With each breath we exhale, thousands of molecules are expelled. Each of us has a “smellprint” that can tell a lot about our state of health. Breath analysis dates back thousands of years. Hippocrates described fetor oris and fetor hepaticus in his treatise on breath aroma and disease; Lavoisier and Laplace in 1784 showed that respiration consumes oxygen and eliminates carbon dioxide; Nebelthau in the mid-1800s showed that diabetics emit breath acetone; and Anstie in 1874 isolated ethanol from breath, which is the basis of breath alcohol testing today.

The end of the 20th century and the beginning of the 21st century, however, have arguably witnessed a revolution in our understanding of the constituents of exhaled breath and the development of the field of breath analysis and testing. A major breakthrough in the scientific study of breath started in the 1970s when chemist...
Dear Colleagues:

Patients with complex pulmonary disorders benefit from the expertise of a multidisciplinary team of specialists. At Cleveland Clinic, experts in four departments — Pulmonary, Allergy and Critical Care Medicine; Thoracic and Cardiovascular Surgery; Thoracic Imaging; and Pulmonary Pathology — collaborate 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 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, M.D.
Chairman, Department of Pulmonary, Allergy & Critical Care Medicine

Thomas W. Rice, M.D.
Head, Section of General Thoracic Surgery; Department of Thoracic & Cardiovascular Surgery

Carol F. Farver, M.D.
Director, Pulmonary Pathology; Division of Pathology & Laboratory Medicine

Moulay Meziane, M.D.
Head, Section of Thoracic Imaging; Division of Radiology

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**Breath Analysis Summit 2007: Clinical Applications of Breath Testing**

**Nov. 1-3**

InterContinental Hotel and Bank of America Conference Center

Cleveland, Ohio

The International Association for Breath Research (IABR) is holding this year’s scientific meeting, the Breath Analysis Summit, Nov. 1-3, 2007, at the InterContinental Hotel and Bank of America Conference Center on Cleveland Clinic’s campus.

The goal of the summit is to discuss new ways to deliver advances to patients, and how to do so in the quickest, safest, most cost-effective way. The summit will bring together industry executives, entrepreneurs, investors, scientists, environmentalists and clinicians to discuss key trends, future directions and upcoming technologies in breath analysis and medicine. The major focus this year will be on medical applications in addition to environmental and bioterrorism issues.

**Topics include:**
- nitric oxide
- exhaled breath condensate
- electronic nose and sensor arrays
- mass spectrometry and bench-top instrumentation
- cutting-edge sensor technologies

**Medical applications include:**
- asthma, COPD, pulmonary hypertension, and other respiratory diseases
- gastrointestinal diseases
- occupational diseases
- critical care
- cancer

The summit is the third annual scientific meeting of IABR. The first was held in Dornbirn, Austria, and last year’s was held in Prague. This summit is a collaboration among the National Aeronautics and Space Administration, the Environmental Protection Agency, the Monell Chemical Senses Center, and the Electrochemical Society. Summit proceedings will be published in the newly established *Journal of Breath Research*.

For abstract submission details, registration and more information about the Breath Analysis Summit, please visit clevelandclinicmeded.com/breath07.
and researcher Linus Pauling demonstrated that there is more to exhaled breath than the classic gases of nitrogen, oxygen, carbon dioxide and water vapor. Based on gas-liquid partition chromatography analysis, Pauling reported the presence of 250 substances in exhaled breath. With modern mass spectrometry (MS) and gas chromatography mass spectrometry (GC-MS) instruments, we can now identify more than 5,000 unique substances in exhaled breath. These substances include elemental gases like nitric oxide and carbon monoxide and a multitude of volatile organic compounds. Exhaled breath also carries aerosolized droplets that have other compounds dissolved in them.

We now have the ability to test for any and all of these components. Thanks to major breakthroughs in new technologies (infrared, electrochemical and chemiluminescence among them) and the availability of desktop mass spectrometers, the field of breath analysis has made considerable advances in the 21st century. Several methods now are in, or about ready to enter, clinical use.

Commercially available analyzers can measure nitric oxide (NO) levels in exhaled breath to the parts per billion (ppb) range and carbon monoxide to the parts per million (ppm) range. Desktop mass spectrometers can measure volatile compounds in breath down to the parts per trillion (ppt) range. Aerosolized droplets in exhaled breath can be captured by a variety of methods and analyzed for a wide range of biomarkers, from metabolic end products and proteins to a variety of cytokines and chemokines, and the possibilities continue to expand. The standardization of sample collection methods was a major hurdle faced by our field as it transitioned from the laboratory to clinical testing. To advance, close collaboration between technical experts (who design devices for clinical applications) and medical experts (who need tests/biomarkers to help diagnose and monitor clinical problems) was required.

One example of a collaborative success is the measurement of exhaled NO for monitoring airway inflammation in asthma. The advent of chemiluminescence analyzers in the early 1990s allowed the detection of low (ppb) levels of NO in exhaled breath. This was quickly followed by the observation that patients with asthma had higher than normal levels of NO in their exhaled breath, which later was linked to eosinophilic airway inflammation. In 2003, the U.S. FDA approved the first desktop NO analyzer for monitoring airway inflammation in asthma. The use of exhaled NO to monitor asthma is useful for a few reasons: It is noninvasive, can be performed repeatedly and can be used in children and patients with severe airflow obstruction, where other techniques are difficult or impossible to perform. Exhaled NO also may be more sensitive than currently available tests in detecting airway inflammation, which may allow more optimum therapy.

