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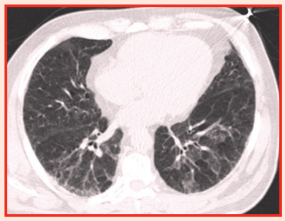
JANUARY 2014



Computed tomography image of subclinical parenchymal lung disease at the 95th percentile of high attenuation areas

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An Advanced Care Team for Pulmonary Emboli

In the summer of 2012, a 40-year-old male underwent neurosurgery for a benign tumor at NewYork-Presbyterian/ Weill Cornell Medical Center. The neurosurgeon had to reach the tumor through the cranium making it a high-risk procedure. Soon after, the patient developed a brain hemorrhage, followed a few days later by shortness of breath and tachypnea. A CT scan showed a very large pulmonary embolism in the right main pulmonary artery.

"This was a significant pulmonary embolus in terms of size and hemodynamics," says Akhilesh K. Sista, MD, the interventional radiologist (IR) consulted for treatment of the patient's embolism with an inferior vena cava filter. As soon as Dr. Sista saw the patient, he gave Oren A. Friedman, MD, a specialist in pulmonology and critical care medicine, a call to discuss the case.

"The patient was becoming hypotensive," notes Dr. Friedman. "The ideal objective would be to break up the clot somehow. But we couldn't give IV tPA at the dose of 100 milligrams over the course of two hours because it could make his head bleed a lot worse. He could become obtunded; the therapy could kill him."

"It seemed reasonable to try to do something in the IR suite to debulk the clot," adds Dr. Sista. "We converted the interventional suite into a mini ICU room. The ICU fellow and the ICU attending managed the patient's vitals, giving him intravenous pressors as needed. The IR team worked on the other side of the patient's neck getting access to his pulmonary artery. We were essentially 'throwing the kitchen sink' at this patient, administering local tPA into his clot on the order of six to 12 milligrams, as opposed to 100 milligrams. We used a mechanical device that is not generally used in pulmonary situations. By the end of the procedure we were able to get his systemic blood pressure up and he was ventilating better. Seven days later the patient was discharged from the hospital. It was a pretty dramatic case for a young guy that could have gone in the wrong direction."

For the patient, the unusual approach was lifesaving. For the physicians involved, it marked a turning point in their perspective on care of patients with pulmonary emboli.

"This case was the impetus for the formation of our group," says James M. Horowitz, MD, the cardiologist involved in the patient's care. "The patient was similar in age to us, which made his

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Idiopathic Pulmonary Fibrosis: What We Know and What We Need to Know

Idiopathic pulmonary fibrosis (IPF) is a little known disease with no cure, yet according to the Pulmonary Fibrosis Foundation some 40,000 people die from IPF annually – the equivalent of deaths from breast cancer – and it is five times more common than cystic fibrosis and Lou Gehrig's disease. An interstitial lung disease characterized by chronic inflammation, IPF causes progressive scarring or thickening of tissues between the lung's alveoli leading to an irreversible loss of the tissues' ability to transport oxygen. Data suggest there are approximately 28 cases per 100,000 people, presenting more in men than women, with onset generally over the age of 50. More than 125,000 people have the diagnosis in the United States, with nearly 50,000 new cases identified annually.

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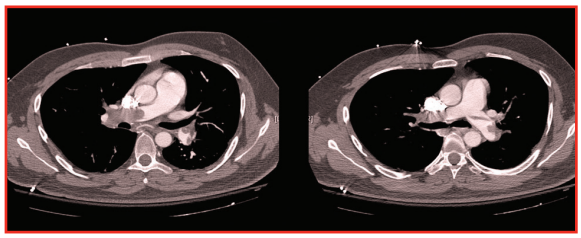
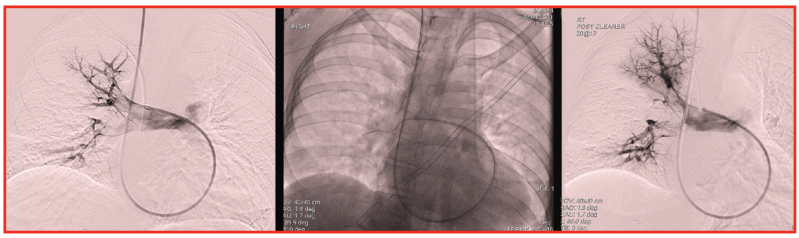
Dr. Selim M. Arcasoy

An Advanced Care Team for Pulmonary Emboli *(continued from page 1)*



Axial images from a contrast-enhanced chest CT performed on the 40-year-old patient with the massive PE demonstrated a large, expansile, central thrombus in the right main pulmonary artery and eccentric nonocclusive acute thrombus in the left pulmonary artery extending to the lower lobe branch.



