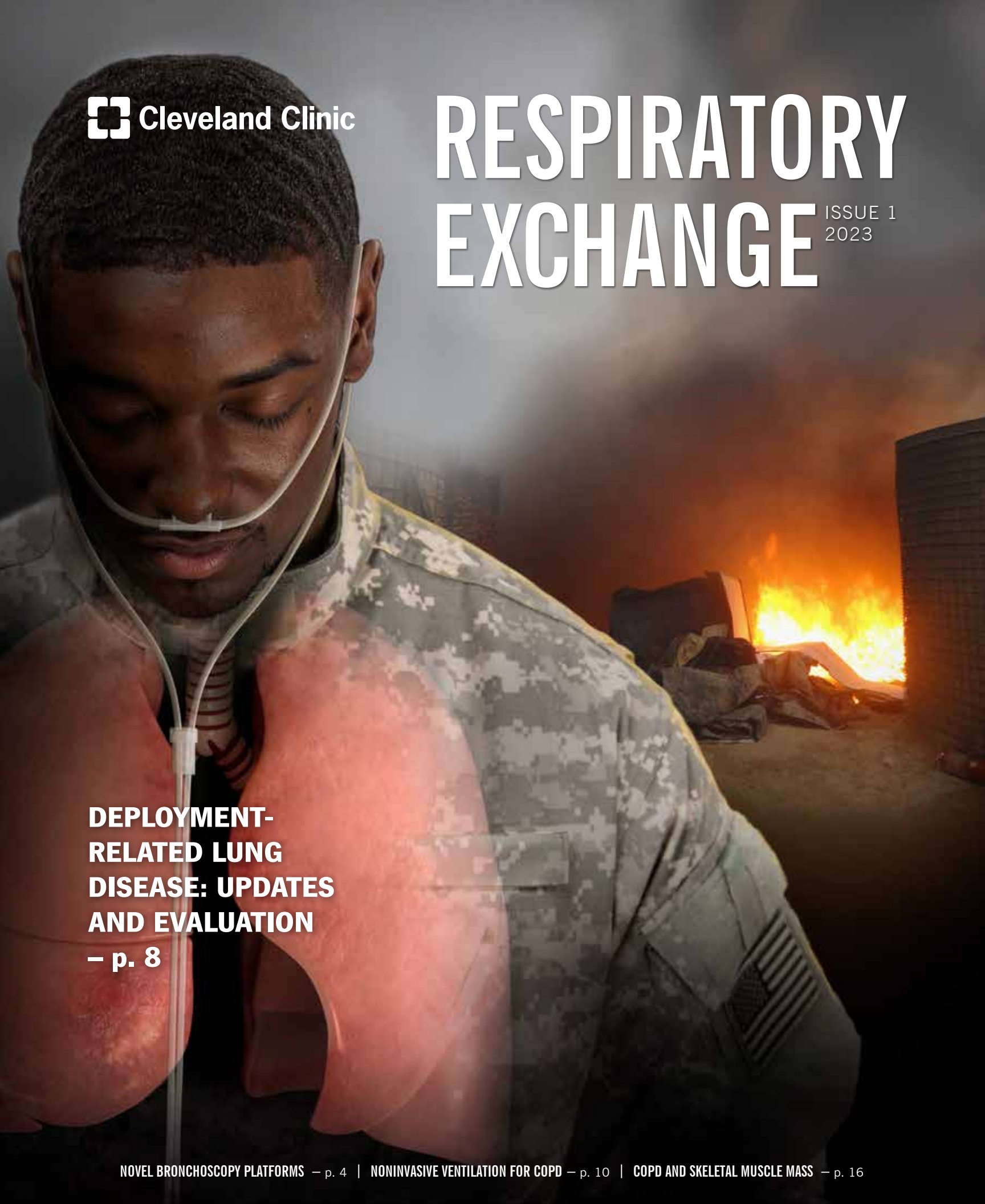


Cleveland Clinic

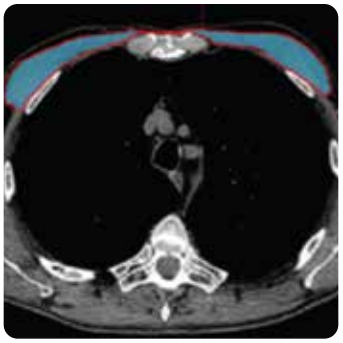
RESPIRATORY EXCHANGE

ISSUE 1
2023

DEPLOYMENT-RELATED LUNG DISEASE: UPDATES AND EVALUATION – p. 8

At the Respiratory Institute, specialists in pulmonology, allergy and immunology, infectious disease, and critical care medicine work in close collaboration to diagnose and manage the full spectrum of pulmonary and allergic disorders, serving more than 200,000 patients annually. The institute is part of Cleveland Clinic, a nonprofit, multispecialty academic medical center integrating outpatient and hospital care with research and education for better patient outcomes and experience. More than 4,500 staff physicians and researchers provide services through 20 patient-centered institutes. Cleveland Clinic is currently ranked as one of the nation's top hospitals by *U.S. News & World Report*.

INSIDE



ON THE COVER — Millions of U.S. veterans have been exposed to contaminants and hazardous pollutants while deployed, and a multitude of lung diseases are associated with deployment-related exposures.

DEAR COLLEAGUES,

RAED DWEIK, MD, MBA
E. Tom and Erika Meyer Professor and Chair
Chair, Cleveland Clinic Respiratory Institute

Just as Agent Orange has become synonymous with the Vietnam War, burn pit exposure has become associated with combat in Iraq, Afghanistan and other countries in the Middle East. When the U.S. military needed to dispose of its trash, huge open-air lots were dug out and filled with all types of waste to be set ablaze. These pits were filled with everything ranging from plastics, computers and paint to discarded medical and human waste. The smoke from these pits was toxic, and fine particulates were released into the air. Over time, it became evident that exposed service members had become ill, and we are now seeing many veterans present with deployment-related lung disease. The cover article for this issue of *Respiratory Exchange* examines the issue and the associated lung diseases and also illustrates how Cleveland Clinic has responded with a dedicated protocol to better treat affected veterans. Jeff Stein, a former U.S. Marine and the nurse coordinator organizing the initiative, and Maeve MacMurdo, MBChB, and Neha Solanki, MD, further explain how the Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics (PACT) Act significantly expands the list of pulmonary diseases now considered presumed to be service connected by the Department of Veterans Affairs. With the expansion of this list of pulmonary diseases, respiratory specialists can expect to see an influx of service members seeking treatment in the near future.

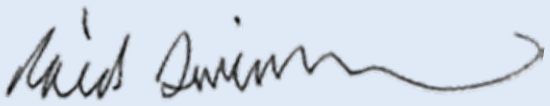
This issue of *Respiratory Exchange* also features commentary from several experts in our department:

- Novel bronchoscopy platforms for biopsy of peripheral pulmonary lesions.
- When to consider evaluation for penicillin allergies.
- Incorporating noninvasive ventilation into treatment plans for patients with chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure.
- The respiratory toxicity of opioids and adapting the standard of care to better treat high-risk patients.
- Determining the cause of high rates of sarcopenia in patients with COPD and developing specific treatments for this patient population.
- Obtaining more accurate intravascular pressure measurements during right heart catheterization.