Our research contributed greatly to the understanding of the role of NO in the pathobiology, diagnosis and monitoring of asthma. As members of the American Thoracic Society / European Respiratory Society joint task force, we helped develop the standardized procedures for the measurement of exhaled NO. Our pulmonary medicine colleagues at Cleveland Clinic also are at the forefront of breath testing, involved in using newer sensor technologies like the electronic nose and sensor arrays for breath analysis to detect lung cancer (see article page 4).

Breath analysis offers a window to lung physiology and disease, and exhaled breath testing is becoming an increasingly important noninvasive diagnostic method that can be used to evaluate health and disease states in the lung and beyond.

Contact Dr. Raed Dweik at 216.445.5763 or dweikr@ccf.org, and Dr. Serpil Erzurum at 216.445.7191 or erzurus@ccf.org.

PUBLICATIONS
As part of a Cleveland Clinic team of pulmonologists and oncologists, we have evaluated the ability of gaseous chemical sensing devices to detect lung cancer by analyzing exhaled breath. Prior study has suggested the pattern of chemicals in the breath, or volatile organic compounds, may be unique in individuals with lung cancer.

Previously, we described the use of a carbon polymer sensor system. The output from this system is a change in the conductivity of the sensors based on the chemicals in the breath that contact them. We also reported the use of a colorimetric sensor array. The sensor used in this system was composed of 36 colored dots impregnated on a disposable cartridge. The dots were made of chemically responsive compounds that change their color based on the pattern of chemicals with which they come in contact. We hypothesized that the pattern of color changes on the sensor would be unique in lung cancer subjects.

In our first study, smellprints were obtained on the exhaled breath of 14 individuals with bronchogenic carcinoma, 19 with alpha-1 antitrypsin deficiency (α1-ATD), six with chronic beryllium disease (CBD), and 20 healthy controls. Unlike α1-ATD and CBD, exhaled breath of lung cancer patients clustered distinctly from controls. This data indicated that the exhaled breath of lung cancer patients has distinct characteristics that can be identified with a carbon polymer sensor system.

Subsequently, a cancer prediction model was prospectively evaluated in a group of 52 individuals, 12 with and 40 without cancer. In the prospective study, exhaled breath analyses by the electronic nose showed 71.4 percent sensitivity (CI: 41.9 to 91.6) and 91.9 percent specificity (CI: 82.1 to 97.3) for the diagnosis of lung cancer.

Our most recent study included 143 subjects, of which 49 had lung cancer, 73 had a variety of lung diseases, and 21 were healthy controls. A model was developed using 70 percent of the study subjects’ breath results. This model was tested on the remaining 30 percent of participants, where it was found to be 73.3 percent sensitive and 72.4 percent specific for the diagnosis of lung cancer.

These results support the potential for breath analysis to be developed into a useful diagnostic test for lung cancer, confirming previously performed work by us and others. We hope to learn more about the unique constituents of the breath of lung cancer subjects and develop analysis systems that accurately screen for, and diagnose, lung cancer in a noninvasive manner.
Malignant Pleural Mesothelioma: Does Earlier Multimodal Treatment Extend Patient Survival?

By Sudish C. Murthy, M.D., Ph.D.

Current therapies for malignant pleural mesothelioma have shown only marginal success at extending patient survival. Median life expectancy still is about 12 months. However, we are hoping to improve this outlook through a multimodality approach (chemotherapy, surgery and chemoradiation) administered earlier in the disease process, when the pleural tumor may still be resectable.

To be eligible for this phase II study, a patient's tumor must be confined to a hemithorax (stage I or II mesothelioma) and be clinically resectable. Participants also must have no co-morbidities and be generally healthy enough to tolerate this aggressive protocol.

Those who qualify are given induction chemotherapy in two cycles, three weeks apart. The initial induction chemotherapy is a combination of two drugs: cisplatin (a sensitizing agent) and pemetrexed (Alimta®), an antifolate, antineoplastic agent that suppresses tumor cell proliferation. One of the key aspects of this study is the earlier use of this drug pair, which was FDA approved in 2005 as first-line chemotherapy against advanced mesothelioma.

At the end of the induction treatment, the chest is re-imaged with CT and PET scans to determine tumor progression. Only those patients whose tumor growth has ceased will continue on to surgery.

Surgical candidates will undergo an extrapleural pneumonectomy (en bloc removal of lung, pleura, pericardium and diaphragm) to ensure maximum cytoreduction. The pericardium and diaphragm are reconstructed using GORE-TEX® mesh to protect the heart and to prevent abdominal organ migration.

Eight weeks after surgery, patients begin a course of adjuvant chemoradiation. Cisplatin is used to sensitize any remaining tumor cells, and a 3-D conformal radiotherapy beam is used to eradicate the residual tumor cells in the chest cavity. This beam is a 45-gray dose of external radiation, computer gated to match the contours of the chest cavity and to minimize side effects.

Thus far, we have enrolled about 10 patients and are looking to recruit another 40 over the next two years.

To refer patients for the study, contact Dr. Sudish Murthy at 216.444.5640 or murthys1@ccf.org.

CME Calendar

Physicians are welcome to attend the following upcoming symposia:

Breath Analysis Summit 2007: Clinical Applications of Breath Testing | Nov. 1-3
InterContinental Hotel and Bank of America Conference Center, Cleveland Clinic
Cleveland, Ohio

Pulmonary Hypertension Summit 2007 | Nov. 16-17
InterContinental Hotel and Bank of America Conference Center, Cleveland Clinic
Cleveland, Ohio

Esophageal Summit | Apr. 17-18, 2008
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.
Single Versus Double Lung Transplantation

By David P. Mason, M.D.

