Raising the BAR in Lung Transplant

By Gösta B. Pettersson MD, PhD, Director Lung Transplant and Heart Lung Transplant Program; Atul C. Mehta, MBBS; and the Cleveland Clinic Lung Transplant Team

With 72 lung transplants performed in 2007, the second highest volume in the United States, Cleveland Clinic continues to remain one of the premier lung transplant centers in the country. The transplant program continues to be a leader in developing and offering innovative approaches in the field of transplantation that may impact short- and long-term outcomes.

Currently, lung transplantation continues to demonstrate mortality of close to 50 percent at five years. Significant early complications following single- and double-lung transplantation include airway healing issues (necrosis, dehiscence and subsequent stenosis), which may lead to lung infections and rejections, and contribute to development of bronchiolitis obliterative syndrome/obliterative bronchiolitis (BOS/OB). All these complication could possibly directly or indirectly relate to ischemia, particularly of the airways and the airway anastomosis.

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Dear Colleagues:

Patients with complex respiratory disorders benefit from the expertise of a multidisciplinary team of specialists. At Cleveland Clinic, experts in the Respiratory Institute (Pulmonary, Allergy and Critical Care Medicine) collaborate with specialists in Thoracic and Cardiovascular Surgery, Thoracic Imaging and Pulmonary Pathology to care for these patients.

In this issue of Respiratory Exchange, you will find articles that illustrate the continued growth of our clinical programs, research funding and application of innovative technologies, particularly in the areas of breath analysis, pulmonary hypertension, asthma, bronchoscopy and lung transplantation.

For additional information about our ongoing clinical and research activities in respiratory disorders, please visit clevelandclinic.org/pulmonary (current and previous issues of Respiratory Exchange are available here) and clevelandclinic.org/thoracic.

We hope you’re able to spend a few minutes reviewing Respiratory Exchange, and that you find it valuable and informative. Please feel free to contact us at our toll-free number for physicians, 866.CCF.LUNG (866.223.5864), if you have any questions or would like to refer a patient. As always, we welcome the opportunity to work with you.

Sincerely,

Herbert P. Wiedemann, MD, MBA
Chairman, Cleveland Clinic
Respiratory Institute

Raising the BAR in Lung Transplant

Currently, the standard surgical approach in lung transplantation involves restoration of only pulmonary artery blood flow to the lungs, but the bronchial artery blood supply is ignored. Bronchial artery revascularization (BAR) is a surgical technique intended to restore bronchial arterial circulation to transplanted lungs. Cleveland Clinic’s Transplant Surgical Team currently is conducting a prospective pilot study offering BAR at the time of transplantation with the reasoning that by restoring bronchial blood supply both short- and long-term outcomes in lung transplant patients may be improved.

Historically, consideration of BAR has been weighed against its technical difficulty, its complications and potential consequences of a failed procedure, combined with the fact that the described complications were not that frequent and BAR might offer minimal or no benefit and therefore unnecessary. Gösta B. Pettersson, MD, PhD, Director, Lung and Heart Lung Transplant program, Cleveland Clinic, has the world’s largest experience with BAR, performing this procedure in more than 100 patients while in Copenhagen.

Recently the Copenhagen lung transplant group published long-term follow up data:

1. The overall survival for this Copenhagen patient series was better than for any other large single center lung transplant series
2. The survival was better for the first five-year period, including all the BAR patients than for the second.
3. Survival was better after en bloc double lungs (all performed with BAR) than after sequential double lungs. The five-year survival after en bloc double-lung transplantation with BAR was an impressive 75 percent and this was better than after sequential double-lung transplantation, despite earlier date of surgery, a higher percentage of COPD and alpha-1-deficiency patients, and older age (mean 47 years vs. 34 years). Although there were patients who had single-lung transplantation or combined heart and lung transplantation with BAR, the number in these groups were small. The Copenhagen clinical experience, with 106 BAR procedures, is unique and larger than the published BAR experience of the rest of the world combined.

Currently, we have enrolled more than 50 patients in the BAR pilot study with 10 procedures performed (five en bloc double-lung transplants and five single-lung transplants) since December 2007. Eight of the nine patients had primary normal airway healing and selective angiography demonstrating revascularization success, the tenth patient not yet examined. One patient had evidence of airway ischemia and necrosis and failed revascularization on angiography, but the anastomosis still eventually healed without stenosis within 10 weeks of surgery.

Thus far, the early experience with BAR at Cleveland Clinic is promising and comparable to the Copenhagen experience with a high success rate associated with normal healing of the airway. Our long term hope is, of course, to duplicate the long-term outcomes of the Copenhagen experience in terms of BOS and better survival. At this time, this is the only study of its kind being offered in the world and has the potential to change the standard approach to lung transplantation.

Recommended Reading


High Altitude Survival

How the biology of Tibetans may help find new treatments for hypoxia-related diseases

By Cynthia Beall, PhD, and Serpil Erzurum, MD

For 20,000 years, people have been thriving in their rugged and unforgiving mountainous terrain, the Tibetan Plateau, nearly three miles above sea level where oxygen levels are low. Despite their oxygen-starved environment, Tibetans are healthy and do not develop altitude-related sickness. Researchers at Cleveland Clinic and Case Western Reserve University have uncovered the unique biology that protects Tibetans from high-altitude sickness, which may lead to new clinical treatments for hypoxia-related diseases.

The low barometric pressure at high altitude causes lower arterial oxygen content among Tibetan highlanders, who somehow maintain normal levels of oxygen use as indicated by basal and maximal oxygen consumption levels that are consistent with sea level predictions.

