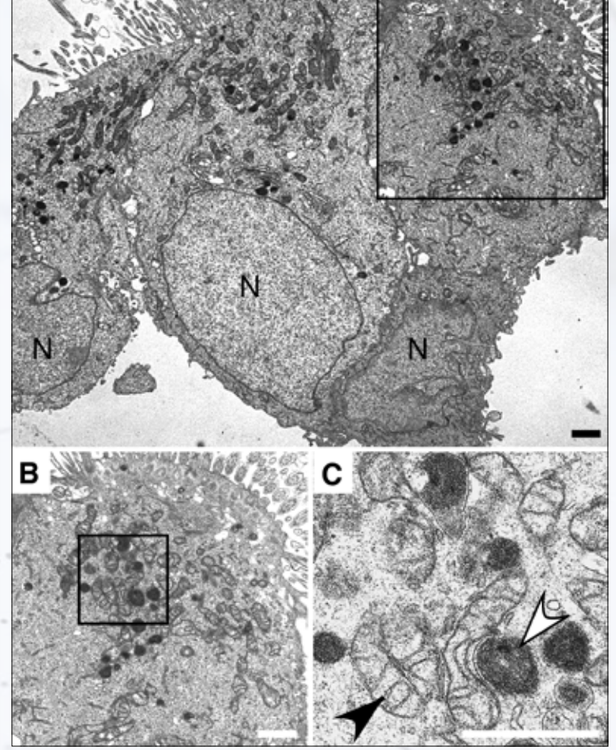
A growing understanding over the past decade is that underlying metabolism contributes in a major way to predisposition to disease, including lung disease. It turns out that your grandmother's adage "You are what you eat" may be true.

MITOCHONDRIA OF PEOPLE WITH ASTHMA ARE LESS RELIANT ON GLYCOLYSIS

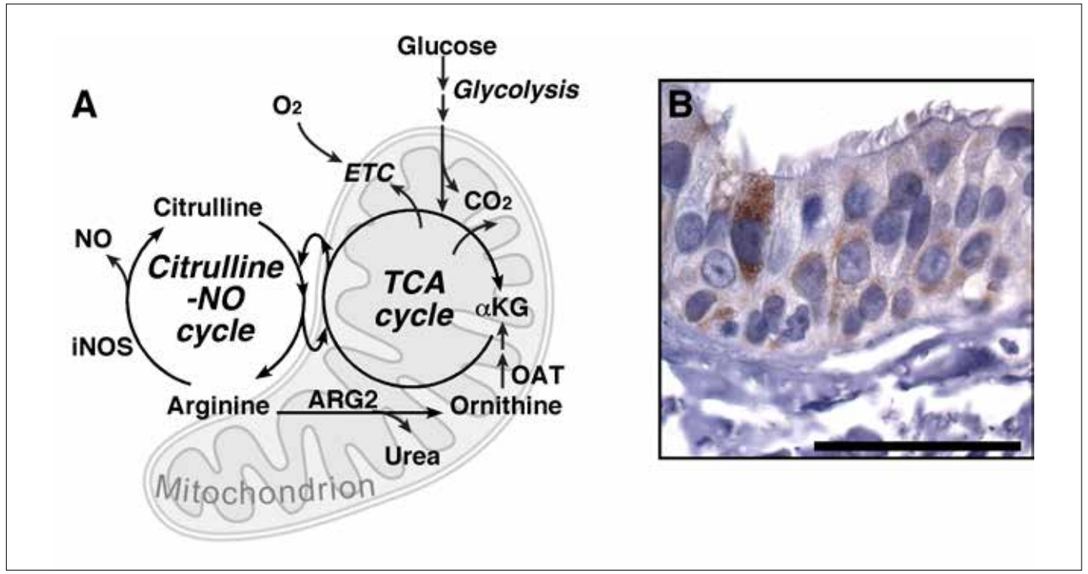
We now recognize that nutritional intake, body fat type and the microbiome can all impact asthma risk and control. Epidemiological studies show a very strong link between asthma and obesity, but causality is not yet established. Plenty of lean people have asthma, and many people with obesity do not.

Our multisite team has been working for the past seven years to elucidate the asthma-metabolism link. In collaboration with Sruti Shiva, PhD, at the University of Pittsburgh, we began our research by studying mitochondrial function in platelets of asthmatic individuals compared with those of healthy individuals.[1] Mitochondria of asthmatics exhibited decreased reliance on glycolysis and greater tricarboxylic acid cycle (TCA) activity, suggesting that oxidative phosphorylation is more efficient in asthmatic individuals (Figure 1).

Mitochondria of asthmatics exhibited decreased reliance on glycolysis and greater TCA activity, suggesting that oxidative phosphorylation is more efficient in asthmatic individuals.



› **Figure 1:** A: Ultrastructure of mitochondria in asthma airway epithelium. N, nucleus. B: Close-up of A. C: Close-up of B. Different mitochondria are shown by arrowheads. All scale bars: 1 μm.



Our most recent study of the mechanisms underlying the changes in mitochondrial metabolism revealed that these alterations may be the result of increased expression of type II arginase (*ARG2*). *ARG2* is localized within mitochondria and serves to break down arginine to ornithine, which through several transamination reactions can form alpha-ketoglutarate and enter the TCA cycle. The findings showed that the greater levels of mitochondrial *ARG2* and arginine flux in asthma accelerate the TCA cycle and cellular respiration (Figure 2).

Interestingly, the *ARG2* gene variants lie within an asthma linkage region on chromosome 14q24, and these were some of the earliest and most consistent single nucleotide polymorphisms discovered in genomewide association studies of asthma. In fact, alterations in the *ARG2* gene are strongly linked to asthma and asthma severity. In our recent mechanistic studies, mice genetically deficient in *ARG2* had alterations in cellular metabolism and more severe asthma inflammation. These studies and prior work indicate asthma is endotypically an arginine-driven metabolic disorder.

NEXT QUESTIONS — NEW MANAGEMENT FOR ASTHMA?

Our discoveries open new lines of speculation. All studies were performed in lean individuals, so we do not yet know if metabolic effects differ between individuals with asthma with or without obesity. Drugs that modify mitochondrial bioenergetics are in development but are untested in asthma. Further work is needed to understand whether and how mitochondrial-targeted therapies and/or diet might impact metabolism and control of asthma.

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Dr. Erzurum, Alfred Lerner Chair of the Lerner Research Institute and staff in Pulmonary Medicine, can be reached at erzurus@ccf.org or 216.444.5724.

Figure 2: Arginine metabolism and bioenergetics in asthma. A: Inducible nitric oxide synthase (iNOS) converts arginine to citrulline and nitric oxide (NO). Arginase 2 (*ARG2*), found in mitochondria, converts arginine to ornithine, which is converted to glutamate by ornithine aminotransferase (OAT). α-ketoglutarate (αKG) then enters the tricarboxylic acid (TCA) cycle for electron transport chain (ETC) to generate ATP energy. The TCA cycle in mitochondria is linked to the citrulline-NO cycle in the cytosol.

B: Greater *ARG2* expression (as demonstrated by brown staining on immunohistochemistry) is found in asthmatic bronchial epithelium. Scale bar: 40 μm.

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Novel Assay Suggests Mechanosensing Pathway Involved in Idiopathic Pulmonary Fibrosis

Olman lab discovers new mechanisms underlying pulmonary fibrosis

Brian D. Southern, MD

Fibrotic disorders such as idiopathic pulmonary fibrosis (IPF) result in progressive scarring and organ dysfunction. In IPF, persistent activation and accumulation of fibroblasts result in excessive connective tissue accumulation and tissue contraction that makes the lung increasingly "stiffer." This increased tissue stiffness serves as a signal for recruitment and activation of more fibroblasts in a feed-forward fashion that perpetuates the fibroproliferative cycle.

A recently published study from the Olman lab at Cleveland Clinic's Lerner Research Institute offers glimpses into this cycle that may one day produce novel therapeutic agents for patients with IPF.

NOVEL ASSAY = NEW INSIGHTS

Much of the research on fibroblast activation in IPF has been performed using plastic or glass tissue culture assay systems that are 1 million orders of magnitude stiffer than actual lung tissue, and may not provide an accurate representation of in vivo fibroblast behavior. In our recent work, we characterize a novel assay system that more closely mimics the natural lung environment of the fibroblast by using actual normal and fibrotic lung tissue.[1]

Briefly, fluorescently labeled human lung fibroblasts were allowed to adhere to normal or fibrotic mouse lung tissue sections. Time-lapse video microscopy was then performed and migratory characteristics were analyzed in fibroblasts attached to normal lung, and compared with those on fibrotic lung. Fibroblasts were also allowed to adhere to the lung tissue sections for 24 to 48 hours, and various markers of myofibroblast differentiation were analyzed. Finally, these assays were performed in the presence of various inhibitors or stimulators to determine whether the responses were different in fibroblasts on normal versus fibrotic lung.

With this system, we identified for the first time that normal lung stimulates migration of fibroblasts, while fibrotic lung stimulates myofibroblast differentiation. We also demonstrated how these two different responses (migration and myofibroblast differentiation) are both mediated through the molecular motor myosin II. Depending on whether the fibroblast interacts with normal or fibrotic lung, myosin II is activated in a way that either results in migration or myofibroblast differentiation (Figure 1).

FOCUS ON MYOSIN II: A PARADIGM SHIFT

The multiple, redundant and overlapping pathways in fibrotic disease have been well-established. A heterogeneous population of patients suffers from IPF, and ample evidence demonstrates that the mechanisms underlying the development of fibrosis may vary between patients.

One of the biggest disappointments in the field of IPF has been the number of clinical trials demonstrating either no efficacy or actual harm with the investigated therapies. Many of these trials tended to focus on individual, soluble mediators or isolated pathways known to play a role in fibrosis. Identifying a potential therapeutic strategy that targets a molecule, such as myosin II, that is downstream and common to multiple fibrosis pathways could represent a significant paradigm shift in the treatment of patients with IPF and other fibrotic disorders.

TRPV4 MEDIATES MECHANOSENSING SIGNAL IN FIBROBLASTS

Previous work from our lab demonstrated for the first time that the mechanosensing signal in fibroblasts is mediated by the transient receptor potential vanilloid 4 (TRPV4) channel.[2] In this work, we showed that the TRPV4 signal converges on this same myosin II protein in fibroblasts (Figure 2). Our data suggest that, in patients with IPF, TRPV4 channel activity and its biological effects are upregulated in lung fibroblasts (Figure 3).