Double lung transplantation (LTx) must be performed for suppurative lung diseases and has become the standard of care for patients with primary pulmonary hypertension. However, there is still debate surrounding the advantage of double LTx over single LTx for other transplant indications. Data suggest a survival advantage for patients undergoing double LTx for emphysema, although this advantage has not been well demonstrated for other diseases such as idiopathic pulmonary fibrosis (IPF).

My colleagues in Cleveland Clinic’s Lung Transplant Program and I believe strongly in the benefit of double LTx over single LTx. We have demonstrated survival advantage, with a low perioperative mortality for both single and double LTx, for all transplant indications including emphysema and IPF. Our outcomes for patients transplanted for IPF are better than national outcomes. Our five-year survival for patients undergoing double LTx is 55 percent. In addition to survival advantage, pulmonary function has been found to be significantly better when two lungs are transplanted instead of one.

At Cleveland Clinic, all lung transplant candidates are considered for double LTx, with few direct contraindications. In 2006, 64 percent of our lung transplant patients received double LTx, and this percentage is steadily increasing. While most transplant programs reserve double LTx for younger patients, we have performed double LTx in patients up to 65 years old with good outcomes.

We specialize in complex lung transplants, including combined double LTx with cardiac surgery procedures, and have performed transplants successfully on many patients referred from other transplant centers.

Reach Dr. David Mason at 216.444.4053 or masond2@ccf.org.

Ohio’s First Lung/Liver Transplant

By Marie Budev, D.O., M.P.H.

This year, Patti Prince became an Ohio “medical first.” After a 12-hour operation, the New York resident became Ohio’s first lung/liver transplant recipient.

In January 2007, a 25-year-old cystic fibrosis patient with end-stage lung and liver disease underwent a 12-hour operation at Cleveland Clinic, becoming Ohio’s first lung and liver transplant recipient. The patient began her workup at Cleveland Clinic in 2006. However, after the birth of her son, her cystic fibrosis disease progressed. Both her lungs and her liver continued to decline, and she began to have frequent and worsening episodes of hemoptysis that required several interventions. Because her liver would not withstand the immunosuppressive therapy needed for new lungs, the team decided to proceed with both a double-lung and a liver transplant simultaneously.

Cardiothoracic surgeon Gosta Pettersson, M.D., Ph.D., Director of Heart/Lung Transplantation, and surgeon Charles Miller, M.D., Director of Liver Transplantation, transplanted the patient’s lungs and liver, respectively. Currently in the United States, only a handful of centers are able to perform this type of multi-organ transplant surgery.

Following an uneventful recovery and four weeks after her landmark operation at Cleveland Clinic, the patient returned home to her family. At her first follow-up visit, she reported that she has begun to play the flute again, a hobby she had given up because of limited respiratory capacity.

Since the inception of Cleveland Clinic’s lung transplant program in 1990, we have performed more than 600 transplants. The program is one of the most active in the country, with an international reputation for its expertise in treating complex, high-risk patients. In December 2006, Cleveland Clinic’s liver transplant program recorded its 1,000th transplant.

To refer a patient for consideration for lung transplant or heartlung transplant, please call Alan Stewart, transplant coordinator, at 216.444.8282, option 3.
Lung Transplant Center of Excellence

This year Cleveland Clinic reached its 600th lung transplant since the program's inception in 1990. Sixty-two lung transplants and two heart/lung transplants were performed in 2006, reinforcing Cleveland Clinic's position among the leading lung transplantation programs, both in Ohio and nationally.

We are one of the nation's premier referral centers for lung transplantation. While carefully expanding our donor acceptance criteria, we also actively participate in donor management and provide further education to our statewide organ procurement agencies to maximize donor utilization and improve the donor lung quality.

A continued emphasis on quality assurance and quality improvement remain central to the program, reflected by an average wait time of 62 days and a decrease in post-transplant length of stay to less than two weeks.

To refer a patient for consideration for lung transplant or heart-lung transplant, please call Alan Stewart, transplant coordinator, at 216.444.8282, option 3.

**Volume from 1990 through 2006: 600 (including 16 Heart/Lung).**

**The Heart/Lungs were Double Lung transplants, but are not included in the Double Lung count above.**

***As of July 21, 2007.***
Endobronchial ultrasound (EBUS) is a new technology being used to evaluate airway, lung and lymph node abnormalities. EBUS offers pulmonologists and thoracic surgeons an improved ability to diagnose disease, stage cancer and determine which patients are candidates for surgery. The three general uses for intra thoracic ultrasound include:

**Peripheral Endobronchial Ultrasound (P-EBUS)**

To better evaluate peripheral lung lesions and increase diagnostic accuracy, we use a peripheral probe. A miniaturized probe is introduced through the working channel of the bronchoscope. The differences in density between the lung lesion and the normal lung architecture are highlighted as the probe is introduced into the abnormal area. A catheter is then left in place and samples are taken. Recent data suggest an improved yield using P-EBUS.

**Balloon Probe**

Often it is difficult to distinguish between tumor invasion in an airway wall versus compression from outside the airway. To help differentiate an abnormal airway (airway involved with cancer) from a normal airway, we can insert an ultrasound probe, enveloped inside a balloon, into the airway. Once the balloon is inflated with saline, the ultrasonic image can show intrinsic (involved airway) from extrinsic (compression outside the airway) involvement. This technique can allow for improved detection of airway invasion and determine which patients are candidates for resection.

