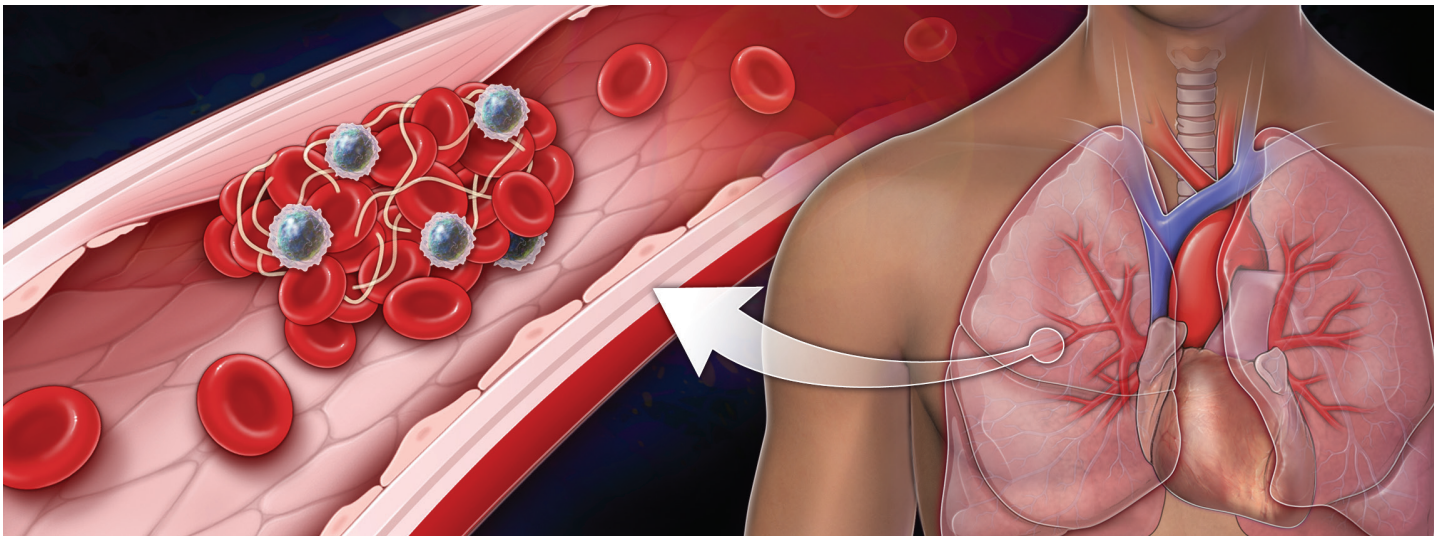
TEMPLE HEALTH

Temple Lung Center | *Updates in research & practice*

PERT Transforms Pulmonary Embolism Care and Practice

By Parth Rali, MD, Director, Pulmonary Embolism Response Team, Temple University Hospital



Pulmonary embolism (PE) is the third most common cardiovascular cause of inpatient hospital death in the United States, and the prevalence of PE risk factors—including surgery, obesity, a sedentary or immobile lifestyle, and advanced age—is increasing. Immobile lifestyle is a big concern in the COVID-19 era, where home isolation and social distancing are highly recommended.

Many PE fatalities can be prevented if the condition is quickly and appropriately treated, yet decision-making has become more complex due to new options and controversy about appropriate care for different patient groups. Establishing pulmonary embolism response teams (PERT) within hospitals and health systems can help improve decision-making through rapid convening of specialists in all necessary areas, and can help ensure access to the most up-to-date treatment options by focusing institutional resources. Pulmonary embolism has been seen in up to 50% of ICU admissions based on emerging data from the COVID-19 patient population.

Treatment is often decided based on patient stratification, yet risk assessment itself is difficult. Not only can a patient's condition progress quickly, but there are multiple, differing sets of standards and guidelines developed by organizations such as the American Heart Association and the European Society of Cardiology. This makes it even more important to have a platform for quick, consensus-based decision-making at the health system level. Recently, the American College of Chest Physicians has released COVID-19 venous thromboembolism (VTE) guidelines that provide some insight into VTE management in the COVID era.