Our commitment to continuously improving patient care remains strong, and I believe that will be evident to you as you read through this issue. Ideally, you will get a sense of our team's passion for advancing care, leading new discoveries and providing exemplary training for future pulmonologists. Be sure to check out the expanded list of clinical studies near the end of this publication, and consider offering your patients the opportunity to participate in our research as we work to continually offer the highest level of respiratory care to all patients.

Thank you for your interest in our program.

Sincerely,



RAED DWEIK, MD, MBA
E. Tom and Erika Meyer Professor and Chair
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NOVEL BRONCHOSCOPY PLATFORMS FOR BIOPSY OF PERIPHERAL PULMONARY LESIONS

The role of interventional pulmonology in lung nodules/lesions care

Written by See-Wei Low, MD; Sangita Goel, MD; Marcela Azevedo, MD; Sonali Sethi, MD

KEY POINTS

In 2018, the FDA approved robot-assisted bronchoscopy (RAB) to facilitate and improve the diagnostic yield of bronchoscopic peripheral pulmonary lesion biopsies.

The two RAB platforms available in the U.S. market are the Monarch Platform and the Ion Endoluminal System.

The Monarch Platform uses electromagnetic navigation guidance, while the Ion system is a shape-sensing technology.

With the U.S. Preventive Services Task Force's publication in 2021 of revised recommendations for lung cancer screening came the expectation that many more patients would be eligible for screening — substantially increasing the number of indeterminate pulmonary nodules identified annually in the United States using low-dose computed tomography.

Because many peripheral pulmonary lesions (PPLs) require biopsy for a definitive diagnosis, minimally invasive diagnostic techniques with outstanding performance and safety profiles are essential.

Over the past two decades, several bronchoscopic modalities were introduced — including electromagnetic navigation bronchoscopy (ENB) with digital tomosynthesis correction and an ultrathin bronchoscope with radial endobronchial ultrasound (rEBUS) — to improve the diagnostic yield of PPL biopsies over that derived from biopsies using conventional bronchoscopy. The lower diagnostic yield with conventional bronchoscopy was thought to be due to the inability to directly visualize in the airway periphery, the lack of tip stability in the bronchoscope, catheter articulation and the presence of CT-to-body divergence. The newer modalities increased the diagnostic yield from 54% to 79% and were able to correct CT-to-body divergence using digital tomosynthesis.[1] The desire to further improve diagnostic yield resulted in the development of robotic bronchoscopy. In 2018, the FDA approved robot-assisted bronchoscopy (RAB) to facilitate and improve the diagnostic yield of bronchoscopic PPL biopsies.

The RAB systems were designed to reach the peripheral lung airways, similar to the traditional electromagnetic navigation system, but with better stability and steerability during the biopsy.

Two RAB platforms are available: the Monarch® Platform (Auris Health Inc., Redwood City, CA) and the Ion Endoluminal System (Intuitive, Sunnyvale, CA); a third platform, Noah Galaxy, is awaiting FDA clearance.

The Monarch Platform uses electromagnetic navigation guidance, while the Ion Endoluminal System relies on shape-sensing technology. Other subtle differences between the two robots are the scope design (Monarch has a scope-in-scope design, and Ion is a single robotic scope), scope diameter (the outer diameter of the Monarch scope is 4.4 mm and 3.5 mm for the Ion Scope), and the need with Ion to remove the vision probe to insert the confirmation or biopsy tool. More recently, Ion also offers the ability to correct CT-to-body divergence when Ion is integrated with the Siemens Healthineers Cios Spin 3D mobile imaging system.

Many have asked which robots are better suited for reaching peripheral nodules with higher accuracy and whether robots are worth the excitement. Sonali Sethi, MD, responded this way: "Early diagnosis and treatment of lung cancer can dramatically improve outcomes. RAB is evolving into an approach that allows us to offer patients a safe, streamlined and timely diagnosis. There is a lot of enthusiasm, and the robotic future is bright as the field continues to evolve in future directions, including advanced confirmatory imaging and bronchoscopic ablation."

©Auris Health Inc. Reproduced with permission.

LEFT. The Monarch Platform from Auris Health Inc. uses electromagnetic navigation guidance. The surgeon uses a video-game-like controller to guide an articulated tube down the patient's throat.

© Ion Intuitive. Reproduced with permission.

LEFT. The Ion Endoluminal System from Intuitive Surgical is a shape-sensing technology that integrates Ion and Siemens Healthineers' Cios Spin mobile imaging system. The integration offers guidance when preprocedure CT images and intraprocedural imaging indicate differences in nodule locations.

Multiple studies have reported improved diagnostic yield with these RAB platforms; however, no one has conducted a randomized trial or a comparative study of these two robotic platforms or compared the RAB to the conventional EMN system. Most recently, RAB was demonstrated to be as accurate as CT-guided transthoracic biopsy (overall diagnostic yield was 87.6% for RAB and 88.4% for CTTB) by Lee-Mateus et al. at Mayo Clinic.[2] In an abstract recently presented by Low et al. at the World Congress for Bronchology and Interventional Pulmonology (WCBIP) 2022, the Ion platform was demonstrated to have a diagnostic yield similar to that of the ILLUMISITE™ platform (Medtronic, Minneapolis, MN) (77% for RAB and 80% for ILLUMISITE™, $p = 0.4$).[3] Comparing diagnostic yield from one study to another is challenging for several reasons, the most important being the lack of a standardized definition of "diagnostic yield." Understanding these limitations, multiple studies have reported similar diagnostic yields (Monarch Platform, 69.1% to 93%[4-6]; Ion system, 79.3% to 95%[7-9]), outcomes and safety of the robots. A head-to-head randomized trial between the robots, but a comparative study is possible.

At Cleveland Clinic, we are privileged to have both RAB platforms. We can integrate real-time imaging during the procedure with Ion utilizing the Cios Spin, as well as incorporate C-Arm Based Tomography (LungVision™ by Body Vision Medical Inc., Campbell, CA) with the Monarch. We look forward to further improving patient care with an increased diagnostic yield of PPLs, minimizing potential complications and providing ablative therapies bronchoscopically. The ultimate vision of incorporating RAB and real-time imaging into the practice is having the ability to diagnose, stage and treat the PPLs during one procedure while the patient is under anesthesia, leading to efficient and effective care.

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See-Wei Low, MD

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DOES MY PATIENT NEED AN EVALUATION FOR PENICILLIN ALLERGY?

