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The Diagnosis and Treatment of Pulmonary Embolism

A Metaphor for Medicine in the Evidence-Based Medicine Era

Vinay Prasad, MD; Jason Rho, MD; Adam Cifu, MD

Background: The history of pulmonary embolism (PE) provides a fascinating portrait of a well-established diagnosis and standard of care treatment moving into the age of evidence-based medicine.

Methods: We examined the history of PE and the practice of treating PE with anticoagulation.

Results: Pulmonary embolism is a diagnostic category whose definition and treatment have both changed in the past century. Initially, PE was recognizable only when massive, with the signs and symptoms of right heart failure. Anticoagulants were established as the cornerstone of PE management with a single randomized controlled trial of 35 patients in 1960 and based on commonsense pathophysiologic reasoning. Since then, the diagnostic category of PE has been broadened, and the advent of computed tomography pulmonary angiography has yielded nearly a doubling of the incidence of the disease, with-

out a concordant decrease in mortality. Although anticoagulation remains the cornerstone of management, open questions remain: what end points are altered by anticoagulation? What is the number needed to treat?

Conclusions: Trials of newer anticoagulants and longer durations of anticoagulation have not yielded real improvements over heparin, inviting doubts regarding its efficacy. Thus, PE is the quintessential diagnosis of medicine not because it represents our greatest success, but because it captures all the complexity of medicine in the evidence-based era. It may serve as a metaphor for many other conditions in medicine, including coronary artery disease. New trials in the field continue to test trivialities, whereas fundamental questions are unanswered.

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AN ONGOING TRIAL¹ EVALUATING whether withholding anticoagulation is safe among patients with subsegmental pulmonary embolism (PE) has reignited fundamental questions concerning the diagnosis and treatment of this condition. Pulmonary embolism may very well be the quintessential diagnosis of medicine. Taught early in medical school as a “can’t miss” diagnosis, PE is discussed daily in the care of hospitalized

managed similarly. Our practice of treating PE with anticoagulation arose from commonsense pathophysiologic reasoning, supported by small studies of clinically apparent disease. For years, we have extended treatment to patients whose conditions would have been unrecognizable initially. As such, PE is analogous to many conditions in medicine. It is a diagnostic category, which has been broadened by technology. Its treatment, a well-established standard of care, is based on scare data. Finally, the most fundamental questions regarding the condition remain unanswered.

Pulmonary embolism has 2 histories. The first is the familiar one. Pulmonary embolism was once nearly universally fatal (mortality estimates ranged from 30%-80%^{2,3}) and only reliably diagnosed after death. The medical profession lacked effective therapies, and the diagnosis was based on the most insensitive physical examination signs (such as those of right heart failure). In the early part of the 20th century, effective therapies (heparin and

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patients and is the subject of countless articles and research studies. Despite this, there are striking gaps in our knowledge. What evidence supports anticoagulation? Are all PEs equally concerning? What is the number needed to treat (with anticoagulation) to prevent recurrence or death? Although it is a heterogeneous disease, ranging from saddle to subsegmental, all PEs are

Author Affiliations: Departments of Medicine, Northwestern Memorial Hospital, Northwestern University (Drs Prasad and Rho), and University of Chicago Medical Center, University of Chicago (Dr Cifu), Chicago, Illinois.

warfarin sodium) were pioneered, and scores of patients were treated. Mortality rates of patients receiving treatment markedly decreased.³ In the latter half of the century, diagnostic techniques improved. First, ventilation perfusion scans⁴ and then computed tomography pulmonary angiography (CTPA) allowed us to detect PE reliably and noninvasively. Risk-scoring algorithms stratified patients who presented with symptoms suggestive of PE, improving our estimates of the disease probability and, thus, our diagnostic accuracy. Most recently, more acceptable and possibly safer anticoagulants have been developed. Pulmonary embolism is a success story of modern medicine.