**Endobronchial Ultrasound Trans-bronchial Needle Aspiration**

The hybrid bronchoscope (convex probe or puncture scope) is currently being used to improve the diagnostic yield of transbronchial needle aspiration (TBNA). The endobronchial ultrasound TBNA scope is designed with a small ultrasound on the tip that allows visualization of the lymph nodes. The scope also features a needle for sampling. The EBUS TBNA scope allows physicians to visualize the lymph nodes and vessels as well as see the needle puncture the lymph node in real-time, providing an improved recovery and a potentially safer procedure for the patient. Our current yield exceeds 94 percent using this technique. We currently are using the EBUS TBNA scope for minimally invasive mediastinal staging as well as initial diagnosis. We are adding a second EBUS TBNA scope so that we may serve more patients.

Contact Dr. Michael Machuzak at 216.444.2718 or machuzm@ccf.org; Dr. Thomas Gildea at 216.444.6490 or gildeat@ccf.org; and Dr. Atul Mehta at 216.444.2911 or mehtaa1@ccf.org.
Diagnostic and Therapeutic Techniques

Cleveland Clinic pulmonologists offer the full range of routine diagnostic and therapeutic techniques, as well as the following specialty techniques:

<table>
<thead>
<tr>
<th>DIAGNOSTIC TECHNIQUE</th>
<th>INDICATION</th>
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<tbody>
<tr>
<td>Autofluorescence bronchoscopy</td>
<td>Detection of cancerous and precancerous airway lesions</td>
</tr>
<tr>
<td>Electromagnetic navigation diagnostic bronchoscopy</td>
<td>Computer-guided bronchoscopy for difficult to reach lung lesions</td>
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<tr>
<td>Mediastinal endobronchial ultrasound</td>
<td>Real-time ultrasound-guided needle aspiration of lymph nodes</td>
</tr>
<tr>
<td>Narrow-band imaging bronchoscopy</td>
<td>Detection of hypervascular airway areas indicative of cancer and precancerous lesions</td>
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<tr>
<td>Peripheral endobronchial ultrasound</td>
<td>Ultrasound confirmation of location for guiding peripheral lesion biopsies</td>
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<tr>
<th>THERAPEUTIC TECHNIQUE</th>
<th>INDICATION</th>
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<tbody>
<tr>
<td>Argon plasma coagulation</td>
<td>Tumor ablation and cauterization</td>
</tr>
<tr>
<td>Balloon bronchoplasty</td>
<td>Dilation of airway obstruction</td>
</tr>
<tr>
<td>Brachytherapy (high-dose rate)</td>
<td>Palliation of malignant airway obstruction</td>
</tr>
<tr>
<td>Broncholith removal</td>
<td>Removal of obstructing calcified lesion eroding into airways (related to remote histoplasmosis)</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Tumor freezing and removal of blood clots from airways</td>
</tr>
<tr>
<td>Endobronchial electrosurgery</td>
<td>Removal and destruction of airway lesions</td>
</tr>
<tr>
<td>Endobronchial mitomycin-C</td>
<td>Topical application to delay airway restenosis</td>
</tr>
<tr>
<td>Endobronchial steroid injection</td>
<td>Inflammatory disease (Wegener’s Granulomatosis)</td>
</tr>
<tr>
<td>Foreign body removal</td>
<td>Multiple indications</td>
</tr>
<tr>
<td>Heimlich valve insertion</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Intraleisional cidofovir injection</td>
<td>Adjunctive treatment of HPV</td>
</tr>
<tr>
<td>Nd-YAG laser photoresection</td>
<td>Palliation of malignant central airway obstruction</td>
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<tr>
<td>Photodynamic therapy</td>
<td>Carcinoma in-situ and palliation of lung cancer</td>
</tr>
<tr>
<td>Rigid bronchoscopy</td>
<td>Multiple indications; specifically needed for silicone stent deployment</td>
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<tr>
<td>Stent removal/revision</td>
<td>Stent malfunction/granulation/fracture</td>
</tr>
<tr>
<td>Stenting: Alveolus Stent Technology System (STS)™, Ultraflex™, Dumon®, Polyflex®, Y-stent</td>
<td>Palliation of central airway obstruction</td>
</tr>
<tr>
<td>TTO2 (transtracheal oxygen catheter) placement</td>
<td>Augmentation of oxygenation of severe hypoxia</td>
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<tr>
<td>Pleurex® catheter insertion</td>
<td>Palliation of malignant pleural effusion</td>
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<tr>
<th>RESEARCH BRONCHOSCOPY</th>
<th>INDICATION</th>
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<tr>
<td>Asthma</td>
<td>Bronchial thermoplasty Alair® System (Asthmatx Inc.)</td>
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<tr>
<td>Emphysema</td>
<td>Bronchial fenestration (Bronchus)</td>
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<td></td>
<td>Bronchoscopic tissue engineering (Aeris™ Technologies)</td>
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<tr>
<td></td>
<td>Endobronchial valve implantation (Spiration, Inc./Emphasys Medical, Inc.)</td>
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Please direct queries regarding our bronchoscopic capabilities to Jodi Krizmanich at 216.445.3180.