A detailed clinical history should be obtained directly from patients to determine their risk of penicillin

Written by Jennifer A. Ohtola, MD, PhD, and Sandra J. Hong, MD

This article has been excerpted and reprinted (without references) from the Cleveland Clinic Journal of Medicine *(2022;89[3]:126-129). The open-access and fully referenced original article is available at https://www.ccjm.org/content/89/3/126.*

KEY POINTS

Between 5% and 10% of the U.S. population has reported an allergy to penicillins, but the prevalence is higher in older and hospitalized patients.

Penicillins are the most common cause of drug-induced fatal and nonfatal anaphylaxis in the United States.

The PEN-FAST decision rule can be used to help clinicians in point-of-care risk assessments.

How common is penicillin allergy?

Beta-lactam antibiotics, which include penicillins, are among the safest and most effective antibiotics and are widely used. However, 5% to 10% of the U.S. population has reported allergies to penicillins, with a higher prevalence in older and hospitalized patients.

Patients with a documented penicillin allergy are more likely to receive alternative broad-spectrum antibiotics, which can lead to higher healthcare expenditures, longer hospital stays, higher risk of adverse events and development of drug-resistant pathogens.

Although most patients may be able to tolerate penicillins safely, keep in mind that penicillins are the most common cause of drug-induced fatal and nonfatal anaphylaxis in the United States, particularly when they are given parenterally. As a general rule, IgE-mediated allergic reactions typically occur within minutes after receiving the drug and may present as anaphylaxis, urticaria, bronchospasm, angioedema or hypotension. Penicillins have also been associated with other severe non—IgE-mediated reactions such as drug reaction with eosinophilia and systemic symptoms and Stevens-Johnson syndrome/toxic epidermal necrolysis.

The PEN-FAST decision rule

PEN-FAST, a penicillin allergy decision rule, was recently developed to aid clinicians in point-of-care risk assessment. A prospective cohort of 622 penicillin allergy-tested patients from two primary Australian sites and three retrospective cohorts from Australia and the United States were subjected to internal and external validation, respectively. The following features associated with a positive penicillin test were used to create the mnemonic PEN-FAST:

- **PEN**icillin allergy reported (proceed with the assessment below)
- **F**ive years or less since a reaction, or unknown interval (2 points)
- **A**naphylaxis or angioedema, or **S**evere cutaneous reaction (2 points)
- **T**reatment was required for the allergy episode (1 point).

A score of 0 indicates a very low risk of a positive penicillin allergy test (< 1%), a score of 1 or 2 indicates a low risk (5%), a score of 3 indicates a moderate risk (20%) and a score of 4 or 5 indicates a high risk (50%). A cutoff of less than 3 points was found to have a negative predictive value of 96.3%.

PEN-FAST has been further validated in a large European cohort of adult patients reporting a reaction to amoxicillin. These studies suggest PEN-FAST may be an effective tool for non—allergy-trained clinicians to use in estimating risk in patients across various populations.

A direct or graded amoxicillin challenge under medical observation may be performed in low-risk patients, i.e., a PEN-FAST score of 2 or less. If no reaction occurs during the observation period, the patient can subsequently take any type of penicillin without restriction. For those with reported allergy to penicillin only, any other beta-lactam (including cephalosporins, carbapenems and monobactams) can be given as indicated. Drug challenge with the culprit penicillin (if not amoxicillin) is also a reasonable option.

Penicillin skin testing is recommended for patients at moderate or high risk (PEN-FAST score ≥ 3) or with unknown history, current pregnancy or hemodynamic instability. The skin test is the most reliable way to demonstrate penicillin-specific IgE antibodies. However, it does not predict the risk of non—IgE-mediated reactions or development of IgE-mediated allergic reactions upon future exposures to penicillins.

Patients who have a positive skin test result are assumed to be allergic to penicillin and should not undergo a penicillin challenge test. However, they can undergo desensitization to penicillin if they truly need it to induce a state of temporary tolerance. It is reasonable to repeat skin testing if many years have passed, due to the waning of penicillin-specific IgE antibodies.

The predictive value of negative penicillin skin testing is approximately 95% and in combination with an oral amoxicillin challenge approaches 100%.

Serum-specific IgE assays are available for a number of selected penicillins, but they have low sensitivity and thus have limited value and are not commonly used.

The bottom line

In patients with a reported penicillin allergy, obtaining a detailed allergy history directly from the patient is essential. Clinical-decision tools such as PEN-FAST may be useful to identify patients for whom the penicillin allergy label can be removed without a formal allergy evaluation, thus facilitating optimal antibiotic therapy and reducing drug costs.

Jennifer A. Ohtola, MD, PhD

Sandra J. Hong, MD

ABOVE. Respiratory diseases are recognized as presumptive in deployers who were exposed to burn pits during the Gulf War and post 9/11 period before and after passage of the PACT Act. Image courtesy of Jeff Stein.

DEPLOYMENT-RELATED LUNG DISEASE: UPDATES AND EVALUATION

New legislation expands care for veterans exposed to burn pits, and Cleveland Clinic has developed a dedicated protocol to better treat deployers experiencing lung disease

Written by Neha Solanki, MD, Jeff Stein and Maeve G. MacMurdo, MBChB

KEY POINTS

Burn pits are open-air waste disposal sites that were utilized on many bases throughout Iraq, Afghanistan and other areas of the Southwest Asia theater of military operations.

A range of lung diseases have been associated with deployment-related exposures, and new legislation expands affected veterans' healthcare and benefits.

Cleveland Clinic has developed a dedicated protocol for evaluation as the number of veterans seeking care is expected to increase.

An estimated 3.5 million U.S. veterans have been exposed to contaminants and hazardous pollutants while deployed.[1] While abroad, service members can be exposed to a variety of environmental pollutants, which include exhaust from military vehicles and particulate matter from deserts and unregulated industry.[2]

Other adverse environmental exposures include aeroallergens and massive sandstorms with sharp particulate matter comprising of metals and aerosolized metals from improvised explosive devices (IEDs).[3]

Another type of pollutant that can penetrate deeply into the lung and impair function is fine particulate matter (PM) or fine particles. These are classified by their diameter, so $PM_{2.5}$ refers to tiny particles that are 2.5 micrometers or less in width. Studies have shown that levels of $PM_{2.5}$ exceeded both U.S. Environmental Protection Agency and U.S. National Ambient Air Quality Standards at multiple bases across the Middle East.[3,4] Exposure to $PM_{2.5}$ has been associated with an increased risk of cardiovascular disease, worsening asthma control and a range of other negative health outcomes — increasingly, the potential for scarring of the lungs (pulmonary fibrosis) associated with chronic high-level exposure to $PM_{2.5}$ is also recognized.[5-7]

A major, and previously unrecognized, source of exposure faced by veterans is burn pits, which contain large quantities of $PM_{2.5}$ and other hazardous pollutants. Burn pits are open-air waste disposal sites that were utilized on many bases throughout Iraq, Afghanistan and other areas of the Southwest Asia theater of military operations to dispose of human waste, refuse and medical supplies. To quote one deployer: "I lived on small patrol bases while forward deployed to Afghanistan. Each patrol base had its own burn pit, and though efforts were made to place the burn away from the personnel, we inevitably

were exposed to the noxious fumes. This occurred on a daily basis: whenever we were disposing of waste; whether feces or other trash items, we had to go into the smoke."