Following an endovascular intervention, the patient's oxygenation and hemodynamics improved significantly and he was discharged from the hospital seven days later. It was the success of this case that catalyzed the creation of the Pulmonary Embolism Advanced Care Team.

situation more personal on some level. It inspired us to venture into thinking about treating pulmonary embolism differently and, perhaps, more aggressively, when indicated. I think we were all struck by the possibilities based on our first case together and thought this deserved more attention."

Those possibilities became reality soon after with the creation of a PE dream team – the Pulmonary Embolism Advanced Care Team, comprised of Drs. Friedman, Horowitz, Sista, and cardiothoracic surgeon Arash Salemi, MD. Together they are hoping to change the algorithm of care for pulmonary emboli, which is implicated in 60,000 to 100,000 deaths per year in the United States.

"All of us recognize that PE is a very deadly disease and that a lot of people out there could benefit from more aggressive therapy," says Dr. Friedman. "There has been a general reticence and reluctance to be more aggressive because of the fear of bleeding complications and of causing more harm."

Mobilizing a Team for a Cross-Specialty Disease

"If you think of medical technology and advancements over the past 50 years, pulmonary embolism is the only disease that I can think of where treatment algorithms haven't changed," says Dr. Horowitz. "We give a heparin drip to help prevent clots from getting worse, but it doesn't do anything for pre-existing clots. If we want to break up the clot, we can give systemic tPA. But physicians are not inclined to do this because of the high risk for bleeding into the brain. Therefore, tPA is generally not used unless the patient is basically in extremis, almost too late to save. The idea that treatment for a condition this prevalent and this deadly hasn't changed in 50 years is insane."

New approaches are now being explored. These include pharmacologic thrombolytic therapy with a lower dose of the IV tPA that is therapeutic, but with fewer side effects; catheter-based therapies for administering low-dose tPA directly into the clot; and mechanical means for extracting clots. "These are techniques that are considered game changers in terms of the management of pulmonary embolisms," notes Dr. Friedman.

"While we think that these, and other methods like them, might revolutionize how we treat PE, we know from experience that getting this done without an interdisciplinary team is impossible," adds Dr. Friedman. "You have to get the MICU consults and the IR consults. You also have to call in cardiology to get the echo of the heart. And then you have to call the surgeon. There are so many people to call that by the time everyone is involved, it could be too late; the person is too sick."

Enter the Pulmonary Embolism Advanced Care Team. One call mobilizes the team quickly for rapid assessment of the patient and intervention with appropriate treatment. "We have developed a 24-hour pager system that works much like what we have for MIs or stroke," says Dr. Horowitz.

"Whenever there's a patient that is remotely sick, we let everybody know and have everybody weigh in. It's truly a multidisciplinary approach," says Dr. Sista. "The pager informs us anytime there is a hemodynamically significant PE or even a less threatening PE that the health care team needs help with. When that page comes to us, we'll immediately go to the bedside and evaluate the patient. We look at the imaging, order any necessary tests, and help the team manage the patient in the acute phase. We'll then triage accordingly."

"While we think that these, and other methods like them, might revolutionize how we treat PE, we know from experience that getting this done without an interdisciplinary team is impossible."

— Dr. Oren A. Friedman

"An important fact about pulmonary embolism is that it's a cross-specialty disease," says Dr. Friedman. "Although, by nature, we're talking about blood clots in the lung, people tend to die of this disease because of cardiovascular collapse. One of the major ways to discriminate who is going to do well and who will not is through echocardiography. It's an incredibly important diagnostic tool that helps us risk stratify people with a PE. A critical feature of our group is having access to echocardiography earlier on; a cardiology expert on hand to review those echocardiograms to identify the sicker patients; and having the relevant experts available to intervene quickly on those patients who need more advanced care."

For example, the team has agreed that if intubation is at all necessary, either because of patient agitation or cardiopulmonary collapse, the patient should be sent to the operating room. "In these cases, general anesthesia can be very complicated. By having the patient in the OR setting, we have a cardiac anesthesiologist already present and we can apply – without delay – such measures as extracorporeal membrane oxygenation in conjunction with surgical embolectomy if it becomes necessary," says Dr. Salemi.

