

Pulmonary Embolism: An International Crisis

BY AARON S. WEINBERG, MD; MICHAEL R. JAFF, DO; AND VICTOR F. TAPSON, MD

Venous thromboembolic disease (VTE) is a worldwide crisis. There are over 10 million cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) diagnosed globally per year, with 1 million cases occurring in the United States and over 700,000 in France, Italy, Germany, Spain, Sweden, and the United Kingdom combined each year.¹⁻³ In 2008, the rates of VTE were so alarming that the United States' Surgeon General declared a formal call to action.^{4,5} In China, the incidence of acute PE tripled from 3.9 per 100,000 in 2000 to 11.7 per 100,000 in 2010 to 2011, and we expect this absolute number to continue to climb as China's population has risen to over 1.4 billion people, representing 18.5% of the world's total population.^{6,7} Whether this rise is due to an absolute increase versus an increased recognition of the disease is unclear. From 2007 to 2016, the rates of VTE-related hospitalization in China increased from 3.2 to 17.5 per 100,000 population.⁸ Thus, acute PE is a major health concern around the world.

Many predisposing risk factors for VTE are also on the rise, which will contribute to the future incidence of the disease. The world is becoming more sedentary and overweight, with one in three Americans (over 93 million adults) considered obese.⁹ The incidence and prevalence of cancer, trauma, surgery, and oral contraceptive/hormonal therapy use, as well as international travel (over 4 billion airline passengers in 2017), is also increasing, which will add to the overall risk of VTE.¹⁰⁻¹⁵ At least 60% of VTE cases occur during or right after hospitalization, making many cases potentially preventable causes of hospital-related death.² This also portends a large future health care expenditure, with the United Kingdom and United States already spending £640 million and \$15.5 billion per year, respectively, for the diagnosis and treatment of VTE.^{16,17}

DVT and PE are part of the same continuum of disease, with over 95% of emboli originating in the lower extremities.¹⁸ When PE occurs, the severity depends on the embolic burden and its effect on the right ventricle as well as underlying cardiopulmonary comorbidities. Death can result from the acute increase in pulmonary artery pressure with increased right ventricular (RV) afterload and dysfunction. The direct obstruction of the pulmonary vasculature as well as vasoconstriction from the release of localized hypoxic and acidotic mediators causes impaired RV contractility as well as increased RV myocardial oxygen consumption and RV ischemia. The reduced RV contractility eventually impacts left-sided filling, causing decreased left ventricular (LV) preload and decreased cardiac output. Anatomically, the

myocardial fibers of the heart encompass both the right and left ventricles and this ventricular interdependence results in decreased LV and RV output. This process can eventually lead to cardiogenic shock and death.¹⁹⁻²¹

PE therefore poses a serious mortality threat. There are over 100,000 PE-related deaths in the United States per year, and 544,000 VTE-related deaths in Europe annually.^{5,22} This translates to approximately one person dying of PE every 6 minutes in the United States and every 15 seconds elsewhere around the world. PE is the third-leading cause of cardiovascular death behind coronary artery disease and stroke, with a 30% 30-day mortality rate if untreated, and 11% of patients die within the first hour of presentation to the hospital.²³

Unfortunately, diagnosing PE can be a serious clinical challenge, and based on autopsy data, patients who die from acute PE are most commonly not diagnosed or even suspected until they are already dead.²⁴ A study of 1,032 patients autopsied patients found 231 cases of PE but with premortem clinical suspicion in only 18%.²⁵ Some of the difficulty in diagnosis stems from the nonspecific signs and symptoms of the disease, with the most common being dyspnea (73%), chest pain (44%), tachypnea (54%), and tachycardia (24%).¹⁸ These findings can be easily mistaken for other conditions, and we have too often seen patients worked up for nephrolithiasis due to flank pain, palpable intercostal tenderness attributed to a musculoskeletal injury, or cardiac catheterization undertaken only to discover later that their symptoms and troponin elevation were, in fact, due to acute PE. Recently, a jury awarded a family \$40 million after their college student died of PE after being sent home from the emergency department with a "viral illness," highlighting the tragic nature and medical legal ramifications of this difficult diagnostic conundrum.²⁶