In our study, we investigated how Tibetans offset physiological hypoxia and achieve normal oxygen delivery. We discovered that Tibetans have higher blood flow in their systemic circulation, which is achieved by higher levels of production of nitric oxide (NO), the main endothelial factor regulating blood flow and vascular resistance.

The natural experimental study design compared Tibetans at 4200m and U.S. residents at 206m. Forearm blood flow, an indicator of systemic blood flow, was measured noninvasively using plethysmography at rest, after breathing supplemental oxygen, and after exercise. The Tibetans had more than double the forearm blood flow of low-altitude residents, resulting in even greater than sea level oxygen delivery to tissues. Strikingly, Tibetans had more than 10-fold higher circulating concentrations of NO.

The findings, which are reported in the article, “Higher Blood Flow and Circulating NO Products Offset High Altitude Hypoxia among Tibetans,” published in the November 6, 2007, Proceedings of the National Academy of Sciences, describe this newly discov-
Searching for Answers in IPF
By Jeffrey T. Chapman, MD

Given the complexity of the immunopathologic process in idiopathic pulmonary fibrosis (IPF), a multi-pronged attack with several medications and novel therapeutic approaches may be required. Currently being tested is an empirical clinical strategy to treat IPF with a combination of agents having low toxicity and cost that might retard progression of this illness.

We have recently joined the National Institutes of Health-funded IPF Clinical Research Network ("IPF-Net"), a group of 11 sites throughout the U.S. formed to evaluate multi-drug therapeutic trials for stabilizing the disease. As a new member of the IFP-Net, we will soon begin enrollment in these trials for patients with newly diagnosed IPF.

One of these upcoming trials is the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF trial), for late-stage disease. This trial has been designed for patients with moderate to severe lung disease. In the 24-week study, eligible patients will receive either sildenafil or placebo for the first 12 weeks, followed by sildenafil for the next 12 weeks. The study expects to enroll about 200 patients beginning later this year.

We also will be enrolling patients for the Evaluating the Effectiveness of Prednisone, Azathioprine, and N-Acetylcysteine in People With Idiopathic Pulmonary Fibrosis (PANTHER study). This study will evaluate the effectiveness of the antioxidant N-acetylcysteine (NAC), alone and in combination with an established IPF medication regimen, at preventing the loss of lung function in people with early-stage IPF.

These trials will be a valuable option for our patients with IPF in our growing interstitial lung disease program.

Dr. Jeffrey Chapman is a Cleveland Clinic pulmonologist and the local PI for the IPF Clinical Research Network. He can be reached at 216.444.4222 or chapmaj@ccf.org.

Cleveland Clinic has recently been accepted into the NHLBI-sponsored Idiopathic Pulmonary Fibrosis Research Network. Dr. Chapman is the site Principal Investigator.

The IPF Network conducts clinical trials, and related pathophysiology studies, related to IPF. The IPF Network is similar to other NHLBI networks that we are participating in, including networks for ARDS, severe asthma, and COPD (long-term oxygen therapy).
Nitric oxide (NO) is endogenously synthesized by nitric oxide synthases (NOSs) that are widely expressed in various tissues including the lungs. Once produced, NO is freely diffusible and enters target cells activating soluble guanylate cyclase to produce guanosine 3’, 5’-cyclic monophosphate (cGMP) that mediates the majority of NO effects. The functions and effects of NO in the lung/airways reflect its key roles as a vasodilator, bronchodilator, neurotransmitter and inflammatory mediator. The unique lung anatomy allows NO produced in the airways to be detected in exhaled breath. This was accomplished in the early 1990s with the advent of chemiluminescence analyzers that could detect low levels of NO in the parts per billion (ppb) range. Interestingly, patients with asthma have high levels of exhaled NO in their exhaled breath that returns to normal levels after treatment with corticosteroids, making exhaled NO a potentially useful marker of airway inflammation. Although these findings clearly suggest a role for NO in asthma pathogenesis, the exact role of NO in asthma and airway reactivity remains elusive despite intense research in this area. Whether NO is beneficial through its bronchodilator and antioxidant effects or harmful by inducing inflammation remains unclear. It also is possible that it may play both roles depending on the level and the airway milieu in a particular patient or at a particular stage of the disease. In either case, measuring exhaled NO has shown clinical utility in monitoring the inflammatory component of asthma.

The use of exhaled NO in monitoring asthma is promising for several reasons. It is non-invasive, it can be performed repeatedly, and it can be used in children and patients with severe airflow obstruction where other techniques are difficult or not possible to perform. Exhaled NO may also be more sensitive than currently available tests in detecting airway inflammation, which may allow more optimum therapy.

Several issues, however, needed to be addressed before exhaled NO could become a useful clinical tool in routine asthma monitoring and management. First, a better understanding of the role of NO in asthma pathogenesis was needed. Second, the methods and equipment for measuring NO needed to be standardized. Third, large population studies were needed to determine the normal range of exhaled NO levels and the effect of confounding factors. Last, but not least, interpretative strategies needed to be devised and put in place for the different potential uses and applications. While the answers have not always been straightforward and simple, most of these issues have either already been addressed or are currently under investigation, allowing exhaled NO measurement to make the transition from the research to the clinical arena.

The American Thoracic Society (ATS) has published standards for performing measurements of exhaled NO. The guidelines recommend the use of the term FENO (the fractional exhaled NO concentration) to describe levels of NO in exhaled breath. FENO is expressed in parts per billion, which is equivalent to nanoliters per liter (nl/L). Several commercial analyzers are available to measure NO levels in exhaled breath based on the ATS guidelines. One such device was approved by the FDA in 2003.