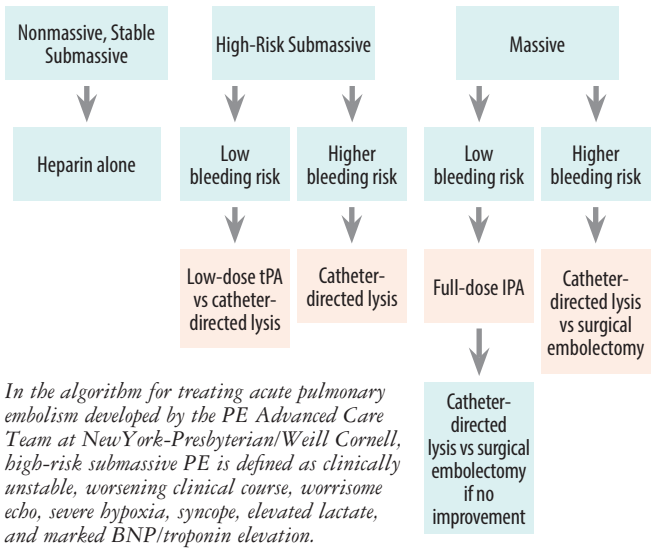
The particular advantage of the Pulmonary Embolism Advanced Care Team is that its members are constantly thinking about and have the most experience with this disease. "There is a lot of clinical

Drs. Arash Salemi, cardiothoracic surgeon; James M. Horowitz, cardiologist; Oren A. Friedman, pulmonologist; and Akhilesh K. Sista, interventional radiologist, created the Pulmonary Embolism Advanced Care Team to ensure rapid assessment and response to patients at the bedside.

equipoise surrounding pulmonary embolisms," says Dr. Friedman. "Because there are major gaps in the literature and vague institutional guidelines available for treating PE, the disease is particularly well-suited to care by a multidisciplinary group. At Weill Cornell, this means that our PE patients have immediate access to consultations by pulmonary, critical care, and cardiology specialists simultaneously. We collectively decide whether or not the person needs more advanced care."

According to Dr. Friedman, this advanced care can mean intravenous thrombolytic therapy, or it may mean getting that person triaged to a critical care ICU where more advanced shock and resuscitation management is applied. "And sometimes," says Dr. Friedman, "it may mean surgical embolectomy to remove the clots in the major pulmonary arteries. Putting all of our minds together gives us an added advantage to taking care of this disease in a much more aggressive way. We also think it's going to demonstrate better outcomes."

Algorithm for Treating Acute PE
PE Advanced Care Team
NewYork-Presbyterian/Weill Cornell



In the algorithm for treating acute pulmonary embolism developed by the PE Advanced Care Team at NewYork-Presbyterian/Weill Cornell, high-risk submassive PE is defined as clinically unstable, worsening clinical course, worrisome echo, severe hypoxia, syncope, elevated lactate, and marked BNP/troponin elevation.

Getting the Word Out

With the Pulmonary Embolism Advanced Care Team well established, Drs. Friedman, Horowitz, Salemi, and Sista knew that they then had to make its existence known among Hospital personnel if they were to really make a difference. To this end, they first established a pager number – *1-CLOT* – to make their service readily accessible. "We wanted something very easy for people to remember if one of their patients has a PE," says Dr. Friedman. "We put our names and pager number on pens and distributed them throughout the Hospital. We also launched a lecture circuit internally, meeting with the different disciplines that commonly see patients with PEs to let them know about the PE Advanced Care Team and what that means for patient care."

In the nine months that the team has been operational, they have seen some dramatic results. Requests for consults are increasing, and patients are being seen earlier and having procedures more quickly. The team meets monthly to review cases and their outcomes, revising algorithms as necessary. Says Dr. Friedman, "What we've learned from each other, and how that has actually changed the care that we give, has really been quite remarkable."

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Idiopathic Pulmonary Fibrosis: What We Know and What We Need to Know *(continued from page 1)*

"Idiopathic pulmonary fibrosis and other fibrotic lung diseases generally are not treatable medically," says Selim M. Arcasoy, MD, Co-Director of the Interstitial Lung Disease Program and Medical Program Director of the Lung Transplantation Program at NewYork-Presbyterian/Columbia University Medical Center. "Patients usually present with a subtle onset of breathlessness with exercise. Over time there is a worsening of breathlessness as oxygen transfer to the blood decreases. Heart failure often develops. Some patients can be stabilized with various medications, but the majority progress to end-stage lung disease requiring evaluation for a lung transplant."

"People with IPF have an average survival of three to five years," says David J. Lederer, MD, MS, Co-Director of the Interstitial Lung Disease Program and Associate Medical Director of the Lung Transplantation Program. "There are a few agents that are being studied in late phase III trials, so we may be able to identify whether or not one of these drugs will be beneficial as early as March or April of 2014. But currently, there is no effective medical therapy available in the United States. Certain drugs aim to reduce the inflammatory reaction and prevent the scarring and thickening of lung tissues, but the only real treatment seems to be lung transplantation."