A range of lung diseases have been associated with deployment-related exposures. Studies have shown a high rate of new-onset asthma and vocal cord dysfunction following deployment.[3] Rare lung disease has also been reported, including multiple cases of constrictive bronchiolitis — an interstitial lung disease characterized by progressive, irreversible destruction of the lung parenchyma.[8] Because of the range and variety of exposures faced by deployers, identifying a specific exposure associated with these lung diseases has been challenging.

Recognizing these challenges, the Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics (PACT) Act significantly expands the list of pulmonary diseases that are now considered "presumptive" by the U.S. Department of Veterans Affairs (VA) (Table 1). The PACT Act reduces the burden of proof for deployers with lung disease potentially related to burn pit exposure and enhances (VA) healthcare eligibility for toxin-exposed veterans. This bipartisan bill is the most significant expansion of veterans' healthcare and benefits in over 30 years.

Pre-PACT	Post-PACT
Asthma	Lung and respiratory tract cancer
Allergic rhinitis	Chronic bronchitis
Sinusitis	Chronic obstructive pulmonary disease (COPD)
	Chronic rhinitis
	Chronic sinusitis
	Granulomatous lung disease
	Interstitial lung disease
	Pleuritis
	Sarcoidosis
	Pulmonary fibrosis

TABLE 1. Respiratory diseases recognized as presumptive in deployers who were exposed to burn pits during the Gulf War and post-9/11 period before and after passage of the PACT Act.

The Respiratory Institute has developed a dedicated protocol for evaluation of deployment-related lung disease. Deployers and veterans may undergo a range of testing by a multidisciplinary team depending on their symptoms, deployment history and prior evaluation, including dedicated chest imaging, evaluation for inducible laryngeal obstruction, and both traditional and invasive cardiopulmonary exercise testing. Jeff Stein, the nurse coordinator of this initiative, previously served in the U.S. Marine Corps. He says:

"My advice to my fellow brothers and sisters who were exposed to these fumes and are currently experiencing respiratory problems is to seek help. You can consult your PCP or your local VA and have them get you referred to a respiratory specialist. The main concern is to get better in order to live the best life possible. We have served our country. We should seek care that heals our ailments and gets us back in the fight."

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Neha Solanki, MD

Maeve G. MacMurdo, MBChB

NONINVASIVE VENTILATION FOR COPD PATIENTS WITH CHRONIC HYPERCAPNIC RESPIRATORY FAILURE

NIV has become an invaluable tool for patients with COPD, but the associated financial and logistical challenges created the need for an ambulatory NIV titration program.

Written by Umur Hatipoğlu, MD, MBA

KEY POINTS

Patients who receive noninvasive ventilation (NIV) as the initial ventilatory assistance modality for acute ventilatory failure have demonstrated a positive response.

Prior studies have reported successful outcomes with high-intensity NIV titrated over a few days, but hospitalization for the purpose of NIV is challenging in the current U.S. healthcare system.

Cleveland Clinic has begun trial of an ambulatory NIV titration program made up of multidisciplinary specialists.

Noninvasive ventilation (NIV) has become an indispensable tool for the treatment of acute hypercapnic respiratory failure related to chronic obstructive pulmonary disease (COPD). Patients who receive NIV as the initial ventilatory assistance modality for acute ventilatory failure have less need for invasive mechanical ventilation, reduced hospital stay and improved mortality.[1]

Recent studies suggest that there could be a role for the use of NIV for stable COPD patients with chronic hypercapnic respiratory failure.[2] For instance, in the HOT-HMV study from the United Kingdom,[3] 116 patients who were on home oxygen and had persistent hypercapnia ($PaCO_2$ > 53 mm Hg) two to four weeks following hospitalization for COPD-related acute respiratory failure were randomized to receive NIV and home oxygen versus home oxygen alone.[3] After one year of follow-up, time to readmission or death was significantly improved in the intervention group (63.4% versus 80.4%).

HOT-HMV and other studies that report successful outcomes utilize high-intensity NIV, defined as a combination of high inspiratory airway pressures with a high backup rate, during nocturnal ventilation with the goal of achieving near or complete normocapnia. In these studies, high-intensity NIV settings were titrated over a few days in the hospital. However, hospitalization for the purpose of NIV titration may be challenging in the current U.S. healthcare environment.[4] Improving telemedicine capabilities could provide a solution to this problem of initiating and managing NIV in the ambulatory setting.

Recently, Duiverman and colleagues from the Netherlands reported on the feasibility and noninferiority of a home NIV initiation program compared to in-hospital initiation.[5] The home program included nurse visits to install the equipment and provide education, close monitoring with transcutaneous pCO2 monitoring and remote ventilator setting changes. While the home program took longer to titrate NIV to goal, it achieved significant cost savings compared with in-hospital initiation.

Considering the financial and logistic challenges of in-hospital and laboratory titration NIV for COPD patients, the Respiratory Institute has begun trialing an ambulatory NIV titration program. A two-hour visit is arranged for patients during which NIV settings are titrated to achieve a 20% reduction in arterial carbon dioxide tension, using transcutaneous PCO2 monitoring in between adjustments. Close attention is paid to additional physiological variables (e.g., tidal volume, blood pressure, pulse rate, respiratory effort and auto-positive end expiratory pressure) and patient comfort.

Additional visits are arranged to achieve high-intensity NIV if normocapnia is not accomplished during the first visit. Patients receive frequent calls to ensure adherence and help with troubleshooting. Clinicians review downloaded adherence data, with the goal of six hours/day of

LEFT. A patient with COPD receives outpatient NIV titration for chronic hypercapnic respiratory failure with close monitoring of transcutaneous CO_2 and other physiological indices.

NIV treatment. Patients have arterial blood gases evaluated during follow-up visits after four to six weeks on the prescribed regimen.

The members of the NIV treatment team include respiratory therapists, a nurse, a COPD coordinator, advanced practice providers and pulmonologists. The program recruits COPD patients who have chronic hypercapnic respiratory failure. Because a quarter of the patients with acute hypercapnic respiratory failure may achieve normocapnia after hospitalization, four weeks are allowed between discharge and assessment of candidacy for the program. Arterial blood gas is measured to ensure hypercapnia is persistent. Clinical assessment and questionnaires are used to exclude other conditions that may result in chronic hypercapnic respiratory failure, such as obesity hypoventilation syndrome and neuromuscular disease. Early experience is encouraging for feasibility, and the program has been well received by patients.

