A Closer Look at CTEPH: Catching the Patients Who Slip Through the Cracks

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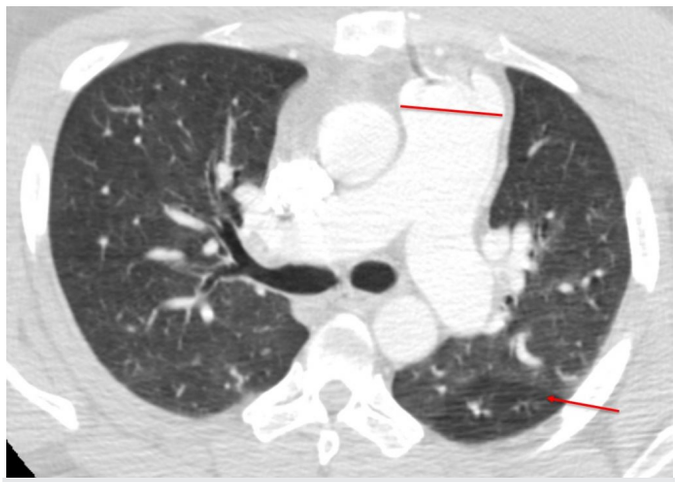
Each year, between 500 and 2,500 Americans are diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH).1 However, according to Dr. Zeenat Safdar, M.D., Director of Clinical Research and Pulmonary Hypertension Program at the Houston Methodist Hospital Lung Center, those numbers may just be the tip of the iceberg. Despite the disease's high mortality rate and high healthcare costs, CTEPH still remains perilously under-recognized and underdiagnosed. In a review article published in the *Methodist DeBakey Cardiovascular Journal*, Sarah Medrek, M.D., and Safdar discuss the epidemiology and pathophysiology of CTEPH. Their hope is to raise awareness and understanding of the disease so that fewer patients fall through the cracks.

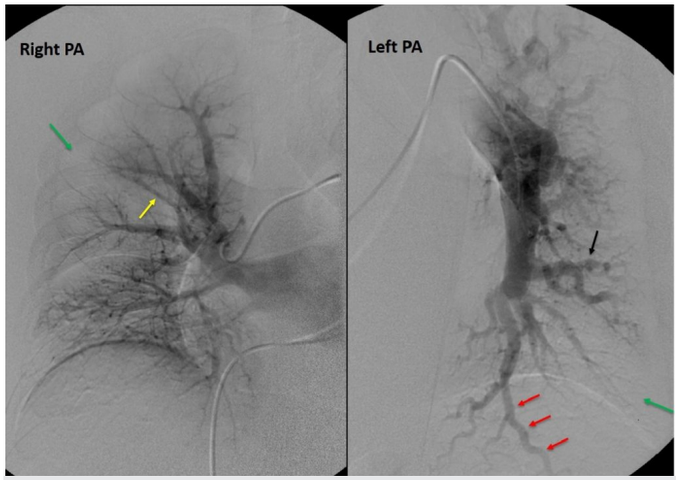
CTEPH occurs when thromboembolic clots develop in the lungs' vasculature and stabilize, thus increasing pulmonary arterial pressure and causing pulmonary hypertension (PH). Unlike acute clots, which can be broken down and resolved with blood thinners, CTEPH clots are progressive; they develop one after another, spreading throughout the pulmonary vasculature. Over time, the clots organize, becoming fibrinous lesions that actually integrate into the vessel walls. As the lesions proliferate, they block off blood flow through the lungs, cutting off critical pathways to replenish oxygen in the blood supply. This is why one of the major symptoms of CTEPH is shortage of breath. The heart's right ventricle has to work harder to pump enough blood through the narrowed vessels. Without treatment, the strain eventually becomes too much for the heart to bear, and patients succumb to right heart failure.

Most, but not all, CTEPH patients develop the disease after pulmonary embolism (PE). Although the precise percentage of PE patients that go on to develop CTEPH is unknown, various studies put the number somewhere between 0.4% and 4.8%. However, Safdar is skeptical about those numbers, and like most CTEPH experts, believes the actual incidence to be significantly higher. "If you look at international data, there's no consensus. The numbers are all over the place, so we really don't know the true incidence," she says.