The standardization of FENO measurement was followed by several large clinical and population studies demonstrating that FENO levels can be useful in the diagnosis of asthma and in monitoring disease activity/airway inflammation and response to therapy. These studies have also identified various possible confounders that affect FENO including age, gender, weight, height, diurnal variation, and food intake, among others. Observations that have been consistent in the literature, however, are that atopic individuals tend to have higher FENO while smokers tend to have lower FENO.

A more difficult problem to address in the NO field has been the establishment of normal healthy population values for FENO. While several studies have tried to address this issue of normative values, they were done in different populations, addressed different potential confounders, and reported their results in different ways. Furthermore, “reference values” derived from a “normal” population may not be applicable in patients with asthma. This raises the question whether normal values are at all useful when it comes to the use of FENO in asthma. Thus, defining different cut points for different clinical settings may be more clinically useful than normative values.
Combined with the fact that there is considerable overlap in FENO between healthy individuals and asthmatics, it is very clear from reviewing the literature that the FENO value by itself is not sufficient. FENO value should be taken within the clinical context: Was the measurement obtained in someone who has symptoms or in an asymptomatic individual? Was it performed as a screening or to aid in the diagnosis? Is the individual known to have asthma? And if so is he/she on therapy? Do they have previous levels and how does this level compare? Once the clinical setting is taken into consideration, certain cut points become very useful: FENO levels above 45-50 ppb predict steroid responsiveness while levels below 35 ppb suggest optimal asthma control in an asthmatic on therapy. FENO levels above 20-25 ppb suggest the presence of asthma in a steroid-naive individual with symptoms while lower levels are not likely to be associated with airway inflammation.

Thus, advances in technology and standardization made FENO measurement simple and allowed us to easily perform it in different settings from diagnosis, to monitoring, to screening, and possibly others. In order for this simple yet powerful tool to achieve its potential, however, we need to understand what FENO levels mean in different clinical settings. While some tests are difficult to perform and easy to interpret, others like FENO are easy to perform but may need considerable skill to interpret.

New guidelines on FENO interpretation are forthcoming from the American Thoracic Society, expected out early 2009.

Recommended Reading


Jean Wall Bennett Chair for Emphysema Research Established

James K. Stoller, MD, MS, Head, Section of Respiratory Therapy, Department of Pulmonary and Critical Care Medicine, is the first to hold the Jean Wall Bennett Chair for Emphysema Research.

This endowed chair is a gift of Mr. Joseph Bennett in memory of his late wife, Jean Wall Bennett, who suffered from the disease and was treated by Dr. Stoller.

The new chair will advance emphysema research at Cleveland Clinic. Dr. Stoller’s interests include emphysema in general and also Alpha-1-Antitrypsin Deficiency, a genetic form of the disease. Active research in both areas is underway.

One current study with Alpha-1-Antitrypsin Deficiency is examining the role of CT as a way to measure the lung disease progression in emphysema as an alternative to breathing tests.

Dr. Stoller is also Cleveland Clinic’s site PI for the largest randomized clinical trial of the effectiveness and safety of long-term home oxygen therapy for COPD (chronic obstructive pulmonary disease). The results will help Medicare decide whether to extend coverage for home oxygen treatment to patients with moderate disease. Currently, Medicare limits coverage of home oxygen therapy to beneficiaries with severe COPD (very low blood oxygen levels while resting).
The changes that a woman's body undergoes during her monthly menstrual cycle could offer clues into potential therapies for people who have advanced lung diseases and need ways to improve how they absorb oxygen.

During a portion of the menstrual cycle, a woman's ovaries and the lining of her uterus become enriched with blood vessels in preparation for possible reproduction. But if there is no fertilized egg, the uterine lining is discarded as the menstrual flow. The uterus returns to its normal state until the process starts again the following month.

Scientists have studied different factors that control blood vessel formation and regression in the uterus. Among these are hormones such as estrogen; proteins that control blood vessel growth such as vascular endothelial growth factor; and adult stem cells, derived from bone marrow that circulates in the blood, called endothelial progenitor cells (or EPC).

The question was do these factors also encourage blood vessel formation in the lungs?

As part of a team of pathologists and pulmonologists, we found that microscopic blood vessels in the lung increase and decrease in the same rhythm as a woman's uterine lining changes. These blood vessels are critical to pulmonary gas transfer – the exchange of oxygen for carbon dioxide that occurs in the lungs with each breath we take. The study monitored and tested 10 healthy, non-smoking women in their early 30s during their menstrual cycles (four healthy, non-smoking males were used as a control group). We also looked at blood vessels in mice receiving estrogen or placebo. Among our findings:

- Mice that received estrogen had a greater number of microvessels and more and smaller alveoli. Together the smaller alveoli and the rich networks of new blood vessels increase the surface area available for transferring gases.
- Circulating EPCs clearly are related to changes in gas exchange in lung tissues.
- The lung-diffusing capacity in women increased by 10 percent when the blood vessel formation was at its peak during the menstrual cycle, demonstrating improved gas transfer.
The research also might lead to new understanding of episodic airflow obstruction, such as asthma, which may worsen in some women around the time of their menstrual cycle.

It’s clear that the same factors that cause blood vessel development in the uterus and ovaries during a menstrual cycle are critical factors to how well lungs transfer gases. This understanding of what governs gas transfer in the lung could lead to therapies that encourage blood vessel formation in the lungs of patients with advanced lung diseases. Any way we can improve or augment oxygen intake by these patients will be a step forward in their care.

The research also might lead to new understanding of episodic airflow obstruction, such as asthma, which may worsen in some women around the time of their menstrual cycle.

Understanding what underlies the cause of these diseases can help us to treat the symptoms better. We are currently recruiting participants for an ongoing study to understand pulmonary arterial hypertension.