Treatment options also evolve quickly. For example, patients with massive, or high-risk, PE need aggressive treatment, yet thrombolytic drugs may limit treatment options by increasing the risk of major bleeding. A major recent advance in this area is the use of interventional approaches, which allow for more concentrated application of thrombolytics (and often a smaller overall dose). Many types of infusion catheters are now available and more are under investigation. For example, the Bashir Endovascular Catheter (BEC), co-created by Temple's Riyaz Bashir, MD, FACC, RVT, for which Temple recently participated in an early feasibility study, and for which a large-scale trial (RESCUE) is expected to start later this year. Percutaneous mechanical embolectomy, an option for patients at high risk of bleeding, is also now available through Temple's interventional radiology team.

Temple PERT was formed in 2017, and has been activated more than 500 times as of March 2020. A designated pulmonary care

{continued on page 5}

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Temple Lung Center
Updates in research & practice

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Humidified Nasal High-Flow Therapy May Be an Effective At-Home Treatment for COPD

By Helga Criner, RN, Clinical Research Nurse, Temple University

A pilot study at Temple suggests that daily use of humidified nasal high-flow (NHF) therapy with an air-oxygen blend as a maintenance therapy could benefit patients discharged from hospital after an acute exacerbation of COPD.

NHF delivers humidified nasal gases to patients who are breathing on their own. For patients with COPD, hypoxemia, and/or hypercapnia, NHF may make breathing easier, reduce shortness of breath, and help keep airways moist. It may also improve gas balance by reducing CO_2 levels. Maintenance use of NHF could be an important way to ameliorate COPD symptoms and help slow disease progression. Yet, once the patient is discharged from the hospital, we have little data about whether it is easy and effective to continue this therapy at home.

Temple's pilot study examined the feasibility of a larger-scale trial of NHF as at-home therapy for patients with chronic gas exchange issues. The study (called "Sleep and Daytime Use of Humidified Nasal High-Flow Oxygen in COPD Outpatients," NCT03221387) followed 28 people who had been hospitalized within the previous 6 months for acute COPD exacerbation. Patients used the AIRVO™ 2 system nightly, after being trained on how to operate and maintain it. The system is designed to be portable and user-friendly.

Out of 26 patients who reported back on day 70 of the study, 23 reported improvement in dyspnea (8 reported marked improvement), while 3 patients had no change. No patient reported worsening dyspnea using NHF. Over time, daily use of NHF appeared to reduce sputum quantity and viscosity, cough, and wheeze among 10 patients who used an electronic daily diary to measure symptoms. In addition, 5 (out of an initial 9 selected) of the trial participants completed a series of three sleep studies; they showed no significant change in sleep measures, including breathing/apnea, nocturnal oxygenation, and sleep quality, although other studies[1] have suggested that high-flow nasal therapy reduces peripheral vascular sympathetic activity during REM sleep.

The AIRVO™ 2 system for nasal high-flow therapy

No patient reported issues with setting up or maintaining the AIRVO™ 2 equipment. Importantly for a daily therapy used while sleeping, no patients reported nasal pain, and average patient-reported discomfort was minimal and did not escalate with continued use. All but one of the 29 patients who completed the trial chose to keep the AIRVO™ 2 device and continued using the equipment after the trial was over.

The results from the pilot suggest that NHF is feasible for daily use at home for 6 to 8 hours at a time and paves the way for larger-scale studies focused on outcomes. ■

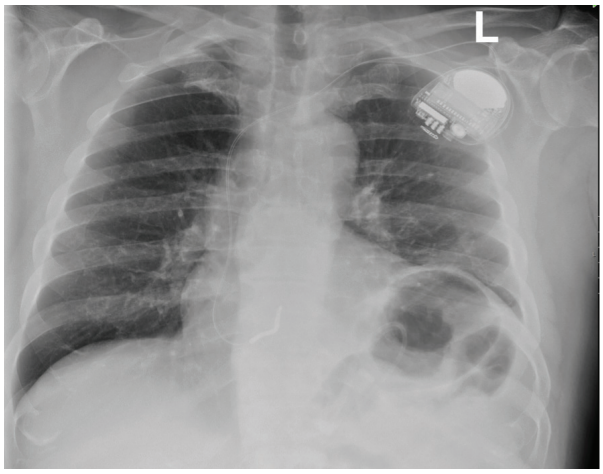
[1] Fricke, K., et al. 2018. "Nasal high flow, but not supplemental O_2, reduces peripheral vascular sympathetic activity during sleep in COPD patients." *Int J Chron Obstruct Pulmon Dis.* 13:3635-3643. doi: 10.2147/COPD.S166093