Together, these studies suggest that the fibroblast senses increases in tissue stiffness through TRPV4 and translates those increases into the activation of myosin II in a way that creates a "profibrotic" fibroblast. Our future work will explore the possibility of a dysregulated myosin II pathway in fibroblasts from IPF patients, and whether manipulation of this fibrotic lung-driven pathway could lead to novel therapeutic agents for the devastating disorder of IPF.

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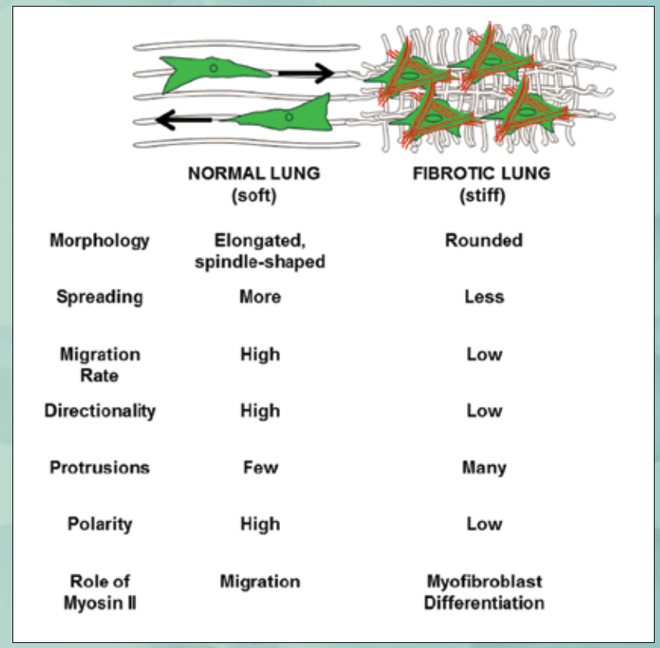


Figure 1: Effect of normal versus fibrotic lung on fibroblast phenotype. The consequence of myosin II activation differs depending on whether a fibroblast is interacting with normal or fibrotic lung extracellular matrix. In normal lung, myosin II activation drives highly directional, polarized migration. In fibrotic lung, myosin II activation results in myofibroblast differentiation. The result is migration of fibroblasts from normal to fibrotic lung, where myofibroblast differentiation is enhanced.

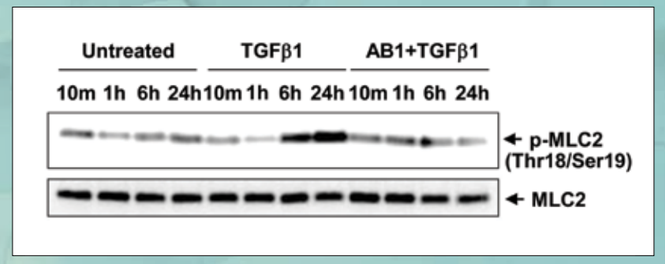


Figure 2: Inhibition of TRPV4 channel activity abrogates myosin II activation. Immunoblots of cell lysates for activated myosin II (p-MLC2) and total myosin II (MLC2). TGFβ1 (transforming growth factor-beta), a stimulator of myofibroblast differentiation, induced activation of MLC2 maximally from six to 24 hours. When fibroblasts were pretreated with AB1, an inhibitor of TRPV4, myosin II activation was blocked.

All figures and legends republished from reference 1 (Southern et al.) with permission from The American Society for Biochemistry and Molecular Biology.

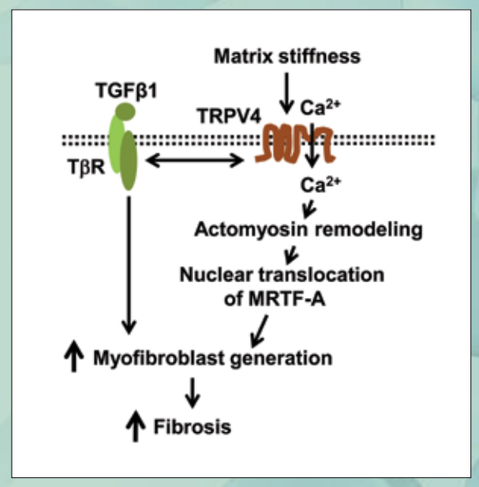


Figure 3: Schematic model showing the mechanistic pathway by which TRPV4 mediates myofibroblast differentiation and pulmonary fibrosis. Our data suggest that TRPV4-dependent calcium (Ca^{2+}) influx activity is sensitized by stiff matrices within the pathophysiological range. Interaction between TRPV4 activity (Ca^{2+} influx) and the profibrotic transforming growth factor-beta 1 (TGFβ1) signals promotes nuclear localization of α-SMA transcription factor, myocardin-related transcription factor A (MRTF-A), via regulation of actomyosin remodeling to potentiate myofibroblast differentiation during fibrogenesis.

Increasing Transplantable Donor Lungs Through Ex Vivo Lung Perfusion

Transforming dysfunctional lungs into transplantable ones

By Toshihiro Okamoto, MD, PhD, and Kenneth R. McCurry, MD

Cold storage of donor organs following procurement and prior to transplant decreases metabolic demand and consumption of energy and has been the standard in transplantation for more than 40 years. Severe damage occurs when energy stores are depleted, including increased oxidative stress, inactivation of the sodium pump, cell death and the release of proinflammatory cytokines. Additionally, following implantation, lungs frequently demonstrate varying degrees of ischemia reperfusion injury (IRI), resulting in postoperative graft dysfunction and complications that have short- and long-term implications. Thus, lung preservation and mitigation of IRI remain two of the main concerns in clinical lung transplantation.

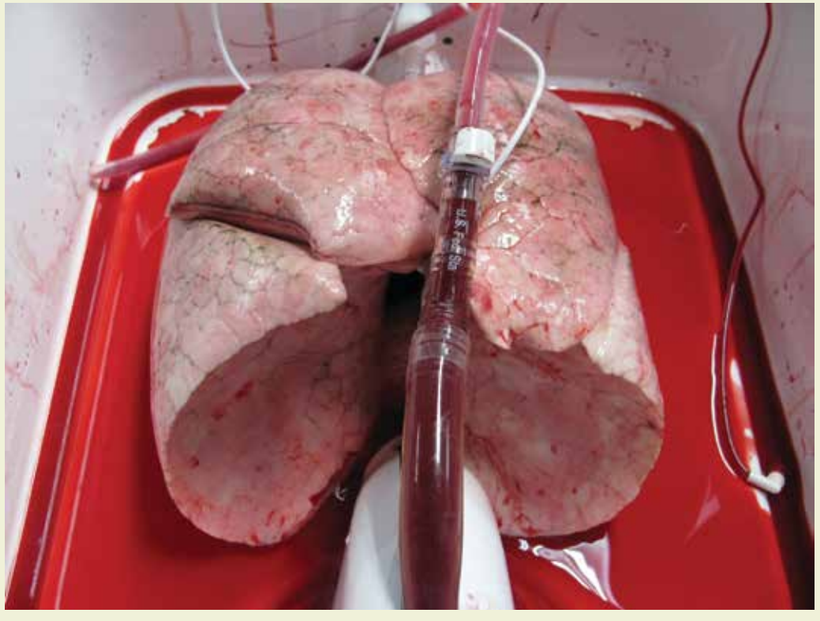
PREVENTING COLD INJURY WITH EX VIVO

Normothermic ex vivo organ perfusion is based on the rationale that providing oxygen and nutrition at physiologic temperatures on an ex vivo perfusion circuit prior to transplantation can prevent cold injury. Furthermore, it is possible that such ex vivo lung perfusion (EVLP) could be used to recondition and repair dysfunctional lungs after procurement, thus making them transplantable and resulting in an increased number of lungs available for transplantation.

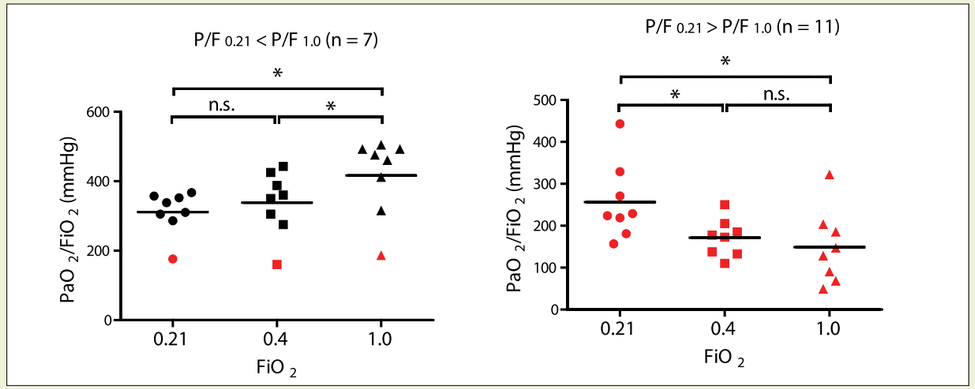
EVLP could prove especially beneficial when untransplantable, dysfunctional donor lungs have pulmonary edema or areas that remain atelectatic despite in situ recruitment. In EVLP, the high oncotic pressure of the perfusate draws water from the lung tissue and alveoli into the extrapulmonary space, reducing pulmonary edema. Atelectasis can be eliminated through strategic ventilation techniques, which include recruitment maneuvers while on EVLP. Importantly, evaluation of donor lung function is possible during EVLP, allowing ongoing assessment of lung function in response to therapeutic maneuvers.

MEETING DEMAND THROUGH RECONDITIONING

In the U.S., 1,600-1,800 lung transplants are performed annually, with many patients dying prior to an organ(s) becoming available for them. Unfortunately, approximately 80 percent of lungs offered for transplantation cannot be utilized due to poor lung function caused by factors including pulmonary edema and atelectasis.



› **Figure 1:** Ex vivo lung perfusion system in the McCurry lab.



› **Figure 2:** The relationship between PaO_2/FiO_2 (P/F) ratio at FiO_2 of 0.21 and P/F ratio at FiO_2 of 1.0 in porcine model. Left: P/F ratio at 3 FiO_2 in the group of P/F 0.21 < P/F 1.0 (group 1, N = 8). Seven cases were judged as suitable (black symbols), whereas one case was judged as not suitable (red symbol). Right: P/F ratio at 3 FiO_2 in the group of P/F 0.21 > P/F 1.0 (group 2, N = 8). All eight cases were judged as not suitable.

Based on these numbers, the use of EVLP to recondition dysfunctional lungs could have a dramatic impact on the number of patients whose lives could be saved with lung transplantation. Indeed, EVLP has been clinically available in Canada for several years, and the Toronto Lung Transplant Program has increased its lung transplant volume by approximately 30 percent using this technology. In the U.S., the clinical use of EVLP is in its infancy but holds great promise for those programs that have the resources and clinical expertise to utilize it.