Women are particularly predisposed to diseases of the arteries and veins within the lungs. These diseases might involve the same causes that we revealed in our research. This gives us hope that we can identify new therapies for women with these types of diseases.

Other collaborators on the project were Serpil Erzurum, MD, Daniel Laskowski, Lauren Licina and Raed Dweik, MD, all of Pathobiology; Herbert Wiedemann, MD, Chairman, Cleveland Clinic Respiratory Institute; and Haruki Sekigushi and Douglas Losordo, MD, both of the Northwestern Memorial Hospital Division of Cardiology in Chicago. The report appeared in the Journal of Applied Physiology (http://jap.physiology.org; 2007 103: 1789-1795). It was supported by the National Institutes of Health’s National Heart, Lung, and Blood Institute.

Dr. Kewal Asosingh is a member of the Pathobiology Department in Lerner Research Institute. Contact him at 216.445.7191 or asosink@ccf.org. Dr. Samar Farha is a pulmonologist in the Cleveland Clinic Respiratory Institute and was the lead researcher on the project. Contact her at 216.444.3229 or farhas@ccf.org.
Changes in bioenergetics of IPAH endothelial cells uncovered

By Weiling Xu, MD, Donald Neumann, MD*, Frank DiFilippo, PhD*, and Serpil C. Erzurum, MD

Cleveland Clinic researchers have identified a metabolic abnormality in the lungs of patients with idiopathic pulmonary arterial hypertension (IPAH), which could lead to new therapies and improved care of this rare but deadly disease. IPAH primarily strikes young adults and is about twice as common in women than in men.

Idiopathic pulmonary arterial hypertension (IPAH) is a fatal disease of unknown etiology characterized by a progressive increase in pulmonary artery pressure and vascular growth. Symptoms include dyspnea, fatigue, syncope, edema and dizziness. Chronic liver disease, some rheumatologic disorders, or congenital heart malformations also can result in an associated pulmonary hypertension. There is evidence from animal models of pulmonary hypertension, mice genetically deficient in endothelial NO synthase, and complementation studies with gene transfer of NO Synthases for the concept that NO is a critical determinant of pulmonary vascular tone. We and others have shown that levels of NO are lower in lungs of patients with IPAH as compared to healthy controls. Separate from its vasodilatory effects, NO binds to several targets within the mitochondrial respiratory chain. For example, NO competes with oxygen for binding to complex IV in the mitochondrial respiratory chain of oxygenated cells. Recently, NO was also found to trigger mitochondrial biogenesis in cells. Previous studies have identified abnormal mitochondrial function, basically site-specific defects in electron transport chain, in avian idiopathic pulmonary hypertension that lead to lower respiratory chain coupling and inefficient use of oxygen, which in turn contribute to the development of pulmonary hypertension syndrome in chickens. Similarly, Fawn Hooded rats (FHR), a spontaneously pulmonary hypertensive strain, have abnormal mitochondria with reduced expression of electron transport chain components. In a recent study, we questioned whether abnormal energy metabolism might be present in the human IPAH. We hypothesized that in the low NO state of IPAH that pulmonary artery endothelial cells may have an altered cellular metabolic energy pathway. To test this, we measured the oxygen consumption, ATP content, glycolytic rate and mitochondrial morphology, activity and expression of mitochondrial complexes of pulmonary artery endothelial cells isolated from IPAH lungs in comparison to pulmonary artery endothelial cells from healthy controls. Our research findings, “Alterations of cellular bioenergetics in pulmonary artery endothelial cells,” were published in the Jan. 16, 2007, issue of the Proceedings of the National Academy of Sciences.

A significant decrease of oxygen consumption was found in IPAH cells as compared with healthy controls. Glucose metabolism was subserving the primary role for energy-requirements of IPAH cells as shown by the measure of nearly 3-fold greater glycolytic rate of IPAH cells as compared to healthy control cells. Positron emission tomography (PET) scan with \(^{18}\)F- fluoro-deoxy-D-glucose (FDG) was used to evaluate the glucose metabolism in the lungs of IPAH patients in comparison to healthy controls. FDG PET scan revealed higher glucose metabolic activities in lungs of IPAH patients than in controls, confirming that the glycolytic rate was also higher in vivo, and that relative uptake of FDG in patient’s lungs may have promise as a marker of IPAH disease activity, or in the diagnosis of the disease.

Overall, this study supports that there is a fundamental alteration in cellular bioenergetics in IPAH, linking the human disease to avian and murine forms of PAH, species in which inefficient cellular use of oxygen has been shown to predispose to development of pulmonary hypertension. The next step in the research is to understand the molecular mechanisms that lead to these alterations, so that we can develop new drug therapies to improve mitochondrial function.

Contact Dr. Serpil C. Erzurum at 216.445.5764 or erzurus@ccf.org.

* Nuclear Medicine, Cleveland Clinic
The year 2007 brought continued growth for the Cleveland Clinic Lung and Heart/Lung Transplant Program, one of the most active in the country.

The Transplant Program completed its 626th transplant since the program’s inception in 1990, and in 2007, performed 72 lung transplants, including three heart/lung transplants and the first lung-liver transplant in Ohio, reinforcing Cleveland Clinic’s position among the leading lung transplantation programs, both in Ohio and nationally. More than 415 end-stage lung disease patients were evaluated from all across the country and the world by the transplant team.

The Transplant Program continues a reputation for accepting and transplanting challenging, complex patients. Cleveland Clinic’s Lung Transplant Team is involved in a series of multicenter trials aimed at therapy of primary graft dysfunction, acute rejection and induction therapy. In addition, our surgeons have pioneered certain transplant surgical techniques, including bronchial artery revascularization, which may improve outcomes further by reducing ischemic injury (see lead article in this issue of Respiratory Exchange).