The second history is more unsettling. Pulmonary embolism was once a feared and difficult diagnosis made on clinical grounds (physical examination, chest radiography, and electrocardiography) and often only discovered after death. In the 1930s, the first case series reported a reduced mortality rate (compared with historical controls) with the use of anticoagulation. Nevertheless, practitioners were reluctant to embrace the new therapies.⁵ Reports of hemorrhage and conflicting results regarding the efficacy of anticoagulation⁶ were cause for caution. A small randomized controlled trial⁵ of 35 patients with suspected PE was conducted to assess the benefit of anticoagulation. The study used physical examination, chest radiography, and electrocardiography alone to diagnose PE. The authors then compared 16 patients who received anticoagulation with 19 patients who did not. There was 1 death in the treatment group compared with 5 in the placebo group. The trial sponsors reported that all 5 deaths in the control arm were secondary to PE, although at least 3 of the patients had comorbid diagnoses (widely metastatic cancer, concomitant pneumonia, and left atrial thrombus), any of which could have been the proximate cause of death. The 1 death in the treatment arm was noted as unrelated to PE; however, anticoagulation may have contributed because the patient died of a gastrointestinal hemorrhage. By modern standards, a trial with this sample size, doubts regarding the comparability of the intervention and control groups, and poor adjudication of outcomes would be considered inconclusive, if ever published.

Nevertheless, anticoagulation became standard of care in the treatment of PE based not only on the data but also on the rational belief that anticoagulation would benefit a disease of thrombosis. The success of the therapy was supported by mortality rates that decreased from 30% (in the era before anticoagulation) to less than 3% (with anticoagulation).³ This success was probably overrated because the PEs being treated had changed from those diagnosed based on clinical findings to those diagnosed radiographically. Only significant hemodynamic events become manifest on examination, so the former is a more serious PE. Not only was our treatment of the disease changing, but also the disease itself was changing.

One could argue that, although based on poor data derived in a population distinct from that being treated, the treatment of PE in the 1990s was reasonable. However, what has happened in the past 10 to 15 years, with the advent of CTPA, has brought us farther from a proven therapeutic base. The Prospective Investigation of Pul-

monary Embolism Diagnosis II study⁷ showed that CTPA was inferior to pulmonary angiography, with a sensitivity and specificity of 83% and 96%, respectively. However, the noninvasive modality was most strongly supported in the 2006 study⁷ showing that patients with a negative CTPA result who were not treated with anticoagulation had only a 1.3% three-month incidence of venous thromboembolism (VTE), a composite of deep vein thrombosis (DVT) and PE. Such a low event rate was thought to be acceptable and not much different than the risks of anticoagulation.

The story of PE since the advent of CTPA is surely a story of overdiagnosis. Wiener et al⁸ tracked the incidence, mortality, and treatment complications of PE in the Nationwide In-patient Sample and Multiple Cause-of-Death databases. In the era before CTPA (1993-1998), the incidence of PE was stable at 62.1 per 100 000 population, and the PE death rate decreased from 13.4 to 12.3 per 100 000 population. After the advent of CTPA (1998-2006), the incidence of PE increased from 62.1 to 112.3 per 100 000 population, and the mortality rate continued its downtrend trend from 12.3 to 11.9 per 100 000 population. Complications (gastrointestinal hemorrhage, intracranial hemorrhage, and secondary thrombocytopenia) from anticoagulation increased from 3.1 to 5.3 per 100 000 population in the period of CTPA. In addition, as the technology of our computed tomography scanners advances, the detection rates of smaller, subsegmental PEs have increased.⁹

Told this way, the story of PE is ambiguous, a disease that is evolving. Once only diagnosed if massive, progressively smaller PEs are now being found. Anticoagulation, the cornerstone of therapy, has never convincingly been shown to be better than placebo with respect to morbidity or mortality. The fact that death rates remain stable whereas incidence has nearly doubled suggests that nearly half of the patients diagnosed as having PE experience only the risks of therapy without the benefit. With no reliable data for a number needed to treat to save a life, has the modern PE become a disease of our making?

As a general principle, there is an indirect way of demonstrating that a treatment is better than placebo in cases such as this, where original studies are lacking. If anticoagulation is clinically beneficial in PE, we might suppose that more reliable or longer anticoagulation would be better than shorter courses. For instance, with myocardial infarction, although we have several trials showing that heparin is superior to placebo, we also have another showing that fondaparinux sodium improves hard outcomes when compared with unfractionated heparin.¹⁰ Surprisingly, similar comparisons have yielded negative results in the PE literature. Although the drug was associated with a lower 3-month recurrence rate for VTE (with a number needed to treat of 81), that end point was driven by future nonfatal PE and DVT and not fatal PE (unchanged). Low-molecular-weight heparins have similarly failed to confer mortality benefit beyond unfractionated heparin.¹¹ Several studies¹²⁻¹⁵ have shown low-molecular-weight heparin to be no worse than heparin with respect to morbidity and mortality, and some have even shown lower rates of bleeding, but this finding does

not represent a benefit but rather a greater harm of heparin.