EVLP AT CLEVELAND CLINIC

We initiated EVLP research activity at Cleveland Clinic in 2011 in the McCurry lab. Several important questions regarding EVLP have been investigated using more than 50 rejected human lungs (Figure 1) and over 30 porcine lungs. One of the most critical questions is the accuracy of evaluating donor lung suitability for transplantation in EVLP, as this is key for patient safety. Parameters utilized to assess lung function for suitability for transplantation can include gas exchange (PaO_2/FiO_2), lung compliance, vascular resistance, lung weight and visual findings.

Deciding whether perfused lungs are transplantable is frequently challenging, especially when PaO_2/FiO_2 is in the marginal range of acceptability (around the current threshold of 300 mm Hg). In investigating this question, we identified the following important findings on the assessment of lung function in EVLP.

Approximately 80 percent of lungs offered for transplantation cannot be utilized due to poor lung function caused by factors including pulmonary edema and atelectasis.

- *The variability of PaO_2/FiO_2 during cellular EVLP.* Previously, PaO_2/FiO_2 was utilized in EVLP as a main indicator of oxygenation and considered constant at any FiO_2. However, we identified that variability of PaO_2/FiO_2 exists at different FiO_2 (0.21, 0.4 and 1.0) in EVLP.[1] Furthermore, we demonstrated that this variability is significant because the pattern of PaO_2/FiO_2 at FiO_2 of 0.21 < PaO_2/FiO_2 at FiO_2 of 1.0 was associated with substantially better oxygenation, higher pulmonary compliance and lower shunt fraction compared with the pattern of PaO_2/FiO_2 at FiO_2 of 0.21 > PaO_2/FiO_2 at FiO_2 of 1.0 in porcine lungs (Figure 2). This algorithm was consistent in human lungs and has significant implications for appropriately assessing and selecting suitable lungs for transplantation in EVLP.

- *A significant correlation between PaO_2/FiO_2 and other physiological parameters (airway and vascular parameters)*: In other novel work, we found that airway parameters (compliance) and vascular parameters (resistance) can be utilized as complementary parameters in the evaluation of lungs in EVLP.[2] Use of these supplementary data improves the accuracy and reliability of lung selection in EVLP.

Currently, Cleveland Clinic's Lung Transplant Program is participating in a clinical trial of EVLP — A Phase 2, Multicenter, Open-Label Study to Measure the Safety of Extending Preservation and Assessment Time of Donor Lungs Using Normothermic Ex Vivo Lung Perfusion and Ventilation (EVLP) as Administered by the Sponsor Using the Toronto EVLP System — sponsored by United Therapeutics (Silver Spring, MD). In this study, donor lungs that are deemed not transplantable are procured and transported to a perfusion facility in Baltimore. During four to six hours of EVLP, lungs are reconditioned and assessed for transplantation suitability. When perfused lungs are judged as transplantable, they are transported to Cleveland Clinic, and lung transplantation is performed. Thus far, our patient survival utilizing this method is 100 percent.

This ability to utilize EVLP has brought other benefits as well. With EVLP as a backup, we can be more aggressive with lung procurement, resulting in conversion of some lungs that we thought needed EVLP into transplantable organs without using EVLP. Between February and September 2016, this has resulted in seven additional patients receiving transplants with 100 percent survival.

Overall, since initiating our clinical EVLP program, we have been able to provide transplantation to approximately 20 percent more patients in 2016 than at this time in 2015. We believe that the ability to offer the life-saving therapy of lung transplantation to more patients will continue to grow as we gain more experience and knowledge.

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Dr. McCurry, Surgical Director of Lung Transplantation, can be reached at mccurrk@ccf.org or 216.445.9303.

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Predictors and Characteristics of Radiation Exposure in the MICU

Weighing risks and benefits of radiation-based imaging modalities

By Sudhir Krishnan, MD, and Jorge Guzman, MD

Critically ill patients admitted to a MICU are often subjected to multiple radiation-based diagnostic studies. The past decade has seen a dramatic rise in the utilization of radiation-based imaging studies, interventional procedures and computed tomography (CT). Medical radiation now accounts for a significant proportion of all radiation exposure in the United States. This has led to increased scrutiny of the stochastic effects (probability of cancer induction) of radiation and the subsequent risk of cancer induction.

In an effort to quantify and characterize medical radiation exposure in the MICU, we conducted a study to examine the radiation burden per episode of care in a cohort of patients admitted to the MICU at Cleveland Clinic's main campus. We found significant levels of exposure in some patients.

STUDY DESIGN AND FINDINGS

To quantify radiation burden in the MICU, our study collated and summated radiation doses from all radiographic studies to arrive at a cumulative effective dose (CED) in millisieverts (mSv).[1]

The absorbed dose (energy deposited by ionizing radiation in biological tissues) is converted into an effective dose by correcting for both the type of radiation used (e.g., gamma versus x-rays) and a weighting factor for the tissue or organ being irradiated. The effective dose calculation allows for summation of doses from all sources of radiation and represents the stochastic effect of low levels of ionizing radiation.

Eighty-four percent of the 4,155 admissions (3,333 unique patients) to the MICU in 2013 were exposed to at least one imaging study. Approximately 2.3 percent (N = 98) of MICU admissions were exposed to a CED greater than the annual federal occupational limit (50 mSv). Twelve admissions (nine MICU survivors) were exposed to doses greater than 100 mSv, similar to those accrued by some Japanese survivors of the atomic bomb blasts in 1945 (Figure 1). This dosage is statistically linked with cancer induction. Fifty-seven percent of the total radiation dose exposure came from CT scans (Figure 2).

RISKS AND BENEFITS OF RADIATION-BASED IMAGING MODALITIES

The diagnostic utility of radiation imaging in the care of the critically ill should not be understated. However, patients in the MICU may be inadvertently exposed to very high dosages of radiation, due to the lack of a dose-tracking system. The risk of exposing patients to increasing radiation doses and the theoretical lifetime risk of cancer

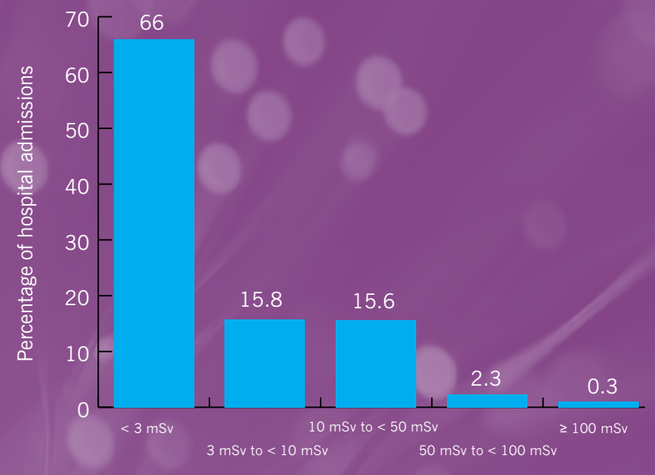

Figure 1: Overall distribution of cumulative effective dose (CED) of radiation in the study population.

induction must be weighed against the purported benefits of further testing.

The proportion of patients exposed to radiation doses in excess of 50 mSV would increase dramatically if one were to collate the radiation burden acquired annually over the course of continued clinical care.

Focusing on statistical risks from radiation imaging should not distract attention from the potential benefits of imaging studies. Effective and judicious utilization of radiological resources provides great benefit to those needing diagnostic imaging studies. In the absence of a local, regional or national authority to monitor the cumulative doses accrued by patients, the requesting physician must be a responsible and economical consumer of radiological resources.

QUANTIFYING DOSES IN ONGOING CARE AND DOSE TRACKING

In our ongoing effort to quantify and explore radiation exposure in the critically ill, we are examining the annual radiation burden accrued by young patients (< 40 years of age) who survived an episode of critical illness in the MICU. Medical radiation doses accrued as a result of ongoing clinical care from various radiographic modalities both in inpatient and outpatient clinical settings, before and after MICU admission, will be summated to arrive at an annual CED. We hope to partner with other healthcare systems in our region to compare our practices and resulting radiation burden per episode of MICU care.

We ultimately hope to develop a software tool that tracks radiation doses and maintains a registry of radiation accrued per episode of clinical care, year and lifetime. Such a longitudinal registry would benefit clinical research and allow the requesting physician and patient to make an informed choice.

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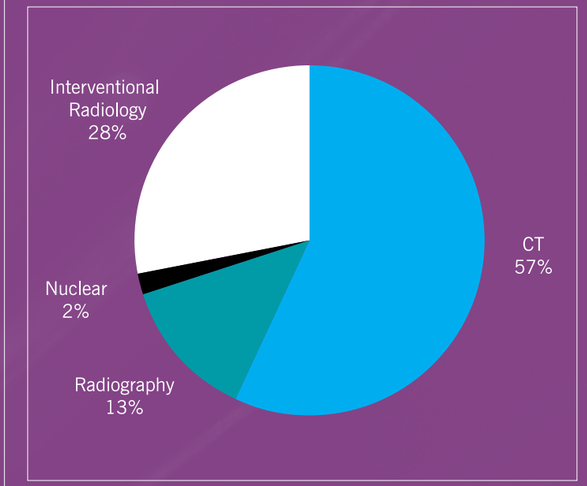
Dr. Guzman, staff in Critical Care Medicine and Chief Medical Officer at Cleveland Clinic Abu Dhabi, can be reached at guzmanj@ccf.org.

Figure 2: Distribution of average CED per episode of care in the MICU by type of radiological study.



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Significant Progress in Understanding, Recognizing and Treating Alpha-1 Antitrypsin Deficiency

Cleveland Clinic's Alpha-1 Antitrypsin Center plays key role in guideline update

James K. Stoller, MD, MS

Alpha-1 antitrypsin deficiency (AATD) is an autosomal codominant condition that predisposes to COPD and liver disease. Since its initial description in 1963, significant progress in understanding the pathogenesis, diagnostic strategies and treatment of AATD has been made. This progress is largely due to intensive research, both at the mechanistic and molecular levels, and to large, collaborative studies like the National Heart, Lung, and Blood Institute Registry of Individuals with Alpha-1 Antitrypsin Deficiency.[1,2] The Alpha-1 Foundation, a patient organization that supports research and serves as a broker between patients and the scientific, clinical and funding communities, has also worked to advance a cure for AATD. This brief review will highlight this progress, including Cleveland Clinic Respiratory Institute's long-standing contributions to understanding and managing individuals with AATD, culminating in participation in a recently updated clinical practice guideline for management of affected individuals.[3]

PROGRESS IN UNDERSTANDING AATD'S PATHOGENESIS

Major strides in understanding the pathogenesis of AATD include characterizing the *SERPINA1* gene (on the long arm of the 14th chromosome) and the AAT protein structure, and clarifying that the most common severely deficient allele, called Z, relates to a single amino acid substitution: lysine for glutamic acid at position 342. This substitution causes the Z-type protein to misfold, polymerize in the liver cell (hepatocyte) and bind less avidly to neutrophil elastase.[4] The result of this polymerization is that the Z-type protein is trapped within the hepatocyte, which lowers the serum and lung levels of AAT, thereby allowing unopposed proteolytic breakdown of elastin in the lung by neutrophil elastase within neutrophils, with consequent emphysema.