The average waiting time for a graft in our program remains stable despite the new Lung Allocation Score (LAS). Currently, our average waiting time is 75 days. The Transplant Program has achieved very strong survival rates that are at or above the national average. Median and long-term outcomes continue to improve, with a one-year survival rate of 86 percent and two-year survival rate of 74 percent. A continued emphasis on quality assurance and quality improvement remains central to the program, reflected by the decrease in post-transplant length of stay to an average of 13 days.


To refer a patient for consideration for lung transplant or heart/lung transplant, please call our transplant coordinator at 216.444.8282, option 3.
Bronchoscopic Techniques May Provide New Treatments for Severe Emphysema Patients

By Thomas Gildea, MD, Michael Machuzak, MD, and Atul Mehta, MD

Emphysema is a serious health issue that afflicts about 3 million people in the U.S., causing nearly 14,000 deaths every year. Current medical treatment for emphysema includes medication and/or supplemental oxygen, pulmonary rehabilitation and, in rare cases, lung volume reduction surgery (LVRS) or lung transplantation.

Although LVRS is an effective procedure, it is associated with a morbidity rate of 40 percent and a mortality rate of 10 percent to 15 percent two years post-surgery (even in an appropriate patient group). For this reason, researchers have developed novel, investigational endobronchial valve devices that allow air to exit from the lung parenchyma, but not to re-enter, potentially leading to less volume that occurs following LVRS. Researchers hope the endobronchial valves may achieve the benefits of LVRS, but without its surgical risks and complications.

**IBV (INTRA-BRONCHIAL VALVE)**

Over the last few years, Cleveland Clinic pulmonologists have been participating in several multicenter trials to assess the efficacy and safety of bronchoscopic treatments for patients with severe emphysema.

One such device is manufactured by Spiration Inc., Redmond, Wash. The IBV® valve is an umbrella-shaped nitinol framed prosthesis with a synthetic polymer cover. The flexible nitinol frame enables the valve to maintain contact with the airway wall and prevent air from passing into the diseased portions of the lungs while allowing for mucus and air to escape. This creates a one-way valve effect and redirects inspired air from the diseased upper lobes to the healthier lower lobes.

While the patient is under anesthesia, the valve is inserted through the working channel of a flexible bronchoscope. The calibrated balloon determines the size of the valve for a preselected airway segment. Under direct vision, the valve deployment device is passed through the working channel of the bronchoscope and installed. The valves are intended to be permanent but they can be removed via a minimally invasive procedure.

In the first human pilot study (Wood et al Journal of Thoracic and Cardiovascular Surgery 2007, Jan:133(1):65-73), 30 patients received IBV valves at five centers, including Cleveland Clinic. Although the clinical trial was not designed to establish the efficacy of the valves, data was collected to provide guidance for future studies. A majority of patients experienced significant improvements in health-related quality of life as measured by the St George’s Respiratory Questionnaire with an improvement of 9.8 (+/-9.6), 6.9 (+/-12.9) and 6.8 (+/-14.3) at one, three and six months, respectively. Nevertheless, the physiological tests did not show statistically significant improvements.

The pilot study continued to include 98 patients and is being published soon. The most common procedure complication was bronchospasm in eight cases. These all resolved but one was serious and two severe. Pneumothorax was the most common device complication and occurred in eight cases. Two cases did not require intervention but one episode was a tension...
pneumothorax with death. Pneumothorax likely results from greater lung volume changes than are necessary for significant improvement, so the treatment pattern was revised.

The improved health-related quality of life outcomes might have been due to a placebo effect among patients participating in a pilot study, and so Spiration is sponsoring a larger research trial that is expected to recruit more than 300 patients at 29 centers, including Cleveland Clinic. This IBV valve study, currently under way, is a randomized, blinded trial, which is expected to eliminate the placebo effect and help investigators determine the physiological efficacy and safety of the IBV valve. Patients will be selected based on strict inclusion and exclusion criteria to reduce the risks for complications.

**EBV (ENDOBRONCHIAL VALVE)**

The Zephyr® EBV valve from Emphasys Medical, Redwood City, Calif., has completed a multicenter clinical trial and is before the FDA for review. Investigators at Cleveland Clinic have case by case permission to use this valve in compassionate use protocols for persistent bronchopleural fistula, treatment for severe emphysema and giant bullae.

**EXHALE AIRWAY STENTS FOR EMPHYSEMA**

Another trial currently enrolling at Cleveland Clinic is the EASE (Exhale Airway Stents for Emphysema) trial sponsored by Broncus Technologies, Mountain View, Calif. This is a randomized, double-blind study to evaluate the safety and effectiveness of the Exhale® drug-eluting stent in patients with homogeneous emphysema and severe hyperinflation. This technique involves creating artificial airways, or "airway bypasses", across the wall of poorly functioning existing airways.

Airway bypass is done in the operating room under general anesthesia. A bronchoscopy is performed where a Doppler probe is used to identify safe areas to place stents. A needle with a balloon is first used to perforate the airway and dilate the opening. A balloon loaded with the drug-eluting stent is then deployed across the airway wall. Trapped air is now able to pass out of the areas of emphysema without getting blocked by the diseased airways characteristic of COPD/emphysema.