1,000 Lung Transplants at Temple

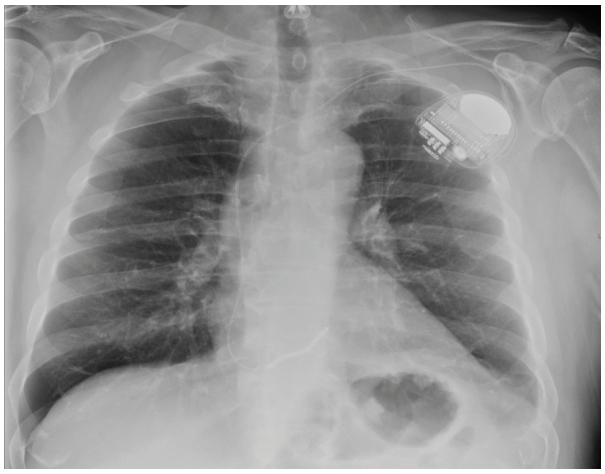
This year, the Temple Lung Center marked its 1,000th lung transplant since the beginning of the program in 1994. Temple remains the highest annual volume lung transplant center in the nation.

Case Study in Thoracic Medicine and Surgery

Dyspnea: When to blame (and repair) an elevated hemidiaphragm



Pre-operative CXR showing an elevated left hemidiaphragm.



Post-operative CXR showing resolution of previously noted left hemidiaphragm elevation.

A 60-year-old man with multiple co-morbidities presented for evaluation of dyspnea. Symptoms were slow and progressive, and he now struggled to swim or tie his shoelaces. A left- and right-heart catheterization was performed prior to presentation due to his history of nonischemic cardiomyopathy and were without coronary disease or pulmonary hypertension; his blood pressure and volume status were well controlled. Pulmonary function tests showed no obstruction and symptoms did not respond to bronchodilators. A CT of the thorax did not reveal parenchymal lung disease or pulmonary embolism but did note atelectasis at the left lung base.

Patient had a long history of cervical spine disease and was now post C5-C6 discectomy and fusion. A CXR showed only an elevated left hemidiaphragm but a SNIFF test was nondiagnostic.

Diagnostic Findings

Pulmonary Function Testing:

- Positional Spirometry: 25% reduction in FVC (seated to the supine)
  - Decrement of 15–25% is suggestive of unilateral diaphragm dysfunction
- Maximal Expiratory Pressure / Maximal Inspiratory Pressure Ratio: 2.5
  - 1.5–3.0 is suggestive of unilateral diaphragm paralysis

Cardiopulmonary Exercise Testing:

- Respiratory limitation with increased respiratory rate and decreased inspiratory capacity suggestive of respiratory muscle dysfunction

Diaphragm Ultrasound:

- Normal excursion and fractional thickening (33%) on right
- Paradoxical motion without fractional thickening on left

Findings were consistent with unilateral diaphragm paralysis.

Treatment & Outcomes

The patient underwent robotic transabdominal plication of the left hemidiaphragm. Following surgery, he had resolution of his positional dyspnea, and near complete resolution of his exertional dyspnea.

Discussion

Respiratory muscle dysfunction, especially diaphragm dysfunction, is a well-documented source of dyspnea. Because of its nonspecific presentation, as well as difficulty in obtaining adequate testing, assessment of respiratory and diaphragm muscle function is often neglected or incomplete.

Chest radiograph is a commonly ordered test in the evaluation of dyspnea. The high sensitivity (90%) makes it a reasonable screening tool for diaphragm dysfunction. However, its lack of specificity and low positive predictive value (PPV 33%) precludes the diagnosis of diaphragm dysfunction and does not provide quantitative assessment of function and relative contribution to dyspnea. Etiologies of "false" diaphragm paralysis must be assessed and ruled out through physical exam, and spirometric and radiographic testing. In some cases, measurement of transdiaphragmatic pressures becomes necessary to confirm the diagnosis.

Diaphragm plication is a well-established procedure for unilateral diaphragm dysfunction and or paralysis. During plication, the diaphragm is immobilized, preventing paradoxical motion and thus improving ventilation. Plication has resulted in improvements in both dyspnea and quality of life scores as well as providing an objective improvement in lung function, results which have proven durable in subsequent long-term follow-up.