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Umur Hatipoğlu, MD, MBA

THE RESPIRATORY TOXICITY OF OPIOIDS IN 2022

A public health tragedy with persistent pathophysiological and therapeutic challenges

Written by Philippe Haouzi, MD

KEY POINTS

Opioid overdoses have increased dramatically over the past decade.

A new NIH-funded program focuses on better understanding and treating opioid-induced ventilatory depression in at-risk respiratory patient populations.

The program is looking primarily at the mechanisms that control breathing recovery following acute opioid overdose and optimizing standard of care practices.

Opioid-induced acute ventilatory depression is responsible for the life-threatening toxicity of opioids, as it can lead to a terminal hypoxic/anoxic cardiac arrest by pulseless electrical activity or ventricular arrhythmia.[1] For multifarious but not fully understood reasons, there has been a dramatic increase in deaths by opioid overdose over the past decade in the U.S.

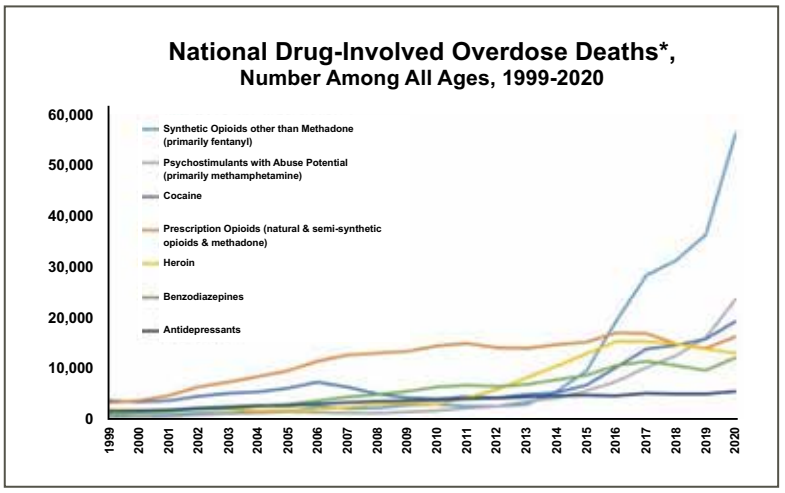

FIGURE 1. Unintentional deaths by drug poisoning in the U.S. since 1999. Note that death by fentanyl has been responsible in recent years for the most deaths by drug poisoning in the country (from the Centers for Disease Control and Prevention, National Center for Health Statistics, released 12/2021).

The data recently released by the Centers for Disease Control and Prevention are extremely concerning. Among the approximately 100,000 annually identified unintentional overdose deaths in the U.S. (involving any drugs or medications), about 70% are related to the use of opioids, such as fentanyl (Figure 1).[2] Opioid-induced breathing depression can affect not only addicted individuals using intravenous injections, but also various subsets of patients. For instance, patients with obesity hypoventilation, sleep-disordered breathing, neuromuscular deficit, or chronic restrictive or obstructive lung diseases, as well as patients in a postoperative setting, are at very high risk for opioid-induced ventilatory depression, sometimes with poor outcomes.[3,4] How to better understand and treat opioid-induced ventilatory depression in these different populations is at the center of the new NIH-funded research program recently developed by the Department of Pulmonary Medicine at Cleveland Clinic. This program is addressing two key questions, noted below.

What are the crucial mechanisms controlling the recovery of breathing following an acute opioid overdose?

Recovering from an acute depression in breathing produced by potent opioid agonists, such as fentanyl, depends on multiple factors that are critical for survival. For instance, when severe levels of hypoxemia are reached ($PaO_2 < 20$ mm Hg), spontaneous recovery from an acute opioid

intoxication is not possible and naloxone becomes totally ineffective.[5] This observation implies that ventilatory support must be provided before naloxone administration in any victims of opioid overdose who are found apneic. Also, mu-opioid receptor desensitization, produced by a mechanism referred to as the "GRK2/ß-arr2" pathway, could be essential for breathing recovery.[6] This pathway allows for a rapid recovery, within minutes, from the depressive effects of an opioid agonist on neurons. Drugs capable of specifically increasing this activity would represent an interesting approach in patients at high risk of breathing depression.[6] Other medications can also alter this desensitizing pathway. For example, the selective serotonin reuptake inhibitor paroxetine has been shown to depress GRK2/ß-arr2 activity, so it should not be prescribed for patients taking opioids.

Finally, opioid-induced muscle rigidity adds potentially lethal consequences to the depression of the drive to breathe.[7-9] Opioid-induced muscle rigidity produces tonic contractions of the chest and abdominal muscles, typically associated with a glottic closure, which in turn impedes breathing recovery. This effect literally counteracts breathing movements for prolonged periods of time.[8-9] Preclinical studies are underway to assess the antidotal potential of kappa agonists and central alpha-2 agonists.[7]

How should the standard of care be adapted to better treat high-risk patients?

Whenever a life-threatening ventilatory depression is present, the use of large doses of naloxone along with cardiopulmonary resuscitation maneuvers, if needed, remains the standard of care.[10] The risk of withdrawal or of suppressing analgesia does not outweigh the need to restore breathing as soon as possible. However, in patients who are not on the verge of dying, a correction of opioid-induced respiratory depression only (without reversing the other effects of the opioid) is appropriate.[4] This strategy is certainly clinically relevant in a postoperative care setting, when sparing the analgesic effects of the opioid is crucial. Also, addicted patients, who can present violent symptoms of acute withdrawal when receiving a large dose of naloxone, would benefit from a reversal of hypoventilation only, if no immediate life-threatening risk is present. There is no currently accepted treatment for helping someone overcome the potent depressive effects of opioids on breathing, despite many attempts to develop new therapeutic agents (from monoclonal antibodies to ventilatory stimulants) as well as new paradigms using already FDA-approved antidotes.

The recent political, medical and cultural changes aimed at stricter regulations of opioid use and easier access to naloxone have not had the impact in reducing deaths by opioid overdose, as many had expected. Yet, efforts must be pursued to better understand the mechanisms of recovery from opioid-induced breathing depression, to offer a successful prevention strategy and to develop alternative countermeasures to restore breathing.

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Philippe Haouzi, MD

HOW TO OBTAIN A 'TRUE' INTRAVASCULAR PRESSURE DURING RIGHT HEART CATHETERIZATION

A pulmonologist describes how using an esophageal balloon can provide a more precise diagnosis and hemodynamic classification of pulmonary hypertension

Written by Adriano Tonelli, MD

KEY POINTS

Adjusting pulmonary hemodynamics for intrathoracic pressure using an esophageal balloon reduces the diagnosis of pulmonary hypertension and postcapillary pulmonary hypertension.

The measurement of the esophageal pressure is obtained by placing a flexible tube through the nose into the lower esophagus using local anesthetics.

A follow-up study is testing other noninvasive tools that could accurately predict the presence of a higher intrathoracic pressure.