Two Pulmonologists Win Innovator Award

Atul C. Mehta, M.D., and Thomas Gildea, M.D., earned the Cleveland Clinic 2006 Innovator Award for a bronchoscopic catheter for the implantation of fiducial markers using flexible biopsy and aspiration needle. With the help of Ari Gershman, M.D. (internal medicine resident, class of 2006), Drs. Mehta and Gildea developed the idea and submitted it to CCF Innovations, Cleveland Clinic’s technology commercialization arm.

“With the advancement of new technologies such as endobronchial ultrasound and electromagnetic guidance, we are being faced with making cancer diagnoses in patients with inoperable disease,” says Dr. Mehta.

“Using these same techniques for therapeutic interventions was the next logical step.”

The use of fiducial implants in other organs is a common and useful technique to help guide focused radiosurgery, thus sparing nearby tissue from radiation damage. The proposed device was based on modifications of transbronchial needles to deliver and deploy fiducial markers in the lung periphery. Currently transbronchial needles cannot reach small and peripheral lesions in most areas of the lung, particularly in the upper lobes.

“We proposed several short flexible needle designs to navigate into the lung periphery and suggested several fiducial marker designs to reduce the chance of migration,” says Dr. Gildea.

Dr. Mehta is the head of the Bronchology Section within Cleveland Clinic’s Department of Pulmonary, Allergy and Critical Care Medicine. Dr. Gildea is Medical Director of the Center for Major Airway Diseases.
Emergent Thromboembolectomy Still Useful in Lytic Therapy Era

By Gonzalo Gonzalez-Stawinski, M.D.

Pulmonary embolisms prove fatal when not diagnosed early and treated effectively. While the advent of thrombolytic therapy and catheter embolectomy have made emergent pulmonary thromboembolectomies rare procedures — roughly 10 are performed at Cleveland Clinic each year — they remain a lifesaving tool of last resort.

A 23-year-old female with a past medical history for Factor 5 Leiden mutation, deep vein thrombosis, pulmonary embolisms, hemolytic anemia, splenectomy, and an inferior venacava filter (placed because of recurrent pulmonary embolisms despite being on coumadin therapy), presented to an outside institution complaining of progressively worsening shortness of breath. Because of her condition and complicated medical background, she was emergently transferred to Cleveland Clinic for management.

Upon arrival, she was immediately admitted to the medical intensive care unit, where a work-up revealed a new pulmonary embolism. An ultrasound of her abdomen revealed thrombus above her previously placed inferior venacava filter, and a pulmonary angiogram revealed acute occlusion of the right lower lobe and right middle lobe pulmonary artery, in addition to several acute occlusions of the right upper lobe pulmonary arteries. Her left pulmonary artery arteriogram revealed multiple peripheral left upper lobe filling defects and absent perfusion to the lingular segment of her left lung.

Pressures obtained during pulmonary angiography revealed a right atrial pressure of 12 mm Hg, right ventricular pressure of 70/18 (38) mm Hg, main pulmonary artery pressure of 72/29 (46) mm Hg, right pulmonary artery pressure of 76/33 (51) mm Hg, and left pulmonary artery pressure of 71/31 (46) mm Hg.

We initiated thrombolytic therapy, which resulted in a slight improvement in her hemodynamic parameters. However, the patient continued to require a considerable amount of supplemental oxygen to maintain adequate blood saturation, and she continued to show signs and symptoms of oxygen deprivation with clinically evident respiratory distress, tachycardia and an altered mental status. Her condition was critical. After a team consult, we decided to perform an emergent bilateral pulmonary thromboembolectomy.

The procedure was approached through a median sternotomy, and the patient was systemically heparinized. She underwent direct aortic and bicaval cannulation. The patient was placed on cardiopulmonary bypass and, with the aid of hypothermic circulatory arrest (HTCA), cooled to approximately 18°C. An exploration of her pulmonary arteries revealed a considerable amount of acute and chronic thrombus obstructing the previously described pulmonary artery. All thrombus burden was removed during intermittent periods of HTCA, and the pulmonary arteries were repaired using a patch technique.

The patient’s postoperative period was unremarkable. On post-op day two, she was extubated and attempted to get out of bed and walk independently. She was weaned from the nasal cannula to room air within 10 days and remained in the hospital another four days until her anticoagulation was well controlled.

Since her hospital discharge, the patient has regained complete independence in her daily activities and currently suffers no limitation. An echocardiogram two months post-surgery revealed normal right ventricular function and no evidence of chronic pulmonary thromboembolism or pulmonary hypertension.

Contact Dr. Gonzalo Gonzalez-Stawinski at 216.444.6708 or gonzalg@ccf.org.
Nationally Known RT to Spearhead Clinical Research

Robert Chatburn, RRT-NPS, has joined Cleveland Clinic’s Section of Respiratory Therapy as Clinical Research Manager. Mr. Chatburn has a national reputation as a leader and mentor in a variety of areas related to respiratory therapy including mechanical ventilation, neonatal care, optimal delivery of nebulized medications and respiratory research methods.

As Clinical Research Manager, Mr. Chatburn currently is involved in the ongoing evaluation of new nebulizer strategies; assessment of change management in respiratory care; various bench studies regarding new ventilator modes and new ventilators; and the development of educational strategies in alpha-1 antitrypsin deficiency.

Mr. Chatburn also is a distinguished teacher, serving on the faculty of Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. He has played a major role in enhancing ventilator education for trainees, both in respiratory therapy and in pulmonary, allergy and critical care medicine.

A fellow of the American Association for Respiratory Care, Mr. Chatburn also serves on the editorial board of Respiratory Care. During his 30-year career, he has published more than 250 peer-reviewed articles, book chapters, books and educational materials. To the right is a list of his recent publications.