Matthew Gordon, MD
Assistant Professor, Thoracic Medicine and Surgery
Lewis Katz School of Medicine at Temple University

New treatment pathways for persistent pulmonary hypertension of the newborn: Temple-Bayer collaboration to advance new therapies

By Marla R. Wolfson, MS, PhD, Professor, Center for Inflammation, Translational and Clinical Lung Research, Temple University

Persistent pulmonary hypertension of the newborn (PPHN, also known as neonatal pulmonary hypertension and persistent fetal circulation syndrome), affects 2% of live births and is a major cause of neonatal mortality. PPHN is a failure to properly transition from placental respiration to breathing with the lungs; the pulmonary vasculature remains resistant to blood flow, leading to right-to-left shunting of blood across the ductus arteriosus or foramen ovale and causing often-severe hypoxemia.

The nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway ordinarily contributes to vasodilation in pulmonary vascular smooth muscle cells at birth, and impaired NO-cGMP signaling contributes to the pathogenesis of PPHN. Inhaled nitric oxide (iNO) is a potent, FDA-approved pulmonary vasodilator in many infants with PPHN, yet up to 40% of patients do not respond to iNO therapy and require ECMO due to refractory pulmonary hypertension.

Temple researchers are among those investigating the mechanisms underlying poor response to iNO therapy. Since NO-mediated vasodilation requires stimulation of soluble guanylate cyclase (sGC) to generate cGMP, we believe that impaired sGC activity may contribute to poor NO responsiveness in the perinatal lung.[1]

Therefore, the discovery of sGC agonists (sGC stimulators and sGC activators) created by Bayer Pharma are a milestone in NO/cGMP pharmacology.[2,3] These compounds are capable of directly stimulating sGC in a NO-independent fashion and are efficacious in preclinical models of pulmonary hypertension.[4] The first in class sGC stimulator riociguat was approved for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.[5,6]

These agents may also offer novel therapeutic approaches to diseases like PPHN. At Temple, we are now investigating in collaboration with Bayer (supported by a restricted research grant of Bayer AG) if sGC agonists could target the pulmonary circulation and pulmonary airway smooth muscle. This preclinical research may help to understand if sGC targeting holds promise for helping newborns at risk from PPHN and could also be the basis for future clinical testing with this novel mechanism. ■

[1]Chester, M., et al. 2011. Cinaciguat, a soluble guanylate cyclase activator, augments cGMP after oxidative stress and causes pulmonary vasodilation in neonatal pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol.* 301(5): L755–L764

[2]Stasch, J.P., et al. 2011. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. *Circulation* 123(20): 2263–2273

[3]Sandner, P., et al. 2019. Correction to: Soluble Guanylate Cyclase Stimulators and Activators [published online ahead of print, 2019 Jul 5]. *Handb Exp Pharmacol.* doi: 10.1007/164_2019_249

[4]Sandner, P., et al. 2018. Discovery and development of sGC stimulators for the treatment of pulmonary hypertension and rare diseases. *Nitric Oxide* 77: 88–95

[5]Stasch, J.P. and Evgenov, O.V. 2013. Soluble guanylate cyclase stimulators in pulmonary hypertension. *Handb Exp Pharmacol.* 218: 279–313

[6]Ghofrani, H.A., et al. 2017. Riociguat: Mode of Action and Clinical Development in Pulmonary Hypertension. *Chest* 151(2): 468–480

{continued from cover}

PERT Transforms Pulmonary Embolism Care and Practice

fellow responds to all incidences of PE, conducts an exam, and acquires necessary patient information, then convenes the on-call PERT. Depending on the severity of the case, a multidisciplinary team of physicians may assemble in person or via conference call, including pulmonary care physicians, interventional radiologists, and cardiologists. Temple's PERT provides access to the full range of FDA-approved thrombolytic drugs and interventional tools (including percutaneous mechanical embolectomy); active clinical research programs around PE; and—perhaps most importantly—experts system-wide who understand all of the options and can make informed decisions about how to move forward. Follow-up care is also prioritized, within two weeks of discharge depending on the severity of the patient's condition; we have seen more than 150 such patients in the past year at the Temple Lung Center.

Temple Health is a founding member of the National Pulmonary Embolism Response Team Consortium, which advances the science and practice of PE care, including through the development of care guidelines and standards. Our local PERT team members, residents, and fellows are actively participating in various committees, presentations, and academic activities through the PERT Consortium™.