Right heart catheterization is needed for the diagnosis and hemodynamic classification of pulmonary hypertension (PH). Pulmonary hypertension is defined as a mean pulmonary artery pressure of more than 20 mm Hg. There are three major hemodynamic types of PH: precapillary, postcapillary, and combined pre- and postcapillary.

The diagnosis of both postcapillary and combined pre- and postcapillary PH requires an elevated pulmonary artery wedge pressure (PAWP), which is defined as a value of 15 mm Hg or above. Postcapillary and combined pre- and postcapillary PH are commonly seen in conditions that affect the left heart, such as heart failure with preserved or reduced ejection fraction.[1]

The most common cause of PH is left heart disease, which is characterized by elevated mean pulmonary artery and wedge pressures. Nevertheless, both pressures could appear elevated in patients with high intrathoracic pressure, such as those with obesity.[2]

We recently tested whether adjusting pulmonary hemodynamics for intrathoracic pressure using an esophageal balloon allows for more precise diagnosis and hemodynamic classification of PH. In a cohort of obese patients with PH, we demonstrated that the true intravascular pressure (determination adjusted for intrathoracic pressure) reduced the diagnosis of PH by a quarter, and markedly decreased the diagnosis of postcapillary or combined pre- and postcapillary PH in patients with obesity.[3]

In our cohort of patients with obesity (body mass index = 44 ± 10 kg/m^2), the esophageal pressure at end-expiration was 14 ± 4 mm Hg (range: 6-25 mm Hg). Therefore, when we adjusted for this determination, both the end-expiration mean pulmonary artery and wedge pressure were significantly reduced. This significant pressure correction has important implications insofar as it could (1) normalize pulmonary pressures and reduce anxiety about tests and treatments for a PH disorder that patients may not have; (2) remove the diagnosis of postcapillary PH and prevent unnecessary diuretics or other treatments; (3) encourage specific interventions for pulmonary arterial hypertension-specific interventions in combined pre- and postcapillary PH.

Esophageal pressure is measured by placing a flexible tube through the nose into the lower esophagus using local anesthetics (Figure 1). The catheter is appropriately positioned by following certain criteria.[3] The end-expiration esophageal pressure measurements can be obtained by the same hemodynamic system used to record the pulmonary pressures. Both end-expiration mean pulmonary pressure and PAWP are then adjusted by the same absolute value (Figure 2). Because both pulmonary pressures are equally affected by the intrathoracic pressure, adjusting the esophageal pressure does not affect the transpulmonary gradient (TPG: mean pulmonary artery pressure – PAWP) or pulmonary vascular resistance (TPG ÷ cardiac output).

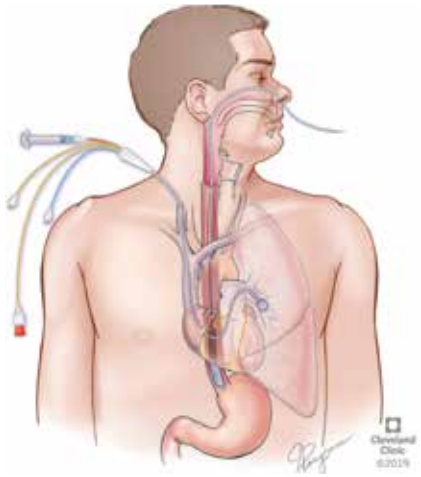

FIGURE 1. Esophageal balloon located in the lower esophagus at the time of right heart catheterization.

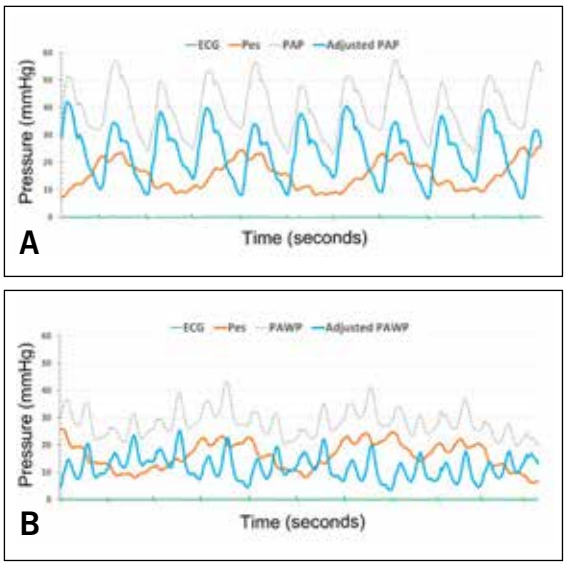

FIGURE 2. Impact of esophageal pressure determination on pulmonary vascular pressures.

Figure panels represent pressure recording of the pulmonary artery (Panel A) and wedge (Panel B) pressures. Panel A shows the pulmonary arterial pressure before (gray tracing) and after (blue tracing) adjusting for the esophageal pressure (Pes, represented in red). Panel B depicts the PAWP before (gray tracing) and after (blue tracing) adjusting for the esophageal pressure (Pes, represented in red).

The measurement of esophageal pressure is important to determine the intrathoracic pressure in those patients for whom there is suspicion that this pressure might be elevated. The degree of obesity does not have a good correlation with the intrathoracic pressure. However, changing positions from supine to sitting reduces intrathoracic pressure and its impact on pulmonary pressure. It does not always reduce the end-expiration intrathoracic pressure to zero, though, and the vascular pressure reduction observed when sitting might be related to a lower preload due to pooling of blood in the lower extremities.

Clinical indicators of increased intrathoracic pressure include the presence of obesity, chronic obstructive lung disease and asthma with air trapping, and chest wall deformities. Hemodynamic indicators of increased intrathoracic pressure include increased right atrial pressure, mean pulmonary artery pressure and PAWP with pronounced respiratory oscillations of pulmonary pressures.

We are testing other noninvasive tools that could predict with a good degree of accuracy the presence of higher intrathoracic pressure. Being able to predict which patients have a probability of having high intrathoracic pressure may help providers plan for esophageal balloon insertion in hemodynamic laboratories in which this intervention is not readily available. Alternatively, measuring esophageal pressure, in supine position and across the respiratory cycle, could also be done by gastroenterology as part of the esophageal manometry commonly performed in patients who have or are likely to have achalasia.

In summary, adjusting pulmonary hemodynamics for esophageal pressure in patients with elevated intrathoracic pressure reduces the number of patients diagnosed with PH and postcapillary PH. Measuring esophageal pressure is relatively simple and should be considered in patients suspected of having high intrathoracic pressure, such as those with obesity and elevated mean pulmonary artery pressure and PAWP.

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Adriano Tonelli, MD

COPD AND SKELETAL MUSCLE MASS: DISCOVERING NEW POSSIBILITIES

Patients with COPD are often affected by sarcopenia, but the underlying mechanisms for the development are poorly understood. New research looks into the causes and potential therapies

Written by Amy Attaway, MD

KEY POINTS

Sarcopenia affects 20%-40% of COPD patients, and it is associated with increased risk for mortality and higher healthcare cost.