The pathogeneses of lung and liver diseases differ. Lung disease is related to a "toxic loss of function" characterized by inadequate amounts and impaired function of the abnormal AAT protein, which places the patient at risk for emphysema. In contrast, the associated liver disease (risk for liver scarring [cirrhosis] and liver cancer [hepatoma]) relates to a "toxic gain of function," in which trapped, polymerized AAT protein in the hepatocytes (especially in ZZ homozygotes) creates a risk for hepatitis, cirrhosis and hepatoma.

ENHANCED AWARENESS AND DIAGNOSTIC STRATEGIES

Along with enhanced understanding of the pathogenesis of AATD has come increased appreciation of AATD's prevalence and, importantly, the profound degree to which AATD is globally under-recognized.[5] Current estimates suggest that 100,000 Americans have severe AATD but that fewer than 10,000 have been diagnosed. Affected individuals frequently experience long delays (i.e., five to eight years) between their first symptom (commonly dyspnea) and initial diagnosis of AATD; in one series, 43 percent of affected individuals reported seeing at least three physicians before the diagnosis was established.[5,6]

Awareness of persisting under-recognition of AATD has prompted the development of strategies to enhance diagnosis to make optimal management available sooner to individuals with AATD. At Cleveland Clinic, prompts in the electronic medical record encourage physicians to test for AATD whenever results of pulmonary function tests show fixed airflow obstruction. These prompts have been associated with a fourfold increase in appropriate testing frequency;[7] still, significant opportunities remain to ensure broader appropriate testing. Multicenter studies have shown that empowering respiratory therapists to counsel patients about testing, or to arrange testing at the point of care (i.e., during pulmonary function testing), helps detect affected individuals.[8,9]

CURRENT AND EMERGING THERAPIES

Finally, significant strides have been made in developing specific therapies for AATD in the 53 years since the condition was first described. Augmentation therapy — the intravenous infusion of purified, pooled human plasma AAT — is recommended for individuals with AATD and emphysema in the official guidelines of the American Thoracic Society and European Respiratory Society,[10] by the Canadian Thoracic Society,[11] and in

the Alpha-1 Foundation's most recent guidelines from a group of "alpha docs."[3] The weight of evidence, including three randomized, placebo-controlled trials, supports the efficacy of augmentation therapy in slowing the progression of emphysema.[4]

At the same time, novel therapies have been and are being actively investigated, including gene therapy with an adeno-associated virus vector given by whole limb perfusion or intrapleurally; administration of inhaled AAT or recombinant AAT; hyaluronic acid inhalation; RNA interference strategies to turn off production of Z protein; and administration of small molecule inhibitors of mutant AAT polymerization.

CLINICAL RESOURCE CENTERS KEY FOR PATIENTS

Patients with AATD undoubtedly benefit from the substantial and rapid scientific and clinical advancements in addressing AATD. To help direct patients toward clinicians who understand AATD, the Alpha-1 Foundation (www.alpha1.org) has acknowledged Clinical Resource Centers (CRCs) with special expertise in managing patients with AATD. Cleveland Clinic's Alpha-1 Antitrypsin Center, one of the founding CRCs, draws from the expertise of colleagues in adult pulmonary medicine, dermatology, and adult and pediatric liver disease to treat these patients and to contribute to ongoing progress in understanding, diagnosing and treating the disease.

Dr. Stoller, Director of the Alpha-1 Antitrypsin Center and Chair of the Education Institute, can be reached at stollej@ccf.org or 216.444.1960.

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The Integrated Respiratory Therapy Enterprise

RT integration drives efficiency, quality, cost savings across health system

By Madhu Sasidhar, MD

As healthcare systems consolidate to achieve efficiencies of scale, care integration is vital to improving the patient experience, ensuring quality and reducing costs. Recently, Cleveland Clinic health system integrated the respiratory care services provided by over 500 therapists at 13 locations in the Cleveland metropolitan area.

MOVING FROM A FRAGMENTED CARE EXPERIENCE

Respiratory therapy (RT) services within our health system in Northeast Ohio previously consisted of 12 business units at nine acute care facilities, one pediatric rehabilitation hospital and three freestanding emergency departments. Each unit created independent clinical protocols, policies and standards. Human resource management, education, research and quality improvement were integrated into the activities of individual units without coordination across units.

Owning only parts of our care continuum was inadequate, and the health system recognized the need for a deliberate strategy of integration for an optimized patient experience.

A FRAMEWORK FOR THE INTEGRATED RT ENTERPRISE

Integration efforts are critically dependent on support from senior leadership. During the early stages of planning, we sought participation from various stakeholders, including leaders of clinical institutes, regional hospital presidents, chief operating officers, operations, nursing and human resources. We identified barriers to success, including the need to have a local respiratory therapy leadership presence for daily operations. Many local leaders of respiratory care were in cross-functional roles that included oversight of services such as echocardiography and outpatient clinics. To provide a seamless transition, these expanded roles were preserved and supported following RT integration.

To support enterprise-level activities, existing roles were redefined and their scope of authority expanded. The RT director is a system-level role with responsibility for strategic planning and helping align goals of each unit with the organization's priorities. Two regional managers, with responsibility for four hospitals each, serve as cross-continuum leaders while providing operational support to local RT leaders. A lead RT supervisor or manager at each hospital is responsible for day-to-day operations and also serves as the main RT contact for other services at the hospital. Information technology, education, research and quality were each assigned coordinator positions with enterprisewide scope of activity.

IMPACTING QUALITY AND VALUE

Integrating RT services across our health system uniquely positions us to implement projects that impact quality and value. We have changed our RT productivity measurement system to better align with value-based care. Systemwide scheduling software will enable us to fully leverage a flexible staffing pool to meet staffing needs across multiple sites.

Enterprise quality improvement utilizes a monthly business review and scorecard to track and compare more than 70 clinical and operational metrics applicable to respiratory care. Our processes for regulatory compliance are being standardized along with enterprise-level RT policies and standard operating procedures.

Our integrated respiratory care service is continuously identifying opportunities for an expanded RT scope of practice that allows therapists to function at the highest level of their license. Specialized RT consult services, chronic disease management for COPD and emergency airway management are some of the areas we have identified and developed using our enterprise resources for education.

The integrated RT enterprise is one example of our health system's adaptation to provide a fully integrated care experience that continuously evolves and is optimized for value.

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Pulmonary Thromboendarterectomy for CTEPH

Why it's underused despite high success rates

By Gustavo Heresi-Davila, MD

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially deadly and underdiagnosed condition that develops from unresorbed pulmonary emboli. Our multidisciplinary team at Cleveland Clinic is one of just a handful across the U.S. that treat CTEPH using the complex surgical procedure known as pulmonary thromboendarterectomy (PTE).

PTE: GRACE UNDER PRESSURE IS A MUST

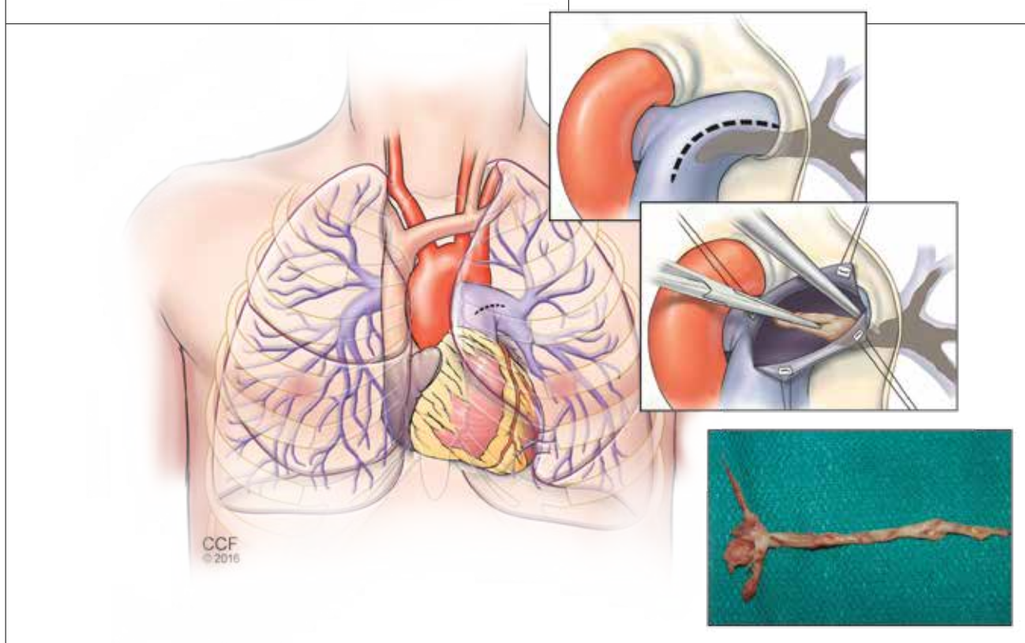
Performing a PTE requires a dedicated team, a highly skilled surgeon and extreme efficiency under pressure. It involves quick yet painstaking removal of thin, scarred clot tissue lining the pulmonary arteries (Figure 1). The patient is rendered hypothermic to allow for periods of circulatory arrest on a cardiopulmonary bypass machine in order to enable a bloodless field.

Ideally, the procedure in each lung should be completed within 20 minutes to avoid the need for reperfusion. It's one of the most difficult surgeries we perform.

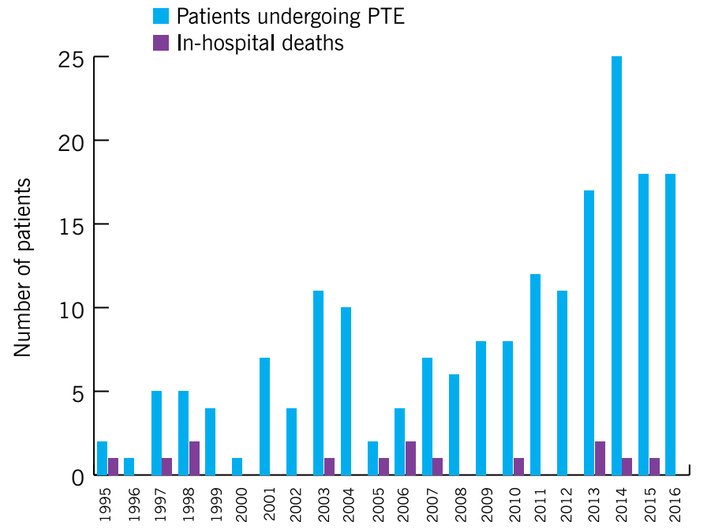
In 2010, we established a team to standardize protocols for PTE patient selection, preoperative evaluation, medical optimization and postoperative follow-up. Our team includes members from pulmonary medicine, cardiothoracic surgery, nuclear medicine, radiology, cardiology, anesthesiology and critical care medicine.