Special Ventilator Unit Produces Favorable Outcomes

By James K. Stoller, M.D., M.S.

Cleveland Clinic ICU patients who depend on mechanical ventilation to breathe but who are otherwise healthy enough to leave the ICU may be transferred to our Respiratory Special Care Unit (ReSCU). Data from Jan. 1 to Dec. 31, 2006, show that 63 percent of our patients transferred to the ReSCU were weaned from ventilation prior to discharge. The rate of hospital survival was 89 percent.

A primary goal of the ReSCU is to have patients breathe without the ventilator. When ventilator independence is not feasible, the goals are to teach patients and family members how to care for the patient and manage the ventilator at home, or to prepare the patient and family members for the patient’s discharge to another facility.

After more than a decade of ventilator unit experience, we have shown that, for carefully selected patients, the rate of achieving complete ventilator independence is high and that the unit is an effective and cost-saving alternative to the ICU.

To refer a ventilator-dependent patient to Cleveland Clinic’s ICU, please call 216.444.4082. Reach Dr. James Stoller at 216.444.1960 or stollej@ccf.org.

2006 Primary ReSCU Stats for the Weaning Ventilator Unit

<table>
<thead>
<tr>
<th>Number of discharged patients</th>
<th>71</th>
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</thead>
<tbody>
<tr>
<td>Total ReSCU days</td>
<td>2,043</td>
</tr>
<tr>
<td>Completely weaned from ventilation</td>
<td>63.3% (45/71)</td>
</tr>
<tr>
<td>Survival</td>
<td>88.7% (63/71)</td>
</tr>
<tr>
<td>ALOS</td>
<td>28.8 days</td>
</tr>
</tbody>
</table>

PUBLICATIONS


Chatburn RL, Deem S. Should weaning protocols be used with all patients who receive mechanical ventilation? Respir Care. 2007;52(5):609-619.


Chatburn RL, Lewarski JS, McCoy RW. Nocturnal oxygenation using a pulsed-dose oxygen-conserving device compared to continuous flow. Respir Care. 2006 Mar;51(3):252-256.


Chatburn RL. Advancing beyond the average: The importance of mentoring in professional achievement. Respir Care. 2004;49(3):304-308.


EGFR: Pathologic Methods for Detection in Non-Small Cell Lung Carcinomas

By Carol Farver, M.D.

Epidermal growth factor receptor (EGFR), a member of the tyrosine kinase receptor family, is known to play an important role in the cellular events of proliferation, differentiation and death in lung epithelial cells. When this receptor is over-expressed or mutated in non-small cell lung carcinoma, it can lead to a more aggressive clinical course and resistance to chemotherapy and radiotherapy.

Quantization and mutational analysis of wildtype EGFR in NSCLC may be helpful in predicting both prognosis and response to therapy. Research is under way at Cleveland Clinic to study the relationship of the number of EGFR-positive cells in an NSCLC tumor to both prognosis and response to anti-EGFR therapies.

A number of laboratory techniques are available to pathologists to quantify and analyze EGFR expression in tissue samples of NSCLC. These techniques include protein expression assays such as immunohistochemistry (IHC) to measure overexpression, DNA assays such as fluorescence in situ hybridization (FISH) to quantify gene copy number, and mutational sequential analysis to look for the presence of activational mutations.

In general, the most common method used in pathology laboratories is IHC, which applies an antibody to EGFR to microscopic slides of tissue samples. This quick and simple technique relies on easily available reagents and allows for quantization of the expression in the tumor. The reliability of this method depends upon the quality of the reagents, most notably the EGFR antibody used, and the preservation and viability of the tumor tissue being tested. Fortunately, standardization of these reagents by the U.S. FDA has provided consistent methodology, resulting in a reliable method for inclusion of patients into clinical trials for use of anti-EGFR therapies.

FISH uses a fluorescence-labeled DNA probe to EGFR to measure its gene copy number in tumor cells. This ranges from no increase in copy number to polysomy to amplification. The advantages of this methodology are similar to IHC, in that it can be used on archival formalin-fixed tissue samples and preserves tissue morphology. The relationship of gene copy number to protein expression and to prognosis and response to therapy is not known. Some studies suggest that gene copy number may be better than protein expression in predicting prognosis. However, its high cost and added technical complexity needed to perform the test limit its widespread use.

The least well-developed technology uses sequencing to find activating mutations in the EGFR gene, because some studies have suggested that certain mutations confer a greater response rate to anti-EGFR therapy. This technology is challenging and requires larger amounts of tissue than normally contained in diagnostic lung biopsies, limiting its availability to only scattered laboratories throughout the country.

To date, the studies that have examined which of these methods is the most reliable in predicting prognosis or response to anti-EGFR therapies are inconclusive, since they have measured different end points (e.g., radiographic response versus time to progression versus overall survival). Clearly, the results of current prospective clinical trials will be needed to clarify the role of these new laboratory technologies.

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Angiogenesis in Asthma

By Mark A. Aronica, M.D., Kewal Asosingh, Ph.D., and Serpil Erzurum, M.D.

Asthma generally is characterized by remodeling of the airway structure, including damage to airway epithelium, eosinophil infiltration, smooth muscle hyperplasia and basement membrane thickening. An increase in the number and size of vessels in the airway wall is a long-recognized occurrence and one of the most consistent features of asthma remodeling, occurring in mild, moderate and severe asthmatic lungs.