Nocturnal hypoxia affects 27%-70% of COPD patients, and research has suggested that nocturnal hypoxia may contribute to sarcopenia in COPD.

Incorporating a three-pronged approach to sarcopenia may help direct future research and therapies.

Chronic obstructive pulmonary disease (COPD) is the fourth most common cause of death in the United States.[1] Sarcopenia, or skeletal muscle loss, affects 20%-40% of COPD patients.[2-4] It is a major comorbidity that impacts survival and physical function in COPD patients.[5-9]

We have previously demonstrated in the Nationwide Inpatient Sample that sarcopenia (defined by billing codes) is associated with increased risk for mortality (adjusted odds ratio [adj OR]: 2.1, 95% confidence intervals [CI]: 1.9-2.2) and higher healthcare costs (approximately 84% greater cost of hospitalization).[10] As illustrated in the figure below, we have also demonstrated in our Cleveland Clinic population of COPD patients referred for lung volume reduction that reductions in the pectoralis muscle cross-sectional area are associated with disease progression in COPD (i.e., mortality, need for lung volume reduction or need for lung transplant).[11] However, despite sarcopenia being a major problem for patients with COPD, the underlying mechanisms that cause sarcopenia remain poorly understood.[12] Because of this, typical strategies to improve sarcopenia, including pulmonary rehabilitation and nutritional therapies, do not consistently improve outcomes for COPD patients.[13]

Why we care about hypoxia

The reason that COPD patients develop skeletal muscle loss is likely multifactorial and includes factors such as poor nutrition, aging, systemic inflammation and medications (i.e., corticosteroids).[14] One of the areas in which we have focused our studies is the impact of hypoxia on skeletal muscle loss. While previous studies focused on the impact of continuous hypoxia on skeletal muscle loss, continuous hypoxia is a condition that is routinely screened for and treated

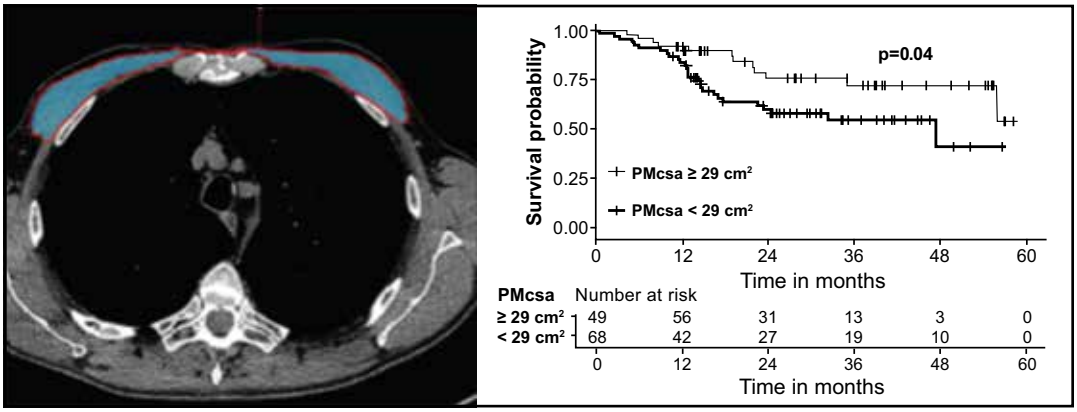

FIGURE. CT scans quantifying pectoralis muscle show increased risk for adverse outcomes in COPD patients with muscle loss. Pectoralis muscle cross-sectional area (PMcsa) was quantified in 117 COPD subjects. Reduction in PMcsa was associated with adverse outcomes (i.e., mortality, need for lung volume reduction, need for lung transplant). (Attaway AH, Welch N, Yadav R, et al. Quantitative Computed Tomography Assessment of Pectoralis and Erector Spinae Muscle Area and Disease Severity in Chronic Obstructive Pulmonary Disease Referred for Lung Volume Reduction. COPD. 2021;18(2):191-200.)

Between 27% and 70% of COPD patients experience **low oxygen saturation** in the blood **during sleep**, and **hypoxia** can occur **throughout sleep**.

in COPD patients per established guidelines.[15] A more clinically relevant form of hypoxia that COPD patients routinely experience is a cycling of hypoxia/normoxia where COPD patients have normal oxygen saturation during the day but develop hypoxia while they are sleeping. Between 27% and 70% of COPD patients experience low oxygen saturation in the blood during sleep,[16-18] and hypoxia can occur throughout sleep.[19]

Observational studies have demonstrated an increased risk for mortality due to nocturnal hypoxia;[20] however, randomized controlled trials have not demonstrated a survival benefit from nocturnal oxygen supplementation.[21-23] Because of this, current guidelines do not recommend screening for or treating nocturnal hypoxia unless patients report symptoms of poor sleep or have evidence of comorbidities such as pulmonary hypertension.[24] However, other studies have suggested that nocturnal hypoxia may contribute to sarcopenia in COPD as demonstrated by: reductions in exercise work rate,[25] six-minute walk test,[26] skeletal muscle contraction of the diaphragm[27] and overall increased systemic inflammation.[28]

A three-pronged approach to sarcopenia and future directions

Our approach to determining whether nocturnal hypoxia contributes to sarcopenia in COPD is three-pronged:

1) Determine whether sarcopenia is associated with nocturnal hypoxia in our Cleveland Clinic population of patients with COPD.
2) Utilize laboratory-based techniques to determine the mechanisms of sarcopenia due to hypoxia/normoxia cycling with in vitro and in vivo models of sarcopenia in COPD.
3) Develop and validate new therapies to improve sarcopenia in COPD using laboratory-based models that will translate to improving outcomes in COPD patients.

While our goal has been to determine the mechanisms of sarcopenia in COPD patients, our research has the potential for broad application because nocturnal hypoxia occurs in other pulmonary disorders associated with sarcopenia including interstitial lung disease and pulmonary hypertension.[29-31]

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Amy Attaway, MD

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DIFFUSE PARENCHYMAL LUNG DISEASE

A Multicenter Trial to Evaluate the Efficacy, Safety and Tolerability of HZN-825 in Subjects with Idiopathic Pulmonary Fibrosis
Principal Investigator: Leslie Tolle, MD
Study Coordinator: Sue Gole, RRT | 216.401.5257

A Randomized, Double-Blind, Placebo-Controlled, Phase III Study of the Efficacy and Safety of Inhaled Treprostinil in Subjects with Idiopathic Pulmonary Fibrosis (TETON)

Principal Investigator: Joseph Parambil, MD
Principal Investigator: Ron Wehrmann, RRT | 216.445.0574

Chronic Fibrosing Interstitial Lung Disease with Progressive Phenotype Prospective Outcomes (ILD-PRO) Registry
Principal Investigator: Daniel Culver, DO
Study Coordinator: Sue Gole, RRT | 216.401.5257

SARCOIDOSIS

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intravenous Efzofitimod in Patients with Pulmonary Sarcoidosis