Pilot trials of this device have been conducted internationally with these airway bypass stents (Cardoso et al Journal of Thoracic and Cardiovascular Surgery 2007 Oct;134(4):974-81). Thirty-five patients received the airway bypass procedure with a median of eight stents implanted per patient. At one-month follow-up, differences in lung function tests of hyperinflation, modified Medical Research Council scale, six-minute walk, and St George's Respiratory Questionnaire were observed. At the six-month follow-up, statistically significant improvements were demonstrated in residual volume and dyspnea. One death occurred due to bleeding during the procedure.

**BIOLOGIC LUNG VOLUME REDUCTION**

Yet another procedure in trials has been developed, biologic lung volume reduction, sponsored by Aeris Therapeutics Inc., Woburn, Mass. A process of instilling biologic chemical reagents into targeted areas of the lung results in scar tissue collapsing areas of diseased lung, improving lung mechanics.

Biologic lung volume reduction (BLVR) is performed by selecting targeted subsegments. A double lumen catheter is advanced out deep into the lung. A mixture of chemicals and a form of fibrin glue is rapidly instilled and allowed to gel in place. The process is repeated in several segments based on the protocol.

Phase I of the study (Reilly J et al Chest. 2007 Apr;131(4):1108-13) enrolled six patients with advanced heterogeneous emphysema. Three patients received unilateral treatment at two pulmonary subsegments and three patients received unilateral treatment at four pulmonary subsegments. BLVR was not associated with any serious complications. Improvements were observed in mean vital capacity (+7.2 +/- 9.5%; range, -2% to +19%), mean residual volume (RV) (-7.8 +/- 8.5%; range, +1% to -22%), mean RV/total lung capacity ratio (-6.6 +/- 4.7%; range, -1% to -15%), mean 6-min walk distance (+14.5 +/- 18.5%; range, 0 to +51%), and in mean dyspnea score.

Cleveland Clinic participated in two Phase II multicenter trials, one for patients with homogenous disease and the other for patients with heterogeneous disease. Results of these trials have not yet been published.

Cleveland Clinic is preparing for the BLVR Phase III clinical trial. Specific inclusion/exclusion criteria have not yet been set.

Cleveland Clinic doctors involved in these trials are Atul C. Mehta, MD, Thomas R. Gildea, MD, and Michael Machuzak, MD.

**Patient recruitment for these studies is under way. For more information, please call Yvonne Meli, RN, BC, at 216.445.4215 or meliy@ccf.org.**

Researchers hope the endobronchial valves may achieve the benefits of LVRS, but without its surgical risks and complications.
Cleveland Clinic Respiratory Institute is committed to offering forums for renowned researchers in pulmonary diseases to present their latest findings and providing professionals with insights they can integrate into their clinical practice. The Respiratory Institute was proud to sponsor five innovation summits in 2007.

**Asthma Summit 2007**
The Asthma Summit focused on research and clinical care advances by global leaders in asthma. The meeting highlighted perspectives on future research that will influence the practice of asthma care, and described the most up to date diagnostic tools, asthma educational programs and new insights into clinical care. More than 175 attendees from around the world were provided detailed information on recent innovations in asthma and potential interface with new technology.

**Major Airway Disease Summit 2007**
The Major Airway Disease Summit in April 2007 focused on the interfaces among innovative technology, research, and clinical care. The summit provided a unique perspective on cutting-edge technologies that will influence the future management of patients with major airway disease.

**Lung Summit 2007: Innovations in Respiratory Therapy Management and Clinical Practice**
This summit in May 2007 addressed the issues of supply of RTs, demand for their services and manpower in respiratory care today. Key issues in managing a respiratory therapy group, current issues regarding new modes and optimal strategies of mechanical ventilation, and optimal aerosol delivery were addressed.

**Breath Analysis Summit 2007: Clinical Applications of Breath Testing**
In November 2007, the Respiratory Institute hosted the first “International Breath Analysis Summit”, which was also the third Scientific Meeting of the International Association for Breath Research (IABR). Directed by Raed A. Dweik, MD, the summit was held in collaboration with NASA, the U.S. EPA, the Monell Chemical Senses Center and the Electrochemical Society. Participants in the two and a half day summit came from 22 countries and 18 states and discussed key trends, future directions and upcoming technologies in breath analysis and medicine.

**Pulmonary Hypertension Summit 2007**
The Pulmonary Hypertension Summit 2007, on November 16 and 17, attracted more than 220 participants from 20 states and five countries to hear presentations by about 40 distinguished Cleveland Clinic and visiting faculty. The next Pulmonary Hypertension Symposium will be Nov. 8, 2008, and the next Pulmonary Hypertension Summit will be in Fall 2009.
Outcomes Data Available

The latest outcomes data from Cleveland Clinic departments involved in the treatment of respiratory diseases are available. Our outcomes booklet offers summary reviews of medical and surgical trends and approaches. Charts, graphs and data illustrate the scope and volume of procedures performed in our departments each year. To view outcomes booklets for respiratory diseases as well as many other Cleveland Clinic medical and surgical disciplines, visit clevelandclinic.org/quality.

Online Access to Your Patient’s Treatment Progress

Whether you are referring from near or far, our new eCleveland Clinic service, DrConnect, can streamline communication from Cleveland Clinic physicians to your office. This new online tool offers you secure access to your patient’s treatment progress at Cleveland Clinic. With one-click convenience, you can track your patient’s care using the secure DrConnect Web site. To establish a DrConnect account, visit eclevelandclinic.org or e-mail drconnect@ccf.org.

Cleveland Clinic Ranked One of America’s Top Hospitals

Cleveland Clinic is ranked among the top hospitals in the country, according to the latest U.S. News & World Report’s annual survey of “America’s Best Hospitals.” In the Respiratory Disorders category, Cleveland Clinic is ranked #5. For details, visit clevelandclinic.org.