With respect to duration of therapy, several studies^{16,17} have shown 6 months of anticoagulation to be no better than 3 months. In addition, all face the question of whether longer duration simply delays events. Longer courses of anticoagulation not only have to show fewer events than shorter ones, but longer courses also must show that events do not subsequently catch up when anticoagulation therapy is ultimately discontinued. This concern has been shown to be real in the DVT literature,¹⁸ where duration seems only to postpone VTE. Delaying thromboembolic events while exposing patients to the harms of anticoagulation is not a real benefit. Accordingly, we might question the appropriateness of recurrent DVT and future nonfatal PE as end points in trials of PE, as opposed to mortality, symptomatic relief, and diminished long-term complications (such as pulmonary hypertension¹⁹). The worst-case scenario (and still compatible with the existing evidence) is that the diagnosis of PE merely identifies a subgroup of patients at high risk of VTE. Anticoagulation then may be only secondary prevention and not aid in PE resolution or death. Worse, the cessation of anticoagulation might be followed by catch-up events. This is particularly worrisome because most trial sponsors do not observe patients for months after the discontinuation of anticoagulation. Likely this should be done in all studies that use the end point of recurrent DVT or nonfatal PE.

Arguing that PE or DVT should not be treated is extreme, and yet the considerations we have highlighted frame the mystery of PE. Does anticoagulation benefit patients with PE? Does it depend on the PE? Probably the answer to both questions is yes. Anticoagulation may benefit large or proximal PE, although we have no idea to what degree or even which end points are altered. In addition, for some PEs, the harms of anticoagulation likely outweigh the benefits. Already there are hints of this. One small study²⁰ screened for silent PE among patients with DVT and randomized them to anticoagulation. A large percentage of patients with DVT had silent PE (46% by ventilation/perfusion scan), and anticoagulation for these patients did not decrease mortality rates or aid resolution of PE on serial ventilation/perfusion scans.

Pulmonary embolism is indeed the quintessential diagnosis of medicine. Not because it represents a great success, but because it captures all the complexity of medicine in the evidence-based era. The diagnostic category of PE has been expanded by advances in technology, and although there have been countless trials for this condition, the most fundamental questions remained unanswered. Revascularization for stable coronary artery disease is a similar story. Early trials established the benefit of coronary artery bypass grafting among the patients with the worst disease (proximal left and 3 vessel). Technology affected the diagnosis and treatment of the disease. Advances in noninvasive detection led to more patients being diagnosed as having coronary artery disease, and the ability to revascularize percutaneously increased treatment. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial in part shattered this paradigm by showing that omitting stents is safe for many patients with stable disease.²¹ Now future

trials are desperately needed to examine still untested areas of revascularization.

Elsewhere,²² we argue that trial funding should move away from industry-sponsored studies and toward a model where funds are pooled into a central and impartial agency that decides what trials to administer. When it comes to PE, the necessity of this proposal is evident. Industry-sponsored studies continue to test trivialities—is my novel oral anticoagulant noninferior to heparin and warfarin? Instead, fundamental questions must first be answered. Which patients with VTE benefit from anticoagulation at all? There is no incentive for companies to test scientific questions, which may only diminish market demand. It is more important to demonstrate that a treatment benefits a patient than it is to demonstrate that one medication is equivalent to another if neither improves health. Future studies examining whether anticoagulation benefits patients with subsegmental PEs (clinicaltrials.gov identifier NCT01455818) will help elucidate which of these pertinent questions need to be addressed first because the paradigm for approaching and treating PEs may be shifting.

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Correspondence: Adam Cifu, MD, University of Chicago Medical Center, University of Chicago, 5841 S Maryland Ave, Chicago, IL 60637 (adamcifu@uchicago.edu).

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