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

Laura Gerik, MS

HOUSTON METHODIST DEBAKEY HEART & VASCULAR CENTER, HOUSTON, TEXAS

"Excerpta" columns are editorials to supplement reviews in each journal issue with author interviews and a look at the practical aspects of the science reviewed in the Journal. Any opinions stated are the author's own. Quotations reflect the ideas of the persons interviewed and do not represent their respective institutions.

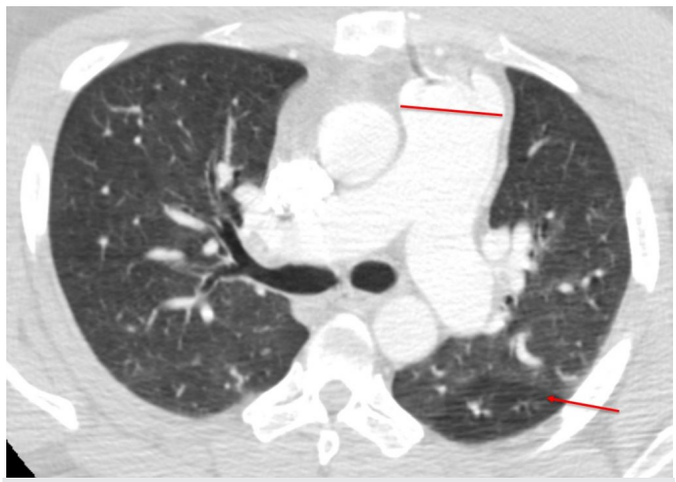
Published online March 10, 2017; Updated June 13, 2021

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.

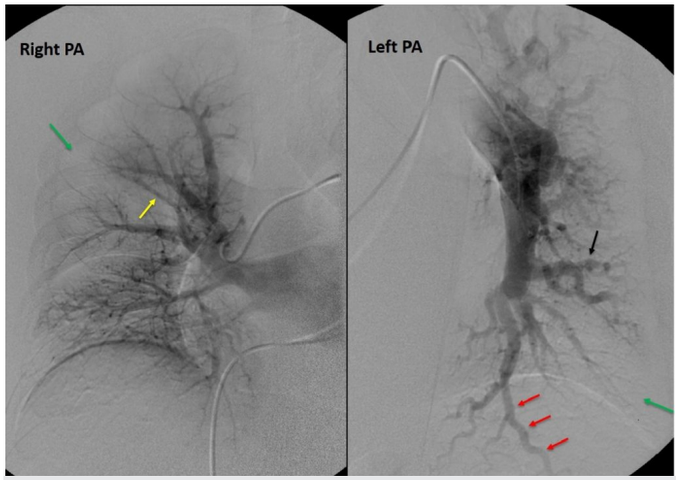
CTEPH occurs when thromboembolic clots develop in the lungs' vasculature and stabilize, thus increasing pulmonary arterial pressure and causing pulmonary hypertension (PH). Unlike acute clots, which can be broken down and resolved with blood thinners, CTEPH clots are progressive; they develop one after 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.

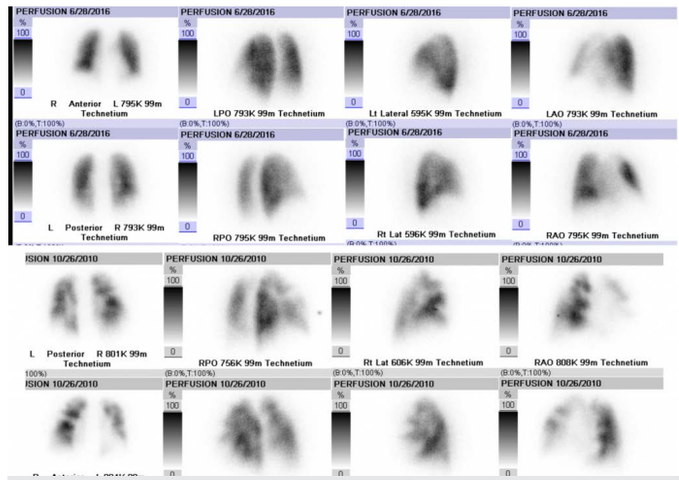
One of the problems with collecting accurate CTEPH epidemiological data is that the studies are, by necessity, retrospective. Since CTEPH symptoms are non-specific (see "From risk factors to treatment: What to do when you suspect CTEPH"), the disease is commonly mistaken for other forms of PH, COPD, 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.