SUCCESS RATES ABOVE 90 PERCENT

Cardiothoracic surgeon Nicholas Smedira, MD, first performed PTE at Cleveland Clinic in the 1990s. Over the past 20 years, Dr. Smedira and team have performed more than 180 PTE procedures, with current CTEPH success rates of 90 to 95 percent. Since 2010, operative mortality has dropped from around 12 percent to less than 4 percent, and volumes have increased. Between 2011 and September 2016, we performed 101 procedures (Figure 2). Rates of significant complications, such as confusion and disorientation from neurologic injury, or respiratory dysfunction due to lung injury, are now below 10 percent.



› **Figure 1:** Pulmonary thromboendarterectomy for CTEPH involves quick but painstaking removal of thin, scarred clot tissue lining the pulmonary arteries. The residual scar is grasped and dissected from the lobar and segmental branches, as shown in the middle inset. The bottom inset shows an operative specimen. The procedure in each lung is ideally completed within 20 minutes to avoid the need for reperfusion.



› **Figure 2:** Pulmonary thromboendarterectomy (PTE) experience, 1995 – September 2016 (N = 187)

These improvements over time are due mainly to major advances in the management of patients on perfusion therapy in anesthesiology and in postoperative critical care management. The surgical technique has remained much the same over the past 20 years.

CTEPH: WHAT REFERRING CLINICIANS NEED TO KNOW

CTEPH should be included in every differential diagnosis of patients with pulmonary hypertension of unclear etiology, and even in those who merely have unexplained shortness of breath or exercise limitation.

Some patients don't exhibit pulmonary hypertension at rest but have symptoms during exercise, as on a cardiopulmonary exercise test or an exercise right heart catheterization. A lung ventilation/perfusion scan is the gold standard screening tool when CTEPH is suspected.

The estimated incidence of CTEPH within two years of initial pulmonary embolism is about 4 percent, but that number doesn't account for the many unrecognized pulmonary emboli. In fact, some 30 to 50 percent of patients diagnosed with CTEPH have no history of pulmonary emboli even though all are likely to have experienced one.

Of the 500,000 U.S. cases of pulmonary emboli per year, conservative estimates place the number of new CTEPH cases at about 2,400 to 5,000 annually. With only roughly 500 PTE operations being performed annually in the U.S., thousands of patients who might benefit from the procedure are not receiving it.

DEBUNKING MISCONCEPTIONS AROUND PTE FOR CTEPH

Part of the reason is that even when CTEPH is diagnosed, misconceptions prevent physicians from referring patients for PTE.

Although about one-third of patients will have contraindications to surgery — most notably very distal and surgically inaccessible clots or significant comorbidities — many other factors are not contraindications, such as older age or obesity. In fact, we have performed successful PTEs in patients in their 70s and 80s and even in morbidly obese patients. Importantly, severe pulmonary hypertension of any degree is no longer a contraindication.

Another misconception is that CTEPH can be managed medically. Although anticoagulants are indicated to prevent further embolic events, they don't improve established CTEPH or pulmonary hypertension. One medication, riociguat (Adempas®), was recently approved by the FDA to treat CTEPH but is indicated only for patients who are not surgical candidates or who have residual or recurrent pulmonary hypertension after surgery.

We do not yet have hard and fast rules to determine which patients are nonoperable. The decision about operability is complex, largely subjective and shaped by the team's experience and expertise, which underscores the need for referral to an expert center.

The stakes are high. If the surgery is a possibility, it offers the best outcome for patients.

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Novel Treatment for Obstructive Sleep Apnea: Hypoglossal Nerve Stimulation

On the frontier of OSA collaborative neurotherapeutics

By Reena Mehra, MD, MS; Alan Kominsky, MD; and Tina Waters, MD

Obstructive sleep apnea (OSA) is a condition characterized by repetitive upper airway collapse and that affects around 15 percent of the U.S. population. The intermittent episodes of upper airway compromise result in apneas (complete collapse) or hypopneas (partial upper airway collapse), with adverse physiologic consequences. These include episodic hypoxemia, hypercapnia, autonomic nervous system fluctuations and direct cardiac mechanical effects due to increases in negative intrathoracic pressure.

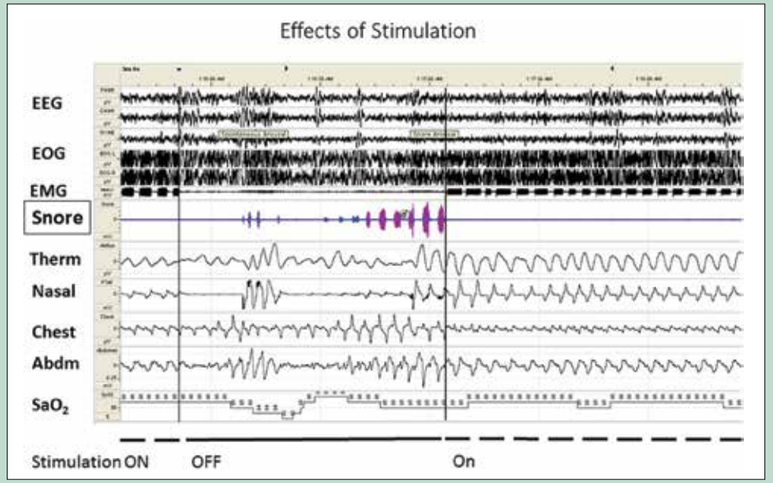
Researchers and clinicians are increasingly recognizing the importance of OSA treatment due to consistent findings from population-based studies that demonstrate the adverse health ramifications of untreated OSA.[1] These include longitudinal risk of increasing incident hypertension, insulin resistance/diabetes mellitus, coronary artery disease, heart failure, stroke and cardiovascular-specific mortality, along with data supporting increased vulnerability to sudden nocturnal cardiac death.

OSA TREATMENT OPTIONS

Nasal continuous positive airway pressure (CPAP) therapy has long been considered standard first-line treatment of symptomatic OSA. Benefits include maintenance of airway patency, improved objective measures of sleep architecture and enhanced subjective quality of sleep.

More recently, oral appliances and upper airway surgical procedures such as uvulopalatoplasty have been introduced as alternative OSA treatment strategies; however, few additional novel therapies have been developed. In the clinical realm, treatment of OSA with CPAP has proved challenging from a patient compliance perspective, with general estimates ranging from 40 to 70 percent treatment adherence. Furthermore, suboptimal CPAP adherence in clinical trials poses a significant limitation in the accurate interpretation of results.

› **Figure 1:** Inspire® Upper Airway Stimulation device. Image courtesy of Inspire Medical Systems Inc.



› **Figure 2:** In this strip chart polysomnogram recording (approximately 2 min), the stimulator is turned ON (as verified by the bursting of the chin EMG) and then turned OFF, and then turned ON again. Abruptly, when the stimulator is turned OFF, there is upper airway obstruction, as illustrated by the flat nasal pressure signal, continued respiratory efforts, and a fall in oxygen saturation. (The thermistor signal is a thermal drift.) EEG=electroencephalogram. EOG=electrooculogram or eye movements. EMG=chin electromyogram. Snore=snore signal by microphone. Therm=thermistor at the nose for airflow. Nasal=nasal pressure transducer for flow. Chest and Abdm=chest and abdomen efforts, respectively, by inductance methods. SaO_2=oxygen saturation by oximetry.

Figure and legend republished from Figure 2 (Kingman et al. *Respir Investig*. 2016 Jul;54(4):241-9. doi: 10.1016/j.resinv.2016.01.006. Epub 2016 Mar 18.) with permission from Elsevier.

Heterogeneity of OSA pathophysiology has also been established, involving interindividual variations in arousal threshold, loop gain, muscle responsiveness and critical closing pressure. For these reasons, development of novel OSA treatments targeting specific aspects of OSA pathophysiology is imperative to facilitate an individualized, precision medicine approach.

HYPOGLOSSAL NERVE STIMULATION

Hypoglossal nerve stimulation is an innovative therapeutic approach available for the treatment of OSA for patients who are unresponsive to or intolerant of other treatments for OSA. This approach stems from the dysfunctional negative pressure genioglossus reflex in many OSA patients. In individuals without OSA, the genioglossus muscle (the primary pharyngeal dilator muscle) responds to negative intraluminal pressure with an increase in electromyographic activity. This is compromised in OSA due to neuromuscular dysfunction.

Initial experimental and small clinical trials showed improvement in airflow and enhanced upper airway stability without arousals during sleep or neuromuscular side effects. These data provided the basis to pursue larger clinical studies. Moreover, direct nasopharyngoscopic examination in these studies demonstrated not only enlargement and stabilization of the retrolingual space, but also the retropalatal airway, suggesting multilevel benefit.

The device operates by generating electrical stimulation, which advances the tongue forward and opens the pharyngeal airway during respiration. It consists of three implanted elements: a breathing sensor, a small electrical impulse generator and a hypoglossal nerve stimulator. Patients activate the system with a handheld remote control device.

Several devices are available, but only one has been approved by the FDA: the Inspire® Upper Airway Stimulation device (Inspire Medical Systems Inc.; Maple Grove, MN). The device is surgically implanted by placing a three-electrode wrap cuff on the distal medial branches of the hypoglossal nerve. The electrodes stimulate the anterior tongue protrusors, mainly consisting of the genioglossus muscle (Figure 1). An intercostal lead senses the fall in intrathoracic pressure during inspiration, thus providing a basis to synchronize muscle activation accordingly (Figure 2).[2]

INTERVENTIONAL TRIAL DATA SUPPORTING BENEFITS OF HYPOGLOSSAL NERVE STIMULATION

In a multicenter, prospective, single-group cohort study, Inspire was implanted and activated one month later. Primary outcomes measured were the apnea hypopnea index (AHI) and oxygen desaturation index (ODI), standard indicators of sleep apnea severity.

Eligible participants had a body mass index < 32 kg/m^2 and moderate-to-severe OSA (AHI of 20 to 50 events per hour), and needed to show absence of complete concentric collapse of the velopharynx as observed on drug-induced sedation endoscopy.