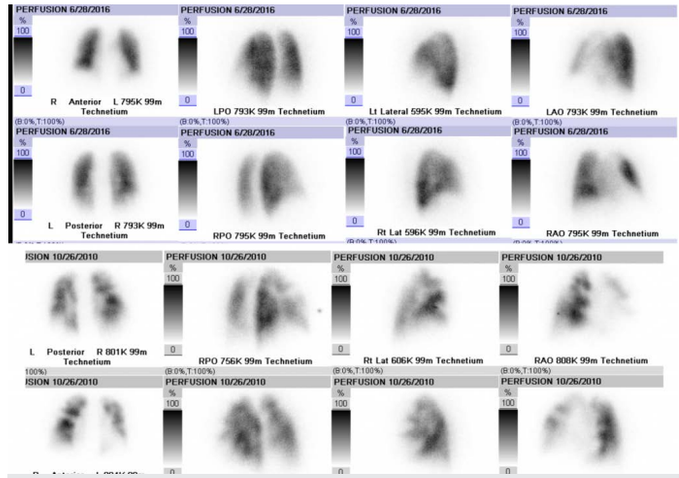
One of the problems with collecting accurate CTEPH epidemiological data is that the studies are, by necessity, retrospective. Since CTEPH symptoms are non-specific (see "From risk factors to treatment: What to do when you suspect CTEPH"), the disease is commonly mistaken for other forms of PH, COPD, or asthma. Thus, retrospective studies don't account for all the patients that are misdiagnosed. Although prospective studies may be more accurate, they're not feasible with such an uncommon disorder. "Very few patients with acute PE go on to develop CTEPH," explains Safdar. "So if you were to follow thousands and thousands of patients in the hope that a very small percent develop the disease, it would not be cost effective. However, the current retrospective studies are almost hit and miss."



This CT scan of a CTEPH patient's chest shows the enlarged pulmonary artery (red line) and the mosaic perfusion of the lung parenchyma (red arrow).



A CTEPH patient's pulmonary angiogram shows how the disease may affect the pulmonary artery (PA). These images show narrowing of PA branches (yellow arrow), decreased perfusion (green arrows), post-stenotic narrowing (yellow arrow), and vessel cutoffs (red arrows).



V/Q scans are the best diagnostic test for CTEPH. Note the patchy perfusion defects (black arrows) in the scan of the patient with CTEPH (top) compared to the homogenous appearance of the lungs in the scan of a patient without CTEPH (bottom).

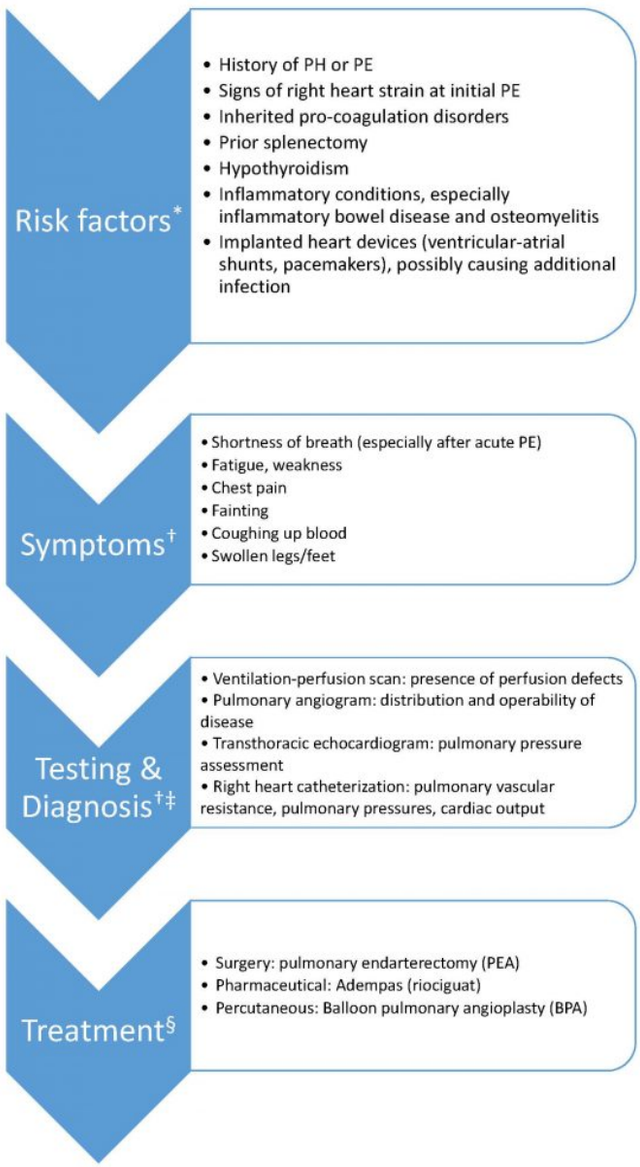
Misdiagnosis and lack of awareness of CTEPH is a systemic problem affecting multiple layers of the medical community. A CTEPH patient complaining of shortness of breath is likely to have normal workups in primary care through the emergency room because typical tests—x-rays, electrocardiograms (EKG), blood work, and listening to the heart and lungs—don't reveal the subtle signs of CTEPH. According to Safdar, one of the main problems is underutilizing a specialized imaging technique.