òIf a patient comes into the ER saying heôs 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,ó she explains. òBut what they donôt 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 itôs not done regularly, CTEPH is missed.ó

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. òThe current recommendation for unprovoked PEsñmeaning a patient had a PE with no chronic cause or pro-coagulant conditionñis to prescribe anticoagulants for six months and then stop. Itôs a reasonable guideline, but the problem is that thereôs no recommendation to reimage at six months or one year,ó 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 treatableñeven curableñcondition. 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 itôs not the best option for everyone.

UNTAPPED POTENTIAL

Nanopatterning stents is merely the tip of the iceberg when it comes to using nanotechnology in cardiovascular medicine. The really thrilling technologies—those that are making science fiction a reality—involve using nanoparticles to mimic or deliver drugs to target specific cells. Such advances could revolutionize the way we treat cardiovascular diseases. However, nanostructured stents are a critical jumping-off point to reach the much broader future of nanomedicine.

The FDA divides nanotechnology into two areas: nanostructured surfaces (those discussed in Webster's article) and nanoparticles. Webster serves on an FDA nanotechnology task force that advises the agency on how to regulate nanomedicine. He explains, "There are two different pathways to commercializing cardiovascular nanomedicine. Nanostructuring current devices is a much faster pathway to FDA approval because we're not changing the chemistry of stents; we're just altering the surface texture. In the nanoparticle area, we're much farther away from approval because we'll have to demonstrate toxicity and biodistribution of where those particles go over time. There are a lot more questions with nanoparticles."

Webster is part of a project that already has a nanopatterned stent under FDA review. Clinicians may not have to wait long for nanopatterned stents to hit the market. In fact, Webster estimates that such stents could be available within a year, although nanoparticle technologies are probably five to ten years away from approval.

In the short-term, Webster hopes that the immediate success of nanopatterned stents will not only help current patients, but also bring nanomedicine into the mainstream. Nanotechnology is already used in oncology and orthopedics, but it is far from reaching its full potential in cardiovascular medicine.

So what kind of future might nanomedicine bring? Webster imagines a time when we move away from stents altogether, or instead use stents as vehicles to deliver nanoparticles to the site of vascular injury. Nanoparticles are so small that the immune system doesn't recognize them. Therefore, it's possible to put drugs into nanoparticles so that the compounds last longer in the circulatory system and target specific tumors or plaques. Theoretically, physicians could use much smaller concentrations of pharmaceuticals to achieve the desired result.

Drug-mimicking nanoparticles are being developed to treat a disease or injury without the drugs' negative side effects. Similarly, nanoparticles could replace certain risky procedures. For instance, researchers are developing nanoparticles that target atherosclerotic plaque and break it up using heat. "Then you don't have to put a catheter inside a patient or do anything invasive. You just send the nanoparticle into that plaque, heat it up via infrared excitation, and then the particle will destroy the plaque and return blood flow," explains Webster.

Other nanoparticles are being used to target cells, even specific organelles within cells. "It's like an arcade game," Webster says. "You can turn off or on certain parts of a cell with those nanoparticles. You can deliver drugs to the nucleus or the mitochondria. We could have the ability to use nanoparticles to get an exact response from a cell, which is incredibly powerful."

Powerful, indeed. These unimaginably tiny particles and structures may be the future of cardiovascular medicine, a future that's much closer than many of us may have imagined. Nanopatterning stents could soon transform the way we manage atherosclerosis and restenosis. Even more importantly, these stents could usher in a nanotechnology revolution.

At least, that's how Webster sees it: "Stents can provide the success story to encourage more people to look at nanomedicine in the cardiology. Right now, nanotechnology is an untapped resource in the cardiovascular sector, so there's incredible promise for using this new size scale in treating cardiovascular disease."

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

REFERENCES

1. Coronary angioplasty and stents. Central New York Cardiology Web site. http://www.cnycardiology.com/coronary-angioplasty-and-stents.html. Copyright 2012. Accessed July 29, 2016.
2. Mozaffarian D, Benjamin EJ, Go AS. Heart disease and stroke statistics—2016 update. Circulation. 2015;CIR.0000000000000350:e1-e323. doi: 10.1161/CIR.0000000000000350.
3. Dangas GD, Claessen BE, Caixeta A. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol. 2010;56(23):1897-1907.
4. Teirstein PS. Drug-eluting stents restenosis: An uncommon yet pervasive problem. Circulation. 2010;122:5-7.