CME Calendar

Physicians are welcome to attend the following upcoming symposia:

**Obesity Summit 2008** | Sept. 10-12
InterContinental Hotel and Bank of America Conference Center, Cleveland Clinic
Cleveland, Ohio

**The 5th Annual Pulmonary Arterial Hypertension Symposium 2008** | Nov. 8
InterContinental Hotel and Bank of America Conference Center, Cleveland Clinic
Cleveland, Ohio

**Biologic Therapies in Special Populations – Infections, Malignancies, Cardiovascular Disease, and Other Comorbidities**
May 7-9, 2009
Featuring: Mini-symposium on ‘Managing Complex Cases in Biologic Therapies’
InterContinental Hotel and Bank of America Conference Center, Cleveland Clinic
Cleveland, Ohio

**17th World Congress for Bronchology, and the 17th World Congress for Bronchoesophagology** | June 16-19, 2012
Cleveland, Ohio

For more information about the above events, call the Cleveland Clinic Department of Continuing Education at 216.444.5696 or 800.762.8173, or visit clevelandclinicmeded.com.
<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Program</th>
<th>Phone</th>
<th>Specialty Interests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbert P. Wiedemann, MD, MBA</td>
<td>Chairman, Respiratory Institute</td>
<td>216.444.8335</td>
<td>Specialty Interests: critical care (including adult respiratory distress syndrome and sepsis), general pulmonary medicine, exercise testing (ergometry evaluation)</td>
</tr>
<tr>
<td>Loutfi Aboussouan, MD</td>
<td></td>
<td>216.839.3820</td>
<td>Specialty Interests: general pulmonary medicine, neuromuscular diseases, sleep medicine, long-term ventilator care</td>
</tr>
<tr>
<td>Muzaffar Ahmad, MD</td>
<td></td>
<td>216.444.6506</td>
<td>Specialty Interests: pulmonary function lab, diagnostic techniques including fiberoptic bronchoscopy, asthma, lung cancer</td>
</tr>
<tr>
<td>Rendell Ashton, MD</td>
<td></td>
<td>216.446.5321</td>
<td>Specialty Interests: critical care, lung cancer, physician education</td>
</tr>
<tr>
<td>Marie Budev, DO, MPH</td>
<td>Associate Medical Director, Lung Transplantation</td>
<td>216.444.3194</td>
<td>Specialty Interests: lung transplantation, pulmonary hypertension, gender specific pulmonary issues</td>
</tr>
<tr>
<td>Robert Castele, MD</td>
<td></td>
<td>440.878.2500</td>
<td>Specialty Interest: general pulmonary medicine</td>
</tr>
<tr>
<td>Jeffrey T. Chapman, MD</td>
<td>Director, Interstitial Lung Disease Program</td>
<td>216.444.4222</td>
<td>Specialty Interests: interstitial lung disease, pulmonary hypertension, lung transplantation</td>
</tr>
<tr>
<td>Daniel Culvee, DO</td>
<td>Director, Sarcoidosis Program</td>
<td>216.444.6508</td>
<td>Specialty Interests: sarcoidosis, interstitial lung disease, hypersensitivity pneumonitis</td>
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<td>Loutfi Aboussouan, MD</td>
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<td>440.878.2500</td>
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</table>
Atul C. Mehta, MD  
Vice Chairman, Department of Pulmonary, Allergy and Critical Care Medicine; Medical Director, Lung Transplantation; Head, Section of Bronchology  
216.444.2911  
Specialty Interests: lung transplantation, lung volume reduction surgery, endobronchial and bronchoscopic procedures and interventions, transtracheal oxygen therapy

Omar A. Minai, MD  
216.445.2610  
Specialty Interests: pulmonary hypertension, interstitial lung diseases, lung cancer, COPD, sleep apnea

Thomas Olbrych, MD  
216.445.8733  
Specialty Interests: general pulmonary medicine, cystic fibrosis

Beverly V. O’Neill, MD  
216.692.7848  
Specialty Interests: general pulmonary medicine, long-term ventilator patients

Joseph G. Parambil, MD  
216.444.7567  
Specialty Interests: interstitial lung disease, pulmonary hypertension, general pulmonary medicine

Anita Reddy, MD  
216.444.4506  
Specialty Interests: critical care, acute lung injury, interstitial lung disease, lung transplant

Hina Sahi, MD  
216.829.3820  
Specialty Interests: general pulmonary medicine

Madhu Sasidhar, MD  
216.445.1838  
Specialty Interests: critical care, lung cancer, general pulmonary medicine

James K. Stoller, MD, MS  
Head, Section of Respiratory Therapy; Executive Director, Leadership Development  
216.444.1960  
Specialty Interests: clinical epidemiology, alpha1-antitrypsin deficiency, respiratory therapy

David M. Lang, MD  
Head, Section of Allergy and Clinical Immunology  
216.445.5810  
Specialty Interests: asthma, allergic disorders, sinusitis, urticaria, anaphylaxis, latex allergy, aspirin sensitivity

Mark A. Aronica, MD  
Joint Appointment with Pathobiology  
216.444.6933  
Specialty Interests: asthma, allergic disorders

Rachel Koelsch, MD  
216.444.6933  
Specialty Interests: pediatric and adult allergic rhinitis, asthma, food allergies, bee and wasp sting allergy, eczema, medication allergies, hives

Lily C. Pien, MD  
216.444.6933  
Specialty Interests: allergic rhinitis, asthma, drug allergies, latex allergy, medical education

Cristine Radojicic, MD  
216.444.6933  
Specialty Interests: pediatric and adult allergic rhinitis, asthma