The study documented a 68 percent reduction in the AHI at 12 months that was not otherwise explained by changes in weight, positional effects or sleep state differences. Secondary outcomes of subjective sleepiness and functional outcomes of sleep also demonstrated improvement at 12 months. A substudy at 12 months also showed that improvements in respiratory indices and measures of quality of life were reversed with transient cessation of therapy.

Currently, 36-month outcomes are available, which support durability of the beneficial effects. Interestingly, the amplitudes required for

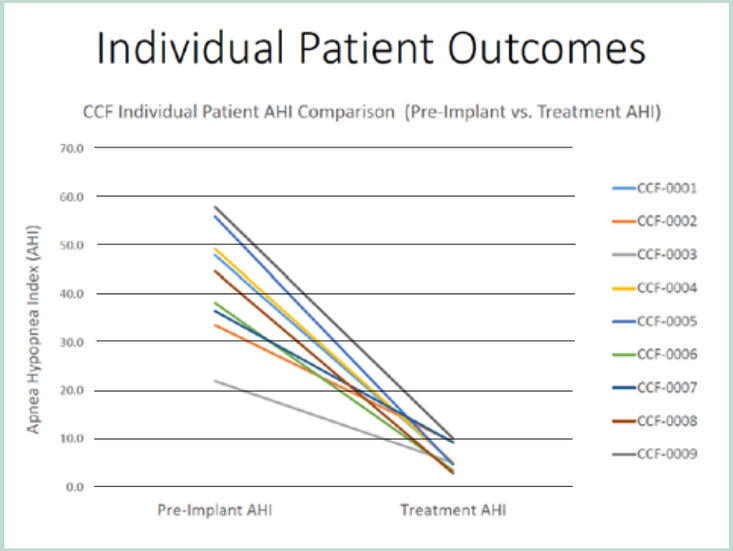


Figure 3: Nine patients have undergone successful implantation of the device, with evidence of objective improvement of sleep apnea severity characterized by reduction of the apnea hypopnea index (AHI) from severe to near-normal range.

effective stimulation were similar at 12 months compared with 36 months, suggesting limited tachyphylaxis.

CLEVELAND CLINIC CENTER OF EXCELLENCE

Cleveland Clinic's Sleep Disorders Center has been identified as a Center of Excellence for Inspire placement, leveraging cross-disciplinary sleep medicine collaborations involving neurology, otorhinolaryngology and pulmonary medicine. This multidisciplinary collaboration is critical to the program's success in melding the perspectives of neural innervation, respiratory physiology and surgical intervention.

Eligible candidates must meet four criteria:

- Age 18 years or older
- An AHI between 20 and 65
- A body mass index of less than 32 kg/m^2
- Failure to respond to previous CPAP use

Prior to implantation, patients who fulfill these criteria undergo sedated endoscopy to ensure that their particular pattern of airway collapse is amenable to hypoglossal nerve stimulation therapy. Also, patients must have undergone a recent sleep study before implantation can be considered. Finally, a repeat sleep study must be performed one month postoperatively so that we can titrate the device to deliver its maximum therapeutic effect.

Thus far, nine patients have undergone successful implantation of the device, with evidence of objective improvement of sleep apnea severity characterized by reduction of the AHI from severe to near-normal range: 42.9 ± 11.5 to 6.0 ± 2.7 (Figure 3). Other outcomes such as patient-reported outcomes and cardiovascular measures are currently being collected to provide the platform for future investigation.

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Teaching Mechanical Ventilation in the 21st Century

Bridging a gap between blackboards and bedsides

By Eduardo Mireles-Cabodevila, MD; Rendell Ashton, MD; Neal Chaisson, MD; Aanchal Kapoor, MD; Abhijit Duggal, MD, MPH, MS; Robert Chatburn, MHHS, RRT-NPS

The advent of positive pressure mechanical ventilation has arguably been one of the biggest advances in modern critical care medicine. Although its use was not routine until the 1960s and '70s, Galen described a similar concept as far back as the third century A.D.: "If you take a dead animal and blow air through its larynx [through a reed], you will fill its bronchi and watch its lungs attain the greatest distention."[1]

This simple manual process has now morphed into a series of highly complex machines and an endless variety of ventilatory options. Currently, there are over 300 different names for modes of ventilation in the United States alone. Lack of a systematic taxonomy to describe modes presents significant problems. Nomenclature is at the whim of ventilator manufacturers, and trendy mode names can be confusing or misleading. As a result, physicians often restrict teaching and practice to the most basic modes of ventilation. Those who venture beyond this often do so with an incomplete understanding of how the ventilator and patient truly interact.

Following the work of Robert Chatburn, MHHS, RRT-NPS, Respiratory Therapy Research Manager at the Respiratory Institute, on a taxonomy of mechanical ventilation, our group of 10 educators began to discuss the growing chasm between current teaching paradigms and ventilator utilization at the bedside. We concluded that medical education in this area felt as antiquated as Galen's reed.

A NOVEL COURSE ON THE PRINCIPLES AND APPLICATION OF MECHANICAL VENTILATION

Our team worked to address several educational gaps by creating a three-phase curriculum on the principles and application of mechanical ventilation. The first phase focuses on establishing a standardized ventilator taxonomy[2] and learning to choose a mode of mechanical ventilation based on physiologic objectives and clinical goals. Trainees also learn to optimize patient interactions according to specific algorithms (Figure). Trainees complete an interactive, online curriculum of 16 modules before moving to the next phase. These narrated modules include embedded graphics, quizzes and links to supporting literature and online ventilator simulators.

The second and third phases of our curriculum occur during an eight-hour Mechanical Ventilation Skills course at Cleveland Clinic's Simulation and Advanced Skills Center. The Simulation Center and its multidisciplinary staff allow users the flexibility to create a realistic ICU atmosphere and to utilize high-fidelity ventilator waveform simulators, interactive monitors and realistic patient profiles.

Phase two begins with a didactic lecture reviewing key concepts from the self-guided online modules, followed by a hands-on rotation through six skills stations where a facilitator assists learner interaction with ventilators. This phase reinforces concepts of mode taxonomy and patient ventilator interaction and allows safe learning of ventilator manipulation. It also teaches trainees to evaluate the response of each mode to different physiological conditions and reinforces the use of appropriate modes to achieve specific ventilation goals.

Phase three occurs during the afternoon portion of the simulation course. Learners move into small groups, where they are exposed to three ICU-based scenarios (ARDS, status asthmaticus and reversal of paralytic medications). In each scenario, teams receive basic clinical information and are exposed to a simulated patient interacting with a ventilator. Learners must choose an appropriate ventilator mode and optimize the settings. Instructors vary patient physiology and patient/ventilator interactions based on a predetermined algorithm created by our team.

Each scenario has specific objectives to reinforce concepts from phases one and two and is designed to be realistic and fully interactive. Time for targeted debriefing and review of the learning objectives is a key element of each scenario.

Finally, groups rotate through an asynchrony troubleshooting workshop. The workshop is designed to introduce a method to evaluate patient-ventilator interactions systematically and to recognize forms of asynchrony correctly. Trainees learn via hands-on interaction with ventilators and a high-fidelity lung simulator with preprogrammed asynchronous activity.

BUILDING BRIDGES TO IMPROVED PATIENT CARE

Our Mechanical Ventilation Skills course represents the Respiratory Institute's commitment to educational excellence and innovation. Using leading-edge institutional resources, international expertise in mechanical ventilation and the latest concepts in education theory, we are building bridges between the classroom and the bedside. Our innovative approach to simulation and teaching is helping trainees identify the best ways to optimize both patient comfort and lung-protective ventilation with modern mechanical ventilators.

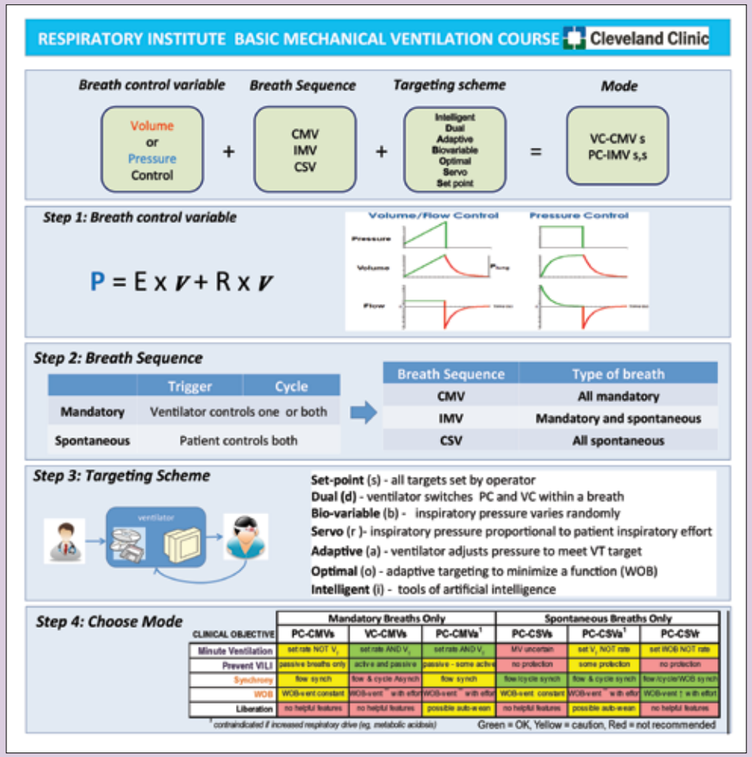

Figure: Fellows learn ventilator taxonomy in a systematic fashion. This allows caregivers to optimize ventilator settings by more fully understanding the individual merits and limits of each mode.

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Case Study: Managing Primary Immunodeficiencies

Complex cases requiring multidisciplinary care

By James Fernandez, MD, PhD, and Maria Barcena Blanch, MD

PRESENTATION

A 57-year-old man with history of COPD, coronary artery disease (CAD), and atrial fibrillation required admission to the hospital due to worsening cardiac symptoms associated with CAD and aortic insufficiency.

Throughout his teenage years and early 30s, he had necrotic skin ulcerations involving his upper and lower extremities that required two- to four-week courses of parenteral antibiotic therapy four to five times per year. His symptoms subsided by the age of 40, with spontaneous resolution of his recurrent skin lesions. He had no further history of recurrent infections involving skin or other systems after the age of 40. However, he developed a severe postoperative infection after a coronary artery bypass graft (CABG) and aortic valve repair performed at age 53, resulting in mediastinitis requiring surgical intervention, skin flap and prolonged IV antibiotic course.

During the current admission, aortic valve replacement and redo CABG were recommended by the cardiac surgical team. Due to this history of postoperative infection and poor wound healing, he was deemed a high-risk surgical candidate and required preoperative evaluation by immunology and infectious disease.