If you're in the Philadelphia region and need a quick and coordinated response on a pulmonary embolism case, call 215-707-TRAN and ask for the Temple Pulmonary Embolism Response Team. To learn about participating in our clinical research and trials regarding PE therapies, contact 215-707-1359. For the latest guidelines on PE care and forming a PERT, explore the PERT Consortium™ at **pertconsortium.org**. ■

Editor's Note: Dr. Bashir is a co-founder and has equity interest in Thrombolex, Inc., a medical device company developing interventional catheter-based therapies for the rapid and effective treatment of acute venous thromboembolic disorders. Temple University also holds a financial interest in Thrombolex, Inc., pursuant to the license granted to Thrombolex for the University's interest in the patent filed for the experimental catheter device developed by Dr. Bashir and Nicholas Green.

Role of Chest Imaging in Bronchoscopic Lung Volume Reduction Using Endobronchial Valves

By Chandra Dass, MBBS, DMRD, Director, Cardiothoracic Imaging, Temple University Hospital

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide. The National Emphysema Treatment Trial (NETT) demonstrated that lung volume reduction surgery can improve pulmonary function, exercise capacity, and quality of life in selected subgroups of COPD patients, yet not all patients are good candidates for surgery. Clinical trials of bronchoscopic lung volume reduction (BLVR) procedures have sought to establish an effective and safe alternative approach for those patients. Of these, endobronchial deployment of one-way valves (EBV) currently has the largest pool of supporting scientific data available.[1,2,3]

An expert panel, including Temple's Dr. Gerard Criner, updated the recommendations for patient selection and best practices for endoscopic lung-volume reduction with EBV in 2019. Based on the results of multiple randomized clinical trials (RCTs),[3] the panel found that certain image-based COPD patient phenotypes show better outcomes from EBV therapy. High-resolution CT imaging plays a major role in patient selection, target lobe identification, and the management of post-procedural adverse events.

With the recent FDA approval of the Pulmonx Zephyr® and Olympus Spiration® Valve systems, bronchoscopic lung volume reduction using one-way EBVs is increasingly used in patients with advanced emphysema who remain symptomatic despite optimal medical management and are poor surgical candidates. To avoid misinterpretation of imaging studies, it is important for pulmonologists to understand the types of EBV used, and the expected normal imaging findings following placement of EBV. See Figures 1 and 2 for examples.

Given the higher incidence of pneumothorax after EBV placement, chest radiographs are required within 4 and 24 hours of EBV valve placement and daily thereafter until discharge. Significant volume reduction or atelectasis of the treated lobe may be observed within the first few days, although in some patients it may take up to a month. Criteria for premature reevaluation of these patients have been established and imaging plays an important role in their evaluation and management. Expert panels recommend a low-dose CT scan at around 30–45 days post-procedure to assess valve placement, particularly if there is breathing deterioration or no perceived

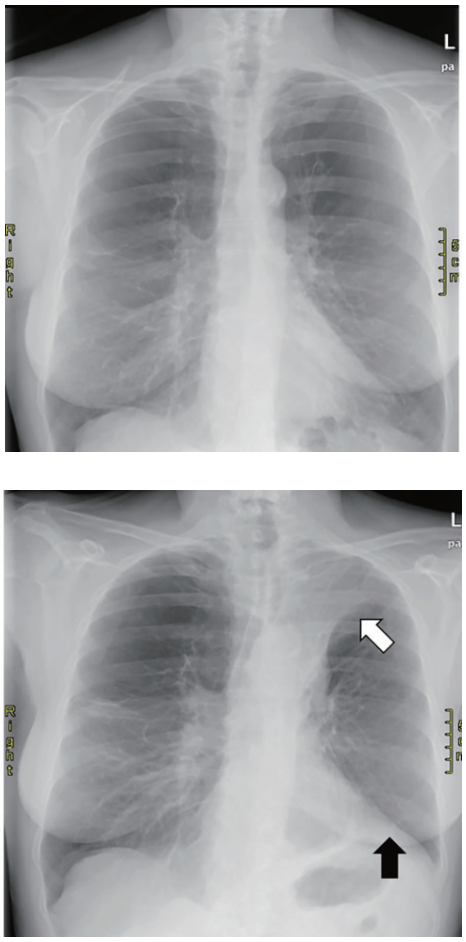


Figure 1. Frontal chest radiographs. a) Pre-procedural radiograph with severe emphysematous upper lobes. b) Complete collapse of the left upper lobe (white arrow) at two weeks after EBV placement. Elevated left dome of diaphragm secondary to volume loss (black arrow).