There are also long-term comorbidities and consequences that arise with VTE. Approximately 20% to 30% of patients with DVT develop postthrombotic syndrome, 1% to 3% of patients with acute PE develop chronic thromboembolic pulmonary hypertension, up to 50% may have exercise limitation, and 33% with DVT/PE will have recurrence within 10 years.²⁷⁻²⁹

There is also a crisis in terms of finding the optimal way to risk stratify and treat these patients. The clinical classification of the severity of acute PE is generally based on the estimated early mortality risk defined by in-hospital or 30-day mortality. Patients are generally risk stratified as high risk (massive), low risk, and intermediate risk (submassive). The most recent European Society of Cardiology guidelines have further

risk stratified these patients into intermediate-low and intermediate-high risk categories.³⁰ This system helps to guide clinical decision-making; however, it is imperfect and neglects certain clinical considerations such as residual proximal lower extremity DVT, degree of pulmonary obstruction index, clot-in-transit, severity of the RV dysfunction, and extent of hemodynamic changes. Decisions in clinical practice cannot be made by, for example, simply distinguishing intermediate-low-risk and intermediate-high-risk patients. In addition, there is now a plethora of treatment options, including multiple percutaneous clot extraction devices, varying doses of systemic and catheter-directed thrombolytic protocols, surgical techniques, different anticoagulants, as well as reduced-dose/prophylactic long-term anticoagulant regimens in the appropriate patients.³¹⁻³⁴

Pulmonary embolism response teams (PERTs) have emerged at hospitals around the world to help navigate this challenging international crisis. A PERT is a multidisciplinary team, analogous to a code stroke or myocardial infarction team, that rapidly evaluates a patient and their risks, formulates a patient-specific treatment plan, and coordinates/mobilizes necessary resources to provide the highest level of care.³⁵ Many PERTs have now also expanded to the outpatient setting through the creation of clinics that specialize in long-term VTE care. The PERT Consortium™ organization has developed into an international thought leader for the guidance and influence of PE care, education, and research.³⁶

Elevating a disease to the level of an international crisis should not be paralyzing but rather should generate recognition and serve as an important call to action. The next few chapters of this treatise will highlight the current state of PE care. Although tremendous strides have been made, more research is needed to improve all facets of PE management, from patient selection and diagnosis to risk stratification and optimal short-/long-term therapeutic modalities to ameliorate both acute and chronic complications of PE. ■

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Aaron S. Weinberg, MD

Assistant Professor of Medicine
Pulmonary Medicine, Critical Care Medicine,
Internal Medicine
VTE Disease & Research
Cedars-Sinai Medical Center
Los Angeles, California
aaron.weinberg@cshs.org
Disclosures: None.

Michael R. Jaff, DO

President, Newton-Wellesley Hospital
Professor of Medicine
Harvard Medical School
Newton, Massachusetts
mjaff@partners.org
Disclosures: Noncompensated advisor for Abbott Vascular, Boston Scientific Corporation; consultant for Medtronic, Philips, Biotronik, Sanofi, Venarum; and equity investor in Embolitech.

Victor F. Tapson, MD

Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Cedars-Sinai Medical Center
Los Angeles, California
victor.tapson@cshs.org
Disclosures: Consultant/advisory board member for Actelion, Arena, Daiichi, BTG Vascular, Inari Medical, Janssen Pharmaceuticals, United Therapeutics; receives speaking honoraria from BTG Vascular and Janssen Pharmaceuticals; receives institutional research funding from Actelion, Arena, Bayer, BMS-Pfizer, Daiichi, BTG Vascular, Inari Medical, Janssen Pharmaceuticals, Penumbra, Reata, United Therapeutics.