According to the results of recent studies, angiogenesis occurs in chronic asthma, indicating a relation between the numbers of blood vessels in the bronchial wall and the severity of asthma. Although an understanding of new vessel formation and its genesis in asthma is still in the early stages, it has been suggested that vascular remodeling may be a critical component in the pathophysiology of asthma.

Recently, endothelial progenitor cells (EPC) have been shown to play an essential role in the formation of new blood vessels. In adults, EPC are defined as a specific subset of bone marrow-derived cells with characteristics similar to those of embryonal angioblasts, i.e., the common hemopoietic and endothelial stem cells. The majority of EPC are believed to be bone marrow resident cells, of which only a minor fraction escape to circulate through the peripheral blood and contribute to the formation of new blood vessels and to vascular homeostasis.

In our study, the results of which were published this year in the Journal of Immunology, we hypothesized that angiogenesis is an early event with onset during the initiation of airway inflammation and is linked to the mobilization of bone marrow-derived EPC. We showed that asthmatic individuals have increased levels of circulating EPC that are highly proliferative and exhibit enhanced incorporation into tubes in an angiogenesis assay. In the experimental allergen challenge mouse model of asthma, EPC mobilization occurred as early as 24 hours after challenge and peaked at day eight. This was followed by an increase in microvessel density that progressed over time with chronic allergen exposure. In addition, the EPC remained elevated, even in the face of resolving inflammation.

Altogether, the data support the concept that EPC recruitment and an angiogenic switch are early events that occur during the derivation of allergic airway inflammation. These data also suggest that angiogenesis is not an epiphenomenon of chronic asthma but an early step in the onset of the disease in which highly proliferating and angiogenic potent EPC play an active role.

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Current Research in Pulmonary Hypertension

By Raed A. Dweik, M.D., and Serpil Erzurum, M.D.

Our Pulmonary Vascular Program colleagues and we are involved in many ongoing investigator-initiated research projects, aimed at understanding the pathophysiology of pulmonary hypertension (PH). Below is a list of current research studies, as well as open clinical trials.

**PH Universal Tissue Repository**

The primary purpose of creating PHUTURE is to support research to uncover the etiology and pathogenesis of PH in pursuit of the ultimate goal of its treatment and cure. This study is enrolling patients with varying degrees of severity and various types of PH.

**PH Registry**

The purpose of this registry is to collect demographic and clinical information as well as results of clinical testing performed on patients with PH as part of their routine clinical care. This registry includes all patients with PH seen within Cleveland Clinic’s Pulmonary Vascular Program. No tests will be performed specifically for inclusion in the registry.

**PH Breakthrough Initiative**

This multicenter collaborative study is designed to 1) define the cellular basis of IPAH through the study of affected lung tissue; 2) describe the molecular pathways involved in the disease; and 3) identify genetic associations with the IPAH clinical phenotype.

**Nitric Oxide and Carbon Monoxide in Pulmonary Hypertension**

This study evaluates the levels of NO and CO and their metabolites in patients with PH to gain a better understanding of the roles these biological markers play in the pathobiology of PH.

**Clinical and Physiologic Predictors of Treatment Response in Pulmonary Hypertension**

This study evaluates new methods for monitoring PH patients over time using noninvasive tests like analysis of exhaled breath and peripheral vascular function.

**Myeloperoxidase as a Biologic Marker in Pulmonary Arterial Hypertension**

This study aims to evaluate the potential role of MPO as well as other inflammatory and biological markers in evaluating the response to therapy in PAH.

**Idiopathic Pulmonary Arterial Hypertension**

In pulmonary arterial hypertension, the pulmonary arteries have characteristic histopathology, typified by neointima formation and angioproliferation. Plexiform lesions, which are a hallmark of IPAH, are made up of abnormal proliferation of monoclonal endothelial cells. Recent studies show that bone marrow-derived endothelial progenitor cells contribute to the formation of new blood vessels. Samar Farha, M.D., and other Cleveland Clinic researchers are investigating whether an inherent abnormality in bone marrow-derived progenitor cells contributes to the pulmonary vascular abnormalities in IPAH. Identification of bone marrow cellular components in the disease will set the stage for novel therapies that target the pro-angiogenic progenitor cells. Patients with IPAH and familial forms of PAH are actively being enrolled in the study.
Recent research performed in the laboratory of Serpil Erzurum, M.D., Chair of Pathobiology, provided new insights into the etiology of pulmonary hypertension and may have implications for the evaluation and management of PH patients. The research appeared in the Proceedings of the National Academy of Sciences of the United States of America.

When compared to healthy patients, the pulmonary artery endothelial cells from IPAH patients reveal that oxygen consumption of IPAH cells is decreased and the rate of absorption of glucose is significantly higher. The research also showed decreased function of mitochondria associated with IPAH. This same combination often is found in the cellular production in tumor cells, which is consistent with the capacity of IPAH lesion cells to proliferate rapidly.

The cause of the decreased oxygen consumption and higher glucose absorption was linked to low levels of nitric oxide (NO), which dilates blood vessels. NO also plays a fundamental role in regulating mitochondrial function and numbers; therefore, variations in the level of NO could affect mitochondria.

Our research results could affect patient care in several ways. First, understanding the absorption of glucose by IPAH cells might lead to new ways to monitor treatment response and measure pulmonary artery pressure or cardiac function. For example, positron emission tomography (PET) scans measure cellular absorption of glucose to produce 3-D images or maps of functional processes in the body or tissues. Because IPAH cells more rapidly absorb glucose, PET scans might be used to identify, measure and monitor IPAH lesions. This would be a new tool to evaluate responses to therapies over time. Second, the increased glucose absorption could be a new target for novel drug therapies. Third, managing the level of NO in IPAH patients could help to regulate mitochondrial function.