"If a patient comes into the ER saying he's short of breath, the most common things doctors will suspect are heart attack or heart failure, or maybe an acute clot or acute PE. But they will rule all this out with routine testing," she explains. "But what they don't realize is that the symptoms could be from a chronic process. For that you have to do both a CTA and a specialized test called a ventilation-perfusion (V/Q) scan. That scan is not part of a routine workup for shortness of breath, and because it's not done regularly, CTEPH is missed."

Another barrier to diagnosis is loss to follow up for acute PE patients. If a patient goes on to develop CTEPH, it generally occurs within two years of the original PE. However, convincing patients to come back to their doctor for repeat EKGs months to years after PE treatment is an uphill battle. Moreover, current guidelines do not suggest routine screening for PE patients, and only about half of these patients return for a follow-up EKG. "The current recommendation for unprovoked PEs—meaning a patient had a PE with no chronic cause or pro-coagulant condition—is to prescribe anticoagulants for six months and then stop. It's a reasonable guideline, but the problem is that there's no recommendation to reimage at six months or one year," says Safdar. Given the two-year window, Safdar believes that waiting longer for reimaging gives physicians a better chance at catching CTEPH patients. Most importantly, she says, any patient who has had an acute PE and goes on to develop shortness of breath should be immediately evaluated for CTEPH.

The great tragedy of under-diagnosis is that CTEPH is a treatable—even curable—condition. The best option is a surgery called pulmonary endarterectomy (PEA), or pulmonary thromboendarterectomy, wherein surgeons perform an open-chest operation to physically remove the clots from the pulmonary veins. For many patients, PEA can completely cure CTEPH. According to Safdar, improvements in PEA technique now allow surgeons to reach more distal clots than ever before. However, some clots are in such small, distal veins that surgery is not an option. For inoperable, persistent, or recurrent CTEPH, the FDA recently approved the first ever medical treatment for CTEPH, a drug called Adempas (riociguat). Although the medicine helps manage CTEPH symptoms and improve quality of life, it is not curative. Another nonsurgical option has recently made its way to the United States from Japan; balloon pulmonary angioplasty (BPA) is a catheter-based treatment used to expand blocked vessels. However, BPA runs the risk of reperfusion injury similar to that seen in open-chest surgery, so it's not the best option for everyone.

Despite the grim outlook for today's undiagnosed CTEPH patients, Safdar is optimistic that increasing awareness and documentation will help identify and treat more patients. One exciting development is a new national CTEPH registry that will help collect more accurate data on the incidence, treatments,



From risk factors to treatment: What to do when you suspect CTEPH.
* Adapted from "Table 1: Clinical risk factors for CTEPH" in: Medrek S, Safdar Z. Epidemiology and pathophysiology of CTEPH: Risk factors and mechanisms. MDCVJ;2016:195-198
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‡ Renapurkar. Emerging Techniques in Evaluation of Chronic Thromboembolic Pulmonary Hypertension (CTEPH). http://thoracicrad.org/meetings/2015/Syllabus/STR_Meeting/materials/sunday/415.pdf.
§ Interview with Dr. Zeenat Safdar. July 26, 2016.

progression, and outcomes of the disease. In addition, researchers have developed a clinical risk predictive score to evaluate PE patients at risk for CTEPH; although the score still needs to be validated by further studies, Safdar is hopeful that a similar tool could soon be available in physician offices and emergency rooms to help doctors identify high-risk individuals.

However, the key to saving lives is convincing physicians to refer patients to CTEPH programs. Right now there are only a handful across the United States, but they're the only places equipped to handle PEA surgery. CTEPH diagnosis and treatments are complex, requiring a skilled multidisciplinary team of pulmonologists, cardiologists, interventional radiologists, and surgeons to develop the best treatment plan for each individual.

"Every CTEPH patient should have a surgical evaluation. However, I should not be the only one deciding whether a patient gets surgery or not. It should be a multidisciplinary team," Safdar asserts. "Patients with suspected CTEPH need to be sent to a specialized CTEPH center. If you don't, you're doing a disservice to the patient."

Conflict of Interest Disclosure:
Laura Gerik is assistant managing editor at the *Methodist DeBakey Cardiovascular Journal*.

REFERENCES

1. CTEPH Basics. http://hcp.cteph.com/basics/. Updated February 2016. Accessed August 8, 2016.