Dr. David J. Lederer

As Co-Directors of the Interstitial Lung Disease Program, along with their colleague Nina M. Patel, MD, Associate Director, Drs. Arcasoy and Lederer have been developing protocols for diagnosis, management, and treatment of these serious diseases based on their research and guided by their clinical experience. "The causes of IPF have been elusive for decades," says Dr. Lederer. "Basic science and translational approaches have provided much-needed insights into the biological pathways that contribute to lung fibrosis, yet despite these advances, IPF remains an idiopathic disease."

According to Dr. Lederer, "Establishing a diagnosis of IPF in the traditional symptom-linked fashion is akin to diagnosing coronary artery disease only after a patient presents with a myocardial infarction. A different approach is needed if we are to examine the biological events that underlie the early development of this disease." Two years ago, Dr. Lederer was awarded a National Institutes of Health RO1 grant to do just that – identify very early, subclinical or preclinical pulmonary fibrosis in older, otherwise healthy adults. "Results of this study will be available in the next six to 12 months," says Dr. Lederer. "The data will clarify our understanding of the genetic risk factors and early clinical presentation of pulmonary fibrosis. We are seeing interesting links between very early findings of early pulmonary fibrosis on CT scans related to cardiovascular disease and a genetic mutation that's been linked to certain forms of cancer."

This major undertaking has its origins in a cardiovascular study initiated over a decade ago in which CT scans were taken on 7,000 healthy, older people to see if early subclinical or silent cardiovascular disease could be identified by looking for calcium in the arteries of the heart. Those same CT scans included images of the lungs. "To identify early pulmonary fibrosis, we're simply using CT scans that were done for the cardiology study," says Dr. Lederer. "These people have come back for repeat CT scans multiple times over the past 12 years. So there is a wealth of data to mine. It's a very exciting area and some very big papers will be coming out in the next one to two years."

Clinical Trials and Tribulations

Until recently, research on potential agents to treat idiopathic pulmonary fibrosis has been disheartening with clinical trials demonstrating either no improvement or side effects that were too toxic. In 2005, studies of potential pharmaceuticals for IPF got a boost with the creation of IPFnet, a clinical research network sponsored by the National Heart, Lung, and Blood Institute charged with developing and evaluating clinical treatment regimens for both early and advanced stages of idiopathic pulmonary fibrosis.

The Division of Pulmonary and Critical Care Medicine at NewYork-Presbyterian/Weill Cornell Medical Center serves as one of the network's 25 research sites across the country and the Weill Cornell-based trials are led by Robert J. Kaner, MD.

"The treatment of IPF is being approached on many levels, targeting various points along the disease process," says Augustine M.K. Choi, MD, a clinician-scientist with expertise in the pathology and biology of lung disease. "Newer agents are under study to suppress the development of scarring and slow fibrous growth, to prevent injury to lung tissue, and to prevent the loss of lung function."

Dr. Augustine M.K. Choi

Dr. Choi, who was recently appointed Physician-in-Chief at NewYork-Presbyterian/Weill Cornell and Chairman of Medicine at Weill Cornell Medical College, pursues research on the regulation and function of cytoprotective molecules in the pathogenesis of lung and vascular tissue injury and repair. He previously served as Chief of Pulmonary and Critical Care Medicine at Brigham and Women's Hospital in Boston.

"There are now several clinical trials in phase II and III that will guide us on which therapies should no longer be considered," says Dr. Choi, "and which may prove more promising to help overcome the resistance of IPF to medical therapies and improve outcomes for these patients."

The Pathway to Lung Transplantation

When Dr. Arcasoy and Joshua R. Sonett, MD, the program's former Surgical Director, joined NewYork-Presbyterian/Columbia more than 12 years ago, its Lung Transplantation Program had a small volume of patients and only modest success rates despite the fact that the program had been established in 1985, just three years after the first lung transplant was performed. Over the last decade, the program has earned a great reputation for the depth of its clinical expertise and rigorous commitment to research to advance treatment options, prevent or delay the progression of serious lung

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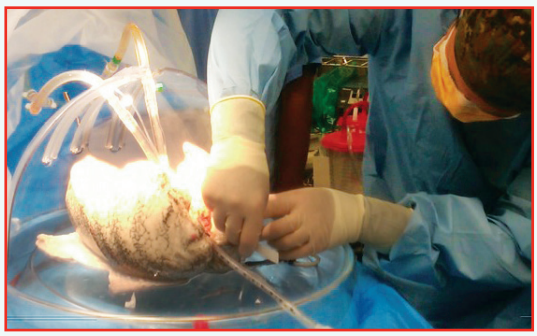
Idiopathic Pulmonary Fibrosis: What We Know and What We Need to Know *(continued from page 4)*

diseases, and improve the quality of life and survival for these patients. Today it is the only lung transplant program in the tri-state area and it is ranked fifth in the country in terms of volume. Survival rates are significantly above the national averages, with one-year survival exceeding 90 percent, a five-year survival at 65 percent, and a 10-year survival rate exceeding 40 percent.