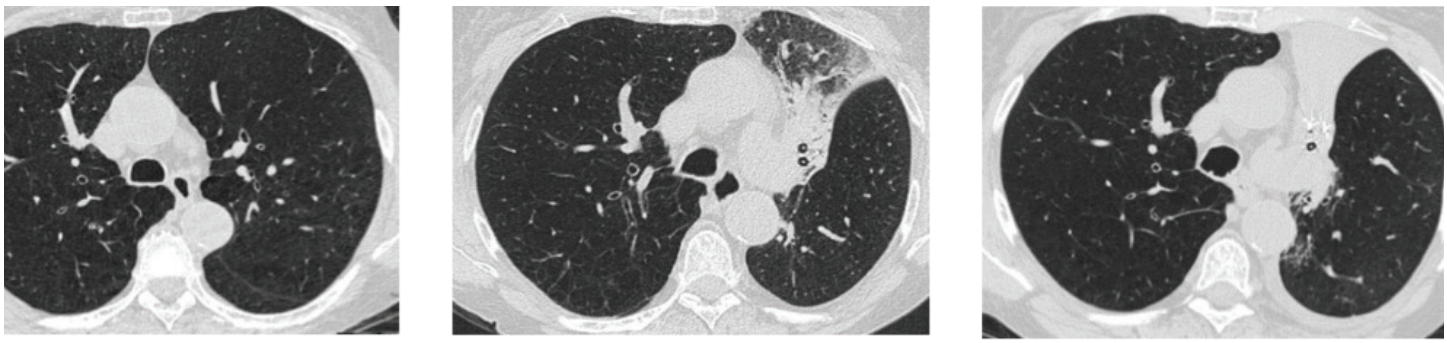


Figure 2. Axial HRCT images at the level of upper lobes. a) Pre-procedural CT showing severe emphysema in both upper lobes. b) Partial collapse of the left upper lobe at 24 hours after EBV placement. c) Complete collapse of the left upper lobe at 30 days with EBVs in situ. Mediastinal shift towards left due to volume loss.

improvement.[4] Evaluation of MDCT scans focuses on the valve count, valve location (migration/malpositioning), and target lobe(s) volume change (ΔTLV).

In conclusion, CT and chest radiography are valuable tools for planning and follow-up evaluation of bronchoscopic lung volume reduction treatment for COPD patients. The outcome of EBV therapy is maximized in certain image-based COPD phenotypes. HRCT imaging plays a major role in patient selection, target lobe identification, and in the management of post-procedural adverse events. ■

[1] Criner, G.J., et al. 2018. A Multicenter Randomized Controlled Trial of Zephyr® Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). *Am J Respir Crit Care Med.* 198(9): 1151–1164. doi: 10.1164/rccm.201803-0590OC.

[2] Criner, G.J., et al. 2019. Improving Lung Function in Severe Heterogenous Emphysema with the Spiration® Valve System (EMPROVE). A Multicenter, Open-Label, Randomized, Controlled Trial. *Am J Respir Crit Care Med.* 200 (11): 1354–1362. doi: 10.1164/rccm.201902-0383OC.

[3] Low, S.W., et al. Endobronchial Valves Therapy for Advanced Emphysema: A meta-analysis of randomized trials. *J Bronchology Interv Pulmonol.* 26: 81–9. doi: 10.1097/LBR.0000000000000527.

[4] Herth, F.J.F., et al. 2017. Endoscopic Lung Volume Reduction: An Expert Panel Recommendation - Update 2017. *Respiration* 94(4): 380–388. doi: 10.1159/000479379.

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NCT04372186

Investigating Otilimab in Patients With Severe Pulmonary COVID-19 Related Disease (OSCAR)
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Study of Efficacy and Safety of MAS825 in Patients With COVID-19 (MAS-COVID)
NCT04382651

A Study to Evaluate the Safety and Efficacy of MSTT1041A (Astegolimab) or UTTR1147A in Patients With Severe COVID-19 Pneumonia (COVASTIL)
NCT04386616

A Study of Baricitinib (LY3009104) in Participants With COVID-19 (COV-BARRIER)
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A Study to Assess Pulsed Inhaled Nitric Oxide vs Placebo in Subjects With Mild or Moderate COVID-19 (COViNOX)
NCT04421508

Safety and Anti-coronavirus Response of Suppression of Host Nucleotide Synthesis in Patients With COVID-19 (CRISIS)
NCT04425252

Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult Patients With COVID-19
NCT04425629

Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients With COVID-19
NCT04426695

A Study of LY3819253 (LY-CoV555) in Participants With Mild to Moderate COVID-19 Illness (BLAZE-1)
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