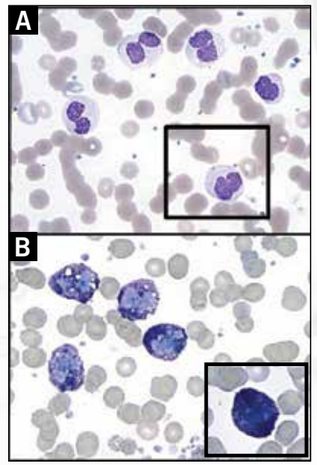

Figure 1 A: Peripheral blood smear showing hyposegmented neutrophils, particularly bilobed neutrophils with significantly reduced cytoplasmic granulation; representative cell is highlighted in box (Wright-Giemsa stain x1000). B: Myeloperoxidase stain shows reduced myeloperoxidase reaction in patient's neutrophils. Normal reaction pattern from healthy donor is shown in insert (images x1000).

EVALUATION

The physical exam was fairly unremarkable. His labs revealed a WBC of 8.36 x 10^3/uL, hemoglobin of 10.7 g/dL, hematocrit 33.6 percent, MCV 88 fL, platelets 462 x 10^3/uL, total protein 6.8 g/dL, with normal liver and renal function tests. Immunologic and infectious workup showed IgE 16.7 mg/dL, IgA 483 mg/dL, IgG 1020 mg/dL, IgM 69 mg/dL, protective titers against tetanus and pneumococcal serotypes, normal LTT mitogen, syphilis IgG negative, nonreactive HIV, and negative hepatitis screen and fungal battery. He underwent redo open heart surgery consisting of aortic valve replacement and CABG without intraoperative complications.

POSTOPERATIVE COMPLICATIONS

His postoperative course was complicated by leukocytosis (WBC 27.6 x 10^3/uL; neutrophils 87 percent, lymphocytes 6.8 percent, monocytes 1.4 percent) and increased ESR (39), wound dehiscence, sternal wound osteomyelitis and development of enterococcal bacteremia. He required treatment with wound vac placement and prolonged IV vancomycin.

Peripheral blood smear showed leukocytosis with neutrophilia with mature segmented neutrophils. Interestingly, the majority of neutrophils showed hyposegmentation, particularly bilobed nucleus similar to Pelger-Huet anomaly, and occasionally small, fragmented nuclei (microlobes) were present. All neutrophils demonstrated pale cytoplasm because of significant decrease in cytoplasmic granulation (Figure 1A). Myeloperoxidase stain showed mild myeloperoxidase reaction in neutrophils; however, it was significantly reduced compared with the reactions in normal neutrophils from a healthy donor (Figure 1B). Although only a few eosinophils were present in the peripheral blood smears, cytoplasmic granules appeared decreased. No other inclusions in the granulocytes or immature granulocytes were noted.

A CLOSER LOOK AND AN ANSWER

Figure 2A-C shows the ultrastructure of granulocytes by electron microscopy, demonstrating mature, segmented neutrophils with many bilobed forms and occasional microlobes. Segmented neutrophils had abundant cytoplasm, rich glycogen particles and Golgi zone. Primary (azurophilic) and tertiary granules were present, but decreased in the neutrophils. Secondary (specific) granules were markedly decreased or absent in the neutrophils examined.

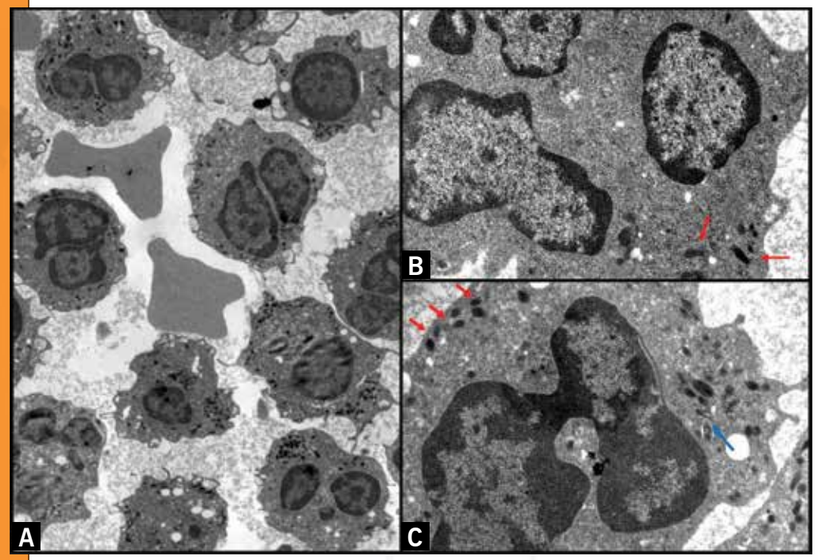

Figure 2: A: Ultrastructure of neutrophils showed predominantly bilobed neutrophils with occasional microlobes (x4,800). B-C: Higher magnification of the neutrophils showed decreased primary (azurophilic; red arrow) and tertiary (blue) granules. Specific (secondary) granules were not present (x23,000).

A heterozygous variant of unknown significance, c.653T>C (p.Val218Ala), was identified in exon 2 of the *CEBPE* gene. A second mutation of the *CEBPE* gene was not detected via gene sequencing, but deletion/duplication analysis was not completed. The presence of large deletions or duplications could not be ruled out. Other deep intronic pathogenic variants as well as variants in other regulatory regions also could not be ruled out.

Based on these findings, we diagnosed the patient with specific granule deficiency. This patient experienced significant burden of disease from infancy to adulthood. Even after remission of his skin lesions, he remains at elevated risk for severe infections, as demonstrated by mediastinitis, osteomyelitis and bacteremia after surgical or invasive interventions.

ADULT IMMUNODEFICIENCY CLINIC: A COLLABORATIVE APPROACH

This case demonstrates the complex characteristics of primary immunodeficiencies (PID). Patients with PID are at risk of multiple complications, including autoimmune disease, which develops in 20 to 25 percent of patients.[1] These patients require continued monitoring not only for infections but also for granulomatous disease of the lungs, autoimmune disorders, lymphoma, malabsorption and other complications. For these reasons, a team approach is vital to the overall care of our PID patients.

The Adult Immunodeficiency Clinic within Cleveland Clinic's R.J. Fasenmyer Center for Clinical Immunology works closely with pulmonologists, rheumatologists, hematologists, oncologists and gastroenterologists to provide the best care for these patients. We and our colleagues frequently make decisions about care as a team, and constant communication among physicians is a necessity.

In the end, patients are better served and appreciate a collaborative effort by multiple physicians with specific expertise in managing their primary immunodeficiency and the complications related to it. With a growing number of adult immunodeficiencies being identified,[2,3] our Adult Immunodeficiency Clinic is fully committed to advancing the care of patients and initiating new research projects in this growing and exciting field.

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3. Yao Q, Shen M, Fernandez J. NOD2-associated autoinflammatory disease and immune deficiency. *J Allergy Clin Immunol Pract*. 2016;4(4):780-782.

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Dr. Barcena Blanch is a 2016 graduate of our Allergy and Clinical Immunology fellowship.

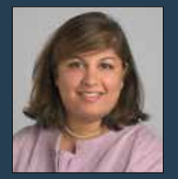
News Briefs

Drs. Erzurum, Kotloff Receive ATS Awards

Serpil Erzurum, MD, Chair of Lerner Research Institute and staff in the Department of Pulmonary Medicine, received the Recognition Award for Scientific Accomplishments at the 2016 American Thoracic Society annual meeting for her work "Cellular and Molecular Mechanisms in Pulmonary Hypertension." She also delivered a keynote address, "Biomarkers for Precision Medicine in Asthma."

Robert Kotloff, MD, Chair of the Department of Pulmonary Medicine, received the Outstanding Educator Award at the 2016 American Thoracic Society annual meeting as recognition for lifetime contributions in education and mentoring in the field of pulmonary medicine.

Dr. Budev Receives Endowed Chair



A $2 million gift by Macon and Joan Brock has established The Macon and Joan Brock Endowed Chair, which will support lung transplant research and education. **Marie Budev, DO, MPH**, is the inaugural chair holder.

Dr. Budev is Medical Director of Cleveland Clinic's Lung and Heart-Lung Transplant Program, one of the largest programs of its kind in the country. In addition to her transplant responsibilities, she is actively involved in the internal medicine residency program as Associate Program Director.

Dr. Budev treats all types of end-stage lung disease, including congenital heart-lung diseases, interstitial lung disease, COPD and pulmonary hypertension. Her research has focused on antibody-mediated rejection and selection of lung transplant candidates.

Textbooks

Daniel Culver, DO; **Robert Kotloff, MD**; **Atul Mehta, MD**; and **James K. Stoller, MD, MS**, served as editors of textbooks published in 2015-2016 and pictured here.

Dr. Erzurum Named Chair of Lerner Research Institute

Serpil Erzurum, MD, was named Chair of Cleveland Clinic's Lerner Research Institute in August 2016. She is the founding Chair of the Department of Pathobiology. Dr. Erzurum's contributions and leadership in pulmonary research have led to diagnostic and therapeutic advances in asthma and pulmonary hypertension and helped identify human physiologic adaptive responses to high-altitude hypoxia. She has published more than 200 peer-reviewed articles and has been principal investigator on more than 20 federal grants with more than $60 million in research funding, including several large, multi-investigator program project grants and network trials. She is a practicing pulmonologist and Cleveland Clinic's lead for the Clinical and Translational Science Center of Cleveland.

In addition to her leadership at Cleveland Clinic, Dr. Erzurum has served the profession as Chair of the Allergy, Immunology and Inflammation Assembly of the American Thoracic Society; Councilor of the Association of American Physicians; member of the NHLBI Advisory Council; and Chair of the Pulmonary Disease Board of the American Board of Internal Medicine.

NewsBriefs

COPD Center Provides Comprehensive, Multidisciplinary Care

The Center for Comprehensive Care in COPD (COPD Center) was established with the aim of providing comprehensive and multidisciplinary care to COPD patients evaluated and managed at Cleveland Clinic Respiratory Institute. The team consists of pulmonologists, thoracic radiologists, thoracic surgeons, physician assistants, nurses and respiratory therapists who specialize in the treatment of COPD. The COPD Center's regular meetings provide an excellent, multidisciplinary venue for discussing management of challenging patients, appropriateness of lung volume reduction modalities and the latest innovations in the management of COPD patients.