Fred H. Hsieh, MD  
Joint Appointment with Pathobiology  
216.444.3504  
Specialty Interests: asthma, allergic disorders, mast cell function

Ruffin J. Graham, MD  
216.444.8756  
Specialty Interests: pulmonary thromboembolism, lung cancer and thromboembolic disease
Jeffrey P. Kanne, MD
216.444.3158
Specialty Interests: hematopoietic stem cell transplantation, interstitial lung disease, lung transplantation, occupational lung diseases, congenital disorders of the heart and lungs

Omar Lababede, MD
216.444.9014
Specialty Interest: thoracic imaging

Tan-Lucien H. Mohammed, MD
216.444.3867
Specialty Interests: cardiopulmonary imaging/transplantation imaging, interstitial lung disease, upper airway disease

Barbara Risius, MD
216.444.6422
Specialty Interest: thoracic radiology

Department of Pulmonary Pathology

Carol F. Farver, MD
Director, Pulmonary Pathology
216.445.7695
Specialty Interest: pulmonary pathology

Andrea Arrossi, MD
216.444.9120
Specialty Interests: pathology of interstitial lung disease, and pleural and pulmonary tumors

Department of Thoracic and Cardiovascular Surgery

Charles V. Biscotti, MD
216.444.0046
Specialty Interests: cytopathology, gynecologic pathology

Omar Lababede, MD
216.444.9014
Specialty Interest: thoracic imaging

Tan-Lucien H. Mohammed, MD
216.444.3867
Specialty Interests: cardiopulmonary imaging/transplantation imaging, interstitial lung disease, upper airway disease

Barbara Risius, MD
216.444.6422
Specialty Interest: thoracic radiology

Gösta Pettersson, MD, PhD
Vice Chairman, Thoracic and Cardiovascular Surgery; Surgical Director, Lung Transplantation
216.444.2035
Specialty Interests: lung and heart-lung transplantation

Gonzalo Gonzalez-Stawinski, MD
216.444.6708
Specialty Interests: heart transplantation, lung transplantation, transplant immunology, reoperative adult cardiac surgery

Nicholas G. Smedira, MD
Surgical Director, Kaufman Center for Heart Failure
216.445.7052
Specialty Interests: lung and heart-lung transplantation, pulmonary thromboendarterectomy

Section of General Thoracic Surgery

Thomas W. Rice, MD
Head, Section of General Thoracic Surgery
216.444.1921
Specialty Interests: esophageal, pulmonary, mediastinal, chest wall and diaphragm surgery, minimally invasive lung volume reduction surgery, lung transplant surgery

David Mason, MD
216.444.4053
Specialty Interests: general thoracic surgery, lung transplantation, minimally invasive thoracoscopic and laparoscopic surgery, lung cancer, esophageal cancer, malignant mesothelioma

Sudish Murthy, MD, PhD
Surgical Director, Center for Major Airway Diseases
216.444.5640
Specialty Interests: esophageal, pulmonary, mediastinal, chest wall and diaphragm surgery, minimally invasive lung volume reduction surgery, lung transplant surgery
CONTACT INFORMATION

General Patient Referral
24/7 hospital transfers or physician consults
800.553.5056

Pulmonary Appointments/Referrals
216.444.6503 or 800.223.2273, ext. 46503

Allergy Appointments/Referrals
216.444.3386 or 800.223.2273, ext. 43386

On the Web at
clevelandclinic.org/pulmonary

INSTITUTE LOCATIONS

Main Campus
9500 Euclid Avenue / A90
Cleveland, OH 44195

Beachwood Family Health and Surgery Center
26900 Cedar Road
Beachwood, OH 44122
Pulmonary and Allergy: 216.839.3800

Brunswick Family Health Center
3724 Center Road, Suite 100
Brunswick, OH 44212
Pulmonary: 330.225.8886

Euclid Hospital
Medical Office Building
99 Northline Circle, Suite 235
Euclid, OH 44119
Pulmonary: 216.692.7848

Hillcrest Hospital Atrium
6780 Mayfield Road
Mayfield Heights, OH 44124
Pulmonary: 440.312.7140

Independence Family Health Center
5001 Rockside Road
Independence, OH 44131
Pulmonary and Allergy: 216.986.4000

Strongsville Family Health and Surgery Center
16761 SouthPark Center
Strongsville, OH 44136
Pulmonary and Allergy: 440.878.2500

Westlake Family Health Center
30033 Clemens Road
Westlake, OH 44145
Allergy: 440.899.5555

Willoughby Hills Family Health Center
2570 SOM Center Road
Willoughby Hills, OH 44094
Allergy: 440.943.2500
Introducing the Future of Healthcare

Innovative new buildings improve patient access, experience.

This fall, Cleveland Clinic is introducing the future of healthcare with the opening of the Sydell and Arnold Miller Family Pavilion and the Glickman Tower.

These buildings, which represent the largest construction and philanthropy project in Cleveland Clinic history, embody the pioneering spirit and commitment to quality that define Cleveland Clinic. These structures are a tangible expression of institutes, our new model of care that organizes patient services by organ and disease.

At 1 million square feet, the Miller Family Pavilion is the country’s largest single-use facility for heart and vascular care. The 12-story Glickman Tower, new home to the Glickman Urological & Kidney Institute, is the tallest building on Cleveland Clinic’s main campus.

Both will help us improve patient experience by increasing our capacity and by consolidating services, so patients can stay in one location for their care.

With 278 private patient rooms, more than 90 ICU beds and a combined total of nearly 200 exam rooms and more than 90 procedure rooms, patients will have faster access to Cleveland Clinic cardiac and urological services.

For details, including a virtual tour, please visit meetthebuildings.com.