A set of donor lungs during ex vivo *assessment and conditioning in preparation for transplantation.*

"Lung transplantation has become a viable final treatment pathway for many advanced lung diseases," says Dr. Arcasoy. "We're able to support and transplant much sicker patients now as compared to 10 years ago, and one of our main interests and expertise is to provide minimally invasive support for oxygenation and carbon dioxide removal in critically ill patients with respiratory failure using a system called Extracorporeal Membrane Oxygenation (ECMO) led by Dr. Matthew Bacchetta. With utilization of this system in some patients who are listed for lung transplantation, patients are able to ambulate, speak, and eat while awaiting availability of lungs in the hospital, whereas in the past, these patients would have to be heavily sedated, immobilized, kept on a mechanical ventilator, and fed with nasogastric tubes and quickly lost their eligibility to undergo lung transplantation.

"We are also investigating the value of new prognostic markers to determine the optimum timing of listing for lung transplantation," adds Dr. Arcasoy. To facilitate these decisions, Drs. Arcasoy and Lederer continue to pursue prognostic markers for patients with IPF that would help in the prioritization of patients for lung transplantation. In a recent study, they looked at titrated oxygen requirement (TOR) – a common bedside measure of gas exchange – to determine whether it predicted mortality in idiopathic pulmonary fibrosis. "We found that a higher TOR was associated with a greater mortality rate independent of forced vital capacity and six-minute walk test results and at least as accurate as pulmonary function and six-minute walk testing at predicting one-year mortality," says Dr. Lederer. "These findings were similar in other interstitial lung diseases."

Dr. Arcasoy notes that their program is doing its best to transplant as many patients as needed, but a shortage of donor organs makes this a challenge. To help address this issue, Dr. Arcasoy's surgical team is now participating in an FDA novel trial to evaluate *Ex Vivo* Lung Perfusion (EVLP), led by the Program's Surgical Director Frank D'Ovidio, MD, PhD. "Essentially, this is a system to assess and rejuvenate lungs that normally would not be used for transplantation according to standard criteria," explains Dr. Arcasoy. "The donor lungs are placed in a sterile container system on a ventilator, warmed to normal body temperature, flushed of donor blood, inflammatory cells, and potentially harmful biologic factors, and treated with antibiotics and anti-inflammatory agents. We assess the lungs over the course of four hours to see if they are viable based on multiple measurements of oxygen levels, lung compliance, pulmonary vascular resistance, and other physiologic factors."

While the immediate goal of EVLP is to increase the pool of available donor lungs that are suitable for transplantation, says Dr. Arcasoy, it also may serve as a platform to study various experimental therapies. "For example, we'd like to manipulate these lungs in this platform to be genetically and immunologically more tolerable to the recipient. We would like to be able to alter the immune system in the lung(s), or decrease the inflammatory response to the lung(s), so that when we transplant them the patient has a better outcome." Since the initiation of the FDA trial, the lung transplant team at NewYork-Presbyterian/Columbia has evaluated 12 sets of lungs and has been able to perform eight transplants that would not have been possible without EVLP. At one-year post-transplant, all of the patients are doing well with outcomes equivalent to those who received lungs that had not been subject to EVLP.

The Need for Tertiary Care

Idiopathic pulmonary fibrosis still provokes more questions than answers. What is known is that a delay in making a correct diagnosis can lead to ineffective, or even harmful, treatments, according to a study conducted by Drs. Lederer, Arcasoy, and their colleagues. The research team followed 129 IPF patients at NewYork-Presbyterian/Columbia. "We looked at the length of time from the onset of shortness of breath to the first visit to the medical center," says Dr. Lederer. "A longer delay was associated with increased risk of death, independent of age, gender, lung capacity, disease severity, and other factors.

"The initial symptoms of IPF are subtle, and accurate diagnosis may not be feasible for community-based pulmonologists," says Dr. Lederer. "Also, doctors sometimes still treat IPF with steroids because the disease is thought to have an inflammatory component. Now scientists know that steroids are counterproductive. A delay in diagnosis can also delay evaluation for a lung transplant. For these reasons, the recognition, or even suspicion, of IPF should prompt referral to a tertiary care center."

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