The COPD Center maintains a referral clinic as well as a COPD exacerbation clinic that provides early follow-up to those patients recently discharged from the hospital. COPD Center physicians have extensive experience in the assessment of patients for advanced surgical procedures such as lung volume reduction surgery and lung transplantation. The center actively participates in clinical trials of various modalities of bronchoscopic lung volume reduction and has long-standing experience in the evaluation and treatment of patients with alpha-1 antitrypsin deficiency. By including representatives from Cleveland Clinic's regional hospitals, the COPD Center also leads institutional and enterprisewide initiatives for improving the care of patients with COPD, such as the COPD care path and electronic inhaler monitoring program.

To refer a patient, please call 216.444.6503 and ask to be directed to

The COPD Center.

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Thoracic Surgery
Sudish Murthy, MD, PhD

Thoracic Radiology
Rahul Renapurkar, MD

Respiratory Therapy
Richard Rice, RRT

Research Coordinator
Yvonne Meli, RN

Respiratory Institute
Selected Clinical Trials

Consider offering your patient enrollment in a leading-edge clinical research trial at our Respiratory Institute. Obtain further information by contacting the study coordinator or principal investigator.

ASTHMA

Functional Medicine in Asthma (FAst) Study

The objective of this study, sponsored by executive administration, is to determine if standardized guideline-based specialist asthma treatment with respect to asthma control (as measured by ACQ/AQLQ) is equivalent to guideline-based specialist treatment plus additional Functional Medicine management approach.

ELIGIBILITY: Women and men ages > 18 and < 65; nonsmokers or former smokers, with 15 pack-years or less history of smoking; clinical history consistent with moderate to severe asthma; measures of airflow obstruction and reactivity consistent with asthma (12% BD response and/or positive methacholine challenge test) historically or at initial/screening visit; FEV1 between 40 and 100% predicted post bronchodilator; uncontrolled asthma categorized (ACT ≤ 19); willing to be seen in Asthma Center and willing to consider Functional Medicine approach as an add-on to Asthma Center care. Exclusion criteria include life-threatening asthma; any disorder, including but not limited to gastrointestinal, renal, neurological, infectious, endocrine, metabolic or other physical impairment, that is not stable in the opinion of the investigator; clinically important pulmonary disease other than asthma; controlled asthma defined by stability and by ACT > 19; current asthma exacerbations; stable lung function.

PRINCIPAL INVESTIGATOR:
Sumita Khatri, MD, MS

STUDY COORDINATOR:
JoAnne Baran-Smiley, BSN, RN
216.444.5023

LYMPHANGIOLEIOMYOMATOSIS

Registry: Multicenter International Durability and Safety of Sirolimus in Lymphangioleiomyomatosis Trial (MIDAS Trial)

Sponsored by NIH via Cincinnati Children's Hospital Medical Center, this study is a real-world, long-term, prospective, observational drug registry of LAM patients taking or considering taking mTOR inhibitor therapy (sirolimus or everolimus) based on clinical indications. Patients will be diagnosed, treated and followed by their physician according to routine clinical practice.

ELIGIBILITY: The study will enroll LAM patients taking or considering taking mTOR inhibitors from participating clinics in academic health centers and community hospitals. All LAM patients who are chronically treated, newly treated or who may be considered for treatment with mTOR inhibitors are eligible to enroll in the study. Patients who have failed or have been intolerant to mTOR inhibitors will also be recruited. Inclusion criteria include: female LAM patients, age 18 or over; signed, dated informed consent form; diagnosis of TSC or LAM; currently on mTOR inhibitors, and previously intolerant of or have failed mTOR inhibitors, or may be considered for mTOR therapy. Exclusion criteria include: inability to attend clinic visit for LAM evaluation at least once per year; inability to give informed consent; and inability or unwillingness to perform pulmonary function testing.

PRINCIPAL INVESTIGATOR
Robert Kotloff, MD

STUDY COORDINATOR
JoAnne Baran-Smiley, BSN, RN
216.444.5023

LUNG TRANSPLANT

A Phase 2b, Randomized, Controlled Trial Evaluating GS-5806 in Lung Transplant (LT) Recipients with Respiratory Syncytial Virus (RSV) Infection

Sponsored by Gilead Sciences Inc., this is a randomized, double-blind, placebo-controlled study evaluating the effect of presatovir on efficacy, PK, safety and tolerability in lung transplant recipients with RSV infection.

ELIGIBILITY: Key inclusion criteria include: males and females ≥ 18 years of age who have received an LT (single or double) or heart/lung transplant > 90 days prior to screening; confirmed to be RSV-positive by local PCR ≤ 7 days prior to IMP administration; new onset or acute worsening, if the symptom is chronic, of at least one of the following respiratory symptoms ≤ 7 days prior to IMP administration on Day 1/baseline: nasal congestion, earache, runny nose, cough, sore throat, shortness of breath or wheezing. Key exclusion criteria include: use of any investigational agents within specified time frame; use of a strong or moderate cytochrome P450 enzyme (CYP); recipient of any other organ transplant prior to screening, with the exception of an LT (single or double) or heart/lung transplant; known viral coinfection in the upper or lower respiratory tract ≤ 14 days prior to screening; active systemic infection or infectious pneumonia

of any etiology; clinically significant kidney dysfunction; clinically significant liver function test abnormalities; and clinically significant elevations in total bilirubin.

PRINCIPAL INVESTIGATOR:
Marie Budev, DO, MPH

STUDY COORDINATOR:
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216.444.5023

SLEEP MEDICINE

Sleep Apnea and Atrial Fibrillation Electrophysiology: Biomarkers and Evaluating Atrial Triggers (SAFEBEAT)

The SAFEBEAT study is an NIH-supported study designed to examine the mechanisms underlying sleep-disordered breathing and paroxysmal atrial fibrillation.

ELIGIBILITY: Individuals 18-80 years old who have been diagnosed with paroxysmal atrial fibrillation and hypertension and have a BMI of 35 or greater. Participants must be able to participate in up to two overnight sleep studies and must not be on any current treatment for sleep apnea.

PRINCIPAL INVESTIGATOR:
Reena Mehra, MD, MS

STUDY COORDINATORS:
Joan Aylor | 216.445.1698

Rawan Nawabit | 216.445.1593

PULMONARY HYPERTENSION

A Phase 3, Placebo-Controlled, Double-Blind, Randomized, Clinical Study to Determine Efficacy, Safety and Tolerability of Pulsed, Inhaled Nitric Oxide (iNo) Versus Placebo in Symptomatic Subjects with Pulmonary Arterial Hypertension (PAH)

Sponsored by Bellerophon Pulse Technologies, this study's main objective is to evaluate the efficacy of inhaled nitric oxide (INO) using the INOpulse device as compared to placebo in patients with PAH.

ELIGIBILITY: Men or women 18-80 years of age diagnosed with WHO Group 1 PAH who are on a stable dose of at least one PAH specific therapy, who are using oxygen therapy, mPAP > 25 mm Hg, PCWP < 15, PVR > 5 Wood units. Exclusion criteria include moderate to severe restrictive lung disease, undergoing dialysis, the use of a CPAP or BiPAP device and riociguat as therapy.

PRINCIPAL INVESTIGATOR:
Gustavo Heresi-Davila, MD

STUDY COORDINATOR:
Holly Radice | 216.444.2140

A Phase 2, Randomized, Double-BLInd, Placebo-Controlled Study of UBEnimex in Patients with Pulmonary ARTerial HYpertension (WHO Group 1) (LIBERTY)

Sponsored by Eiger BioPharmaceuticals, this study's main objective is to evaluate the safety and efficacy of ubenimex as compared with placebo in patients with Pulmonary Arterial Hypertension.

ELIGIBILITY: Men or women 18-75 years of age diagnosed with WHO Group 1 PAH, on a stable dose of PAH specific therapy for at least three months prior to screening, mPAP > 25 mm Hg, PCWP < 15, PVR > 3.75 Wood units. Exclusion criteria include significant restrictive lung disease, history of portal hypertension or liver disease, and having an active infection.

PRINCIPAL INVESTIGATOR:
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STUDY COORDINATOR:
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INTERVENTIONAL BRONCHOSCOPY

Safety and Effectiveness of the Spiration Valve System in Air Leaks: VAST (Valves Against Standard Therapy)

This study is designed to evaluate the clinical effectiveness of the SVS for treatment of prolonged air leak in non-mechanically ventilated patients.

ELIGIBILITY: Adults with an air leak ≥ 100 mL/min, as measured by a digital thoracic drainage system; air leak present on at least the fifth day following origination. Exclusion criteria include air leak only on forced exhalation or cough; primary pneumothorax; prior interventions including pleurodesis, surgery, blood patch and pneumoperitoneum or valve placement.

PRINCIPAL INVESTIGATOR:
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STUDY COORDINATOR:
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SARCOIDOSIS

A Multiple-Dose, Subject- and Investigator-Blinded, Placebo-Controlled, Parallel Design Study to Assess the Efficacy, Safety and Tolerability of ACZ885 (Canakinumab) in Patients with Pulmonary Sarcoidosis

Sponsored by Novartis, this is a Phase 2 trial investigating the effect of ACZ885, a monoclonal antibody targeting interleukin-1 beta, versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in percent predicted forced vital capacity (FVC) at week 24.

ELIGIBILITY: Ages 18-80 with biopsy-proven, clinically active disease having all of the following criteria: MMRC dyspnea scale > 1, 2; threshold FVC 50-80% of predicted; evidence of parenchymal lung involvement by HRCT. Subjects must weigh at least 50 kg. Subjects must be able to communicate well with the investigator and to understand and comply with the requirements of the study. Disease duration of > 1 year. Selected exclusion criteria include current inhaled use of tobacco products; known hypersensitivity to canakinumab; prior treatment with any biologic drug targeting the immune system within 180 days of randomization or history of any previous use of rituximab; FVC < 50% of predicted; diagnosis of pulmonary hypertension requiring treatment.

PRINCIPAL INVESTIGATOR:
Daniel Culver, DO

STUDY COORDINATOR:
Christopher Estling | 216.445.8951

INTERSTITIAL LUNG DISEASE

Genetic Risk for Granulomatous Interstitial Lung Disease

The objective of this NIH-supported study is to identify genetic risk factors for sarcoidosis.

ELIGIBILITY: Patient must be Caucasian. Biopsy-proven sarcoidosis or Lofgren's syndrome and at least one of the following, documenting pulmonary disease involvement due to sarcoidosis: a biopsy from the lung (either via bronchoscopy or otherwise) or chest lymph nodes demonstrating granulomas; pulmonary parenchymal involvement with Scadding chest x-ray stage I, II, III, IV, in the past or present; abnormal spirometry and/or DLCO (< 80% predicted). Exclusion criteria include positive lung washing or biopsy cultures for fungi or mycobacterial disease or the inability to undergo venipuncture.

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