Principal Investigator: Daniel Culver, DO
Study Coordinator: Shweta Josh | 216.445.7291

A Study to Assess the Efficacy and Safety of Namilumab in Participants with Chronic Pulmonary Sarcoidosis (RESOLVE-Lung)
Principal Investigator: Manuel Lessa Ribeiro Neto, MD
Study Coordinator: Shweta Josh | 216.445.7291

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INFECTIOUS DISEASE

Prospective Observational Study of Human Immunodeficiency Virus (HIV) Positive Deceased Donor Renal Transplantation for HIV-Positive Recipients
Principal Investigator: Christine Koval, MD
Study Coordinator: Julie Sikora | 216.538.9571

Breath Analysis to Detect Lung Disease (COVID Breath Study)
Principal Investigator: Nabin Shrestha, MD
Study Coordinator: Meg Mitchell | 216.905.3491

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INTERVENTIONAL PULMONOLOGY

A Sham Controlled Prospective Randomized Clinical Trial of the RejuvenAir® System for the Treatment of Moderate to Severe Chronic Obstructive Pulmonary Disease with Chronic Bronchitis (SPRAY-CB)
Principal Investigator: Thomas Gildea, MD
Study Coordinator: Yvonne Meli, RN, BC, CCRP | 216.445.4215

Transbronchial Biopsy Assisted by Robot Guidance in the Evaluation of Tumors of the Lung (TARGET)
Principal Investigator: Michael Machuzak, MD
Study Coordinator: Yvonne Meli, RN, BC, CCRP | 216.445.4215

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LUNG CANCER

DECAMP 1 PLUS Proposal: Prediction of Lung Cancer Using Noninvasive Biomarkers
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Susan Charme | 216.318.5687

DNA Evaluation of Fragments for Early Interception - Lung Cancer Training Study (DELFI-L101 Study)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Cara Pannell | 216.308.6864

Nodify XL2 Classifier Clinical Utility Study in Low to Moderate Risk Lung Nodules (ALTITUDE)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Brinda Patel | 216.390.5108

Determination and Validation of Lung EpiCheck®: A Multianalyte Assay for Lung Cancer Prediction
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Susan Charme | 216.318.5687

CFMEDIP-SEQ Assay Multicenter Prospective Observational Validation for Early Cancer Detection, Minimal Residual Disease, and Relapse (CAMPERR)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Samantha Goode | 216.440.7733

Detecting cancers Earlier Through Elective plasma-based CancerSEEK Testing – Ascertaining Serial Cancer patients to Enable New Diagnostic II (DETECT-ASCEND 2)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Samantha Goode | 216.440.7733

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LUNG TRANSPLANT

Improving Frailty with a Rigorous Ambulation Intervention in Lung Transplant Patients (iFRAIL)
Principal Investigator: Marie Budev, DO, MPH
Study Coordinator: Rijuta Singh | 216.894.3826

A Phase III, Prospective, Multicenter, Randomized, Controlled Clinical Trial to Demonstrate the Effectiveness and Safety of Liposomal Cyclosporine A (L-CsA) Inhalation Solution Delivered via the PARI Investigational eFlow® Device plus Standard of Care versus Standard of Care Alone in the Treatment of Bronchiolitis Obliterans Syndrome in Patients post Lung Transplantation (BOSTON-1 and BOSTON-2)
Principal Investigator: Marie Budev, DO, MPH
Study Coordinator: JoAnne Baran-Smiley, BSN, RN | 216.469.2855

Cleveland Clinic Lung Transplant Biorepository
Principal Investigator: Maryam Valapour, MD
Study Coordinator: Erin McNamee | 216.210.8616

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PULMONARY HYPERTENSION

A Study to Evaluate Efficacy and Safety of Macitentan 75 mg in Inoperable or Persistent/Recurrent Chronic Thromboembolic Pulmonary Hypertension (MACiTEPH)
Principal Investigator: Gustavo Heresi, MD
Study Coordinator: Natalie Taylor | 216.903.4705

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy in Newly Diagnosed Intermediate- and High-risk PAH Patients (HYPERION)
Principal Investigator: Kristin Highland, MD
Study Coordinator: Natalie Taylor | 216.903.4705

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RARE LUNG DISEASES

ALPHA-1 ANTITRYPSIN DEFICIENCY

Alvelestat (MPH996) for the Treatment of ALpha-1 ANTitrypsin Deficiency (ATALANTa)
Principal Investigators: Umur Hatipoglu, MD; James Stoller, MD
Study Coordinator: Erica Corrao, RRT | 216.444.0843

A Multi-center, Single-Dose and Repeat-Dose Over Eight Weeks, Sequential Cohort Study to Evaluate Safety and Tolerability as well as Pharmacokinetics of Two Different Doses of Alpha1-Proteinase Inhibitor Subcutaneous (Human) 15% Administered Subcutaneously in Subjects with Alpha1-Antitrypsin Deficiency
Principal Investigator: Vickram Tejwani, MD
Study Coordinator: Erica Corrao, RRT | 216.347.4515

BRONCHIECTASIS

ENCORE - A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of an Amikacin Liposome Inhalation Suspension (ALIS)-Based Regimen in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by *Mycobacterium avium* Complex (MAC)
Principal Investigator: Lucileia Johnson, MD
Study Coordinator: Sheffa Almahd, RRT | 216.287.0906

ASPEN - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety, and Tolerability of INS1007 Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis
Principal Investigator: Lauryn Benninger, DO
Study Coordinator: Sheffa Almahd, RRT | 216.287.0906

LYMPHANGIOLEIOMYOMATOSIS

Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS) Clinical Study
Principal Investigator: Joseph Parambil, MD
Study Coordinator: JoAnne Baran-Smiley, BSN, RN | 216.469.2855

PULMONARY ALVEOLAR PROTEINOSIS

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Once-Daily Inhaled Molgramostim Nebulizer Solution in Adult Subjects with Autoimmune Pulmonary Alveolar Proteinosis aPAP (IMPALA 2)
Principal Investigator: Leslie Tolle, MD
Study Coordinator: Sue Gole, RRT | 216.445.5836

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Cleveland Clinic is a nonprofit, multispecialty academic medical center integrating outpatient and hospital care with research and education for better patient outcomes and experience. More than 4,500 staff physicians and researchers provide services through 20 patient-centered institutes. Cleveland Clinic is a 6,026-bed healthcare system with a main campus in Cleveland, 18 hospitals and over 220 outpatient locations. The health system includes five hospitals in Southeast Florida with more than 1,000 beds, a medical center for brain health in Las Vegas, a sports and executive health center in Toronto, a 364-bed hospital in Abu Dhabi, and a 184-bed hospital in London. Cleveland Clinic is currently ranked as one of the nation's top hospitals by *U.S. News & World Report*.

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Cleveland Clinic

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› Eduardo Mireles-Cabodevila, MD
› Robert L. Chatburn, MHHS, RRT-NPS, FAARC

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