These findings offer hope to develop new ways to measure progression of IPAH in patients as well as to develop novel therapies that will improve patient care for people who had few options before.

Cleveland Clinic research collaborators included Raed Dweik, M.D., and Constance Jennings, M.D., Pulmonary, Allergy and Critical Care Medicine; Weiling Xu, Thomas Koeck, Michelle Koo, Allison Janocha and Dennis Stuehr, Ph.D., Pathobiology; and Donald Neumann, M.D., Ph.D., and Frank DiFilippo, Ph.D., Nuclear Medicine. Rubin M. Tudor, M.D., Division of Cardiopulmonary Pathology at Johns Hopkins University School of Medicine, also collaborated.

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**PUBLICATIONS**


Cleveland Clinic Pulmonary Vascular Program

In 2006, physicians in our Pulmonary Vascular Program evaluated and managed more than 600 unique patients for PH. Many are on various therapies: 188 received therapy with prostanoids [epoprostenol (Flolan®), treprostinil (Remodulin®), or iloprost (Ventavis®)]; 194 received endothelin-receptor antagonist therapy (bosentan (Tracleer®)); 184 received phosphodiesterase inhibitor therapy [sildenafil (Viagra®, Revatio®)]; and 31 received other therapies including experimental medications as part of clinical trials. More than 170 are on combination therapy.

Pulmonary Hypertension Summit 2007

Nov. 16-17

InterContinental Hotel and Bank of America Conference Center Cleveland, Ohio

Last year’s Pulmonary Hypertension Summit attracted 250 people who hailed from five countries and 13 states. Participants included physicians, researchers, nurses, physician assistants, social workers, pharmacists, respiratory therapists, patients and caregivers, and exhibitors. Over the two days, more than 45 distinguished visiting and Cleveland Clinic faculty presented the latest advances in pulmonary hypertension.

This year’s summit will include a case-based session to demonstrate the practical aspects of pulmonary hypertension management. Several patient-oriented sessions also are planned. Patients with PH and their families are invited to attend free of charge. They must register by calling Traci Dingman at 216.445.5763.

For details and registration information for professionals, visit clevelandclinicmeded.com/PHsummit07.

Pulmonary Hypertension Sponsored Studies

We are actively enrolling patients in the following trials:

FREEDOM: A 16-week, international, multicenter, double-blind, randomized, placebo-controlled comparison of the efficacy and safety of oral UT-15C sustained release tablets (alone or in combination with an endothelin receptor antagonist and/or a phosphodiesterase-5 inhibitor in subjects with pulmonary arterial hypertension

PI: Omar Minai, M.D., 216.445.2610

ARIES-3: A phase III, long-term, open-label, multicenter safety and efficacy study of ambrisentan in subjects with pulmonary hypertension

PI: Constance Jennings, M.D., 216.445.4184

Rapid switch from intravenous epoprostenol to intravenous Remodulin® (treprostinil sodium) in patients with stable pulmonary arterial hypertension: safety, efficacy and treatment satisfaction

PI: Omar Minai, M.D., 216.445.2610

REVEAL Registry: We are actively participating in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), a multicenter, observational U.S.-based study of the clinical course and disease management of patients with pulmonary arterial hypertension. All consecutive consenting patients diagnosed with World Health Organization (WHO) Group I PAH according to specific hemodynamic criteria at participating institutions are enrolled. Participating patients will be followed for a minimum of five years from the time of enrollment.

The objectives of the registry are to:

• characterize the demographics and clinical course of the patient population diagnosed with WHO Group I PAH
• evaluate differences in patient outcomes according to WHO Group I classification subgroup
• compare patient outcomes in patients who do and do not meet pre-specified traditional hemodynamic criteria defining the diagnosis of PAH
• identify clinical predictors of short-term and long-term outcomes
• assess the relationship between PAH medications (individually and in combination) and patient outcomes
• collect timely and relevant data that will assist in the evolving research needs of the PAH community

More than 100 Cleveland Clinic patients have been enrolled in the REVEAL registry to date.

PI: Raed Dweik, M.D., 216.445.5763

To enroll a patient in REVEAL, contact Jennie Newman at 216.444.7950 or newmanj3@ccf.org.

For more information about the other studies, contact Lynn Harbeitner at 216.445.1056 or harbeil@ccf.org.
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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.
NIH Grants 2006-2007

Mark Aronica, M.D., Pathobiology, received $1.9 million for five years for “Extracellular Matrix Synthesis and Turnover in Asthma.” Funded by the National Institute of Allergy & Infectious Diseases.

Serpil Erzurum, M.D., Chair of Pathobiology, received $3.25 million for five years for “Redox Determinants of Severe Asthma.” Funded by the National Heart, Lung, and Blood Institute.

James Stoller, M.D., Head of Respiratory Therapy and Vice Chairman of Medicine, received $2 million over six years for “Long-Term Oxygen Treatment Trial (LOTT).” Funded by the National Heart, Lung, and Blood Institute.

Herbert Wiedemann, M.D., Chairman of Pulmonary, Allergy and Critical Care Medicine, was awarded a contract renewal for Cleveland Clinic’s participation in the Acute Respiratory Distress Syndrome Network (ARDSNet). Funded by the National Heart, Lung, and Blood Institute.

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.