Despite nearly 4 decades of creative scientific and clinical scrutiny by physicians and surgeons, worldwide pulmonary thromboembolism remains a dreaded, life-threatening illness.

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Natural History Statistics
Older statistics estimate that in the United States, acute pulmonary thromboembolism afflicts 500 000 to 600 000 persons annually and is either a primary or secondary cause of death in 150 000 to 200 000 of these individuals. Extrapolation of a population-based study from data accumulated in 1985 through 1986 in Worcester, Mass, suggests that each year there are ∼170 000 new cases of clinically recognized venous thromboembolism treated in short-stay hospitals and 99 000 hospitalizations for recurrent disease. When the disease process was followed from the time of clinical recognition, the 1-year mortality rate in a national multicenter project (PIOPED) was reported as ∼25%, with 2.5% dying from pulmonary embolism itself and most patients dying from the major diseases that are associated with pulmonary thromboembolism, including cancer, various infections, cardiovascular diseases, and other pulmonary diseases. Other studies have reported that in patients without preexisting cardiac or pulmonary disease, the 1-year mortality rate ranged from 3% to 9%. If a massive pulmonary embolism occurs associated with systemic hypotension, the in-hospital mortality rate is ∼18%. The persistence of pulmonary hypertension after embolization has been associated with increased mortality rates; the higher the pulmonary artery pressure, the lower the survival rate at 5 years. Furthermore, it has been predicted, with admitted imprecision, that 0.01% of patients develop what is now commonly referred to as chronic pulmonary thromboembolic pulmonary hypertension.

Impediments to Investigation of Natural History
Although these statistics are often reiterated, they likely belie an accurate description of the natural history of the disease. In fact, there are a number of impediments to precise characterization of the incidence and course of the disease: (1) many episodes of acute pulmonary thromboembolism go undetected, perhaps as many as 50%; (2) the clinical presentation mimics the characteristics of a number of other common and uncommon disease entities, resulting in mistaken diagnoses; (3) detection at autopsy requires close inspection of the pulmonary vascular tree to uncover either small acute emboli or the residua of chronic thromboemboli; (4) the sensitivity and specificity of diagnostic tests for the disease remain either weak or poorly defined; and (5) even if recognized correctly, the broad spectrum of anatomic and functional consequences of the disease hinders categorization of patient groups.

Specific Features of Natural History
Specific features of the natural history that have been well established are nevertheless worthy of restatement. Serial pulmonary angiographic and lung scan studies, reported in the late 1960s, revealed that the great majority of acute pulmonary thromboemboli undergo in vivo fibrinolysis (either spontaneous or pharmacologically induced by heparin), mechanical dislodgment within 1 to 21 days of lodgment in the lung vasculature, or both. These salutary processes are associated with a reduction in the degree of pulmonary vascular obstruction, a decrease in right ventricular afterload, and symptomatic improvement. Approximately 15% to 25% of patients, however, show only partial resolution of pulmonary vascular obstruction as revealed by persistent abnormal perfusion patterns on a follow-up lung scan performed 3 to 4 months after the primary embolic event. Such individuals may show dissociation between their lung scan and their clinical state (ie, they are asymptomatic or only mildly symptomatic, whereas ≥1 segmental ventilation/perfusion mismatch continues to be seen on the scan). This observation is undoubtedly testimony to the reserve capacity of the pulmonary vasculature.

The change of the pulmonary artery pressure in a pulmonary embolism is dependent on the morphological and functional integrity of the right ventricle and the relative acuteness of the event. A subacute massive event, that is, one occurring in the presence of antecedent (>2 weeks) obstruction of the pulmonary vascular tree and associated with ≥50% obstruction of the pulmonary vascular tree, is associated with significantly higher elevation of the pulmonary artery pressure than that seen in an initial, acute massive embolism. Presumably, the higher pressure reflects the interplay among the percentage obstruction of the pulmonary vascular bed, the degree of reflex pulmonary arteriolar vasoconstriction, and those hypertrophic and dilatory adapta-
tions of the right ventricle that enable generation of a higher right ventricular pressure.

During a period of months or years, some patients develop progressive cardiorespiratory symptoms and chronic and relatively severe pulmonary hypertension and eventually show progressive right ventricular hypertrophy, dilation, systemic venous hypertension, and a reduced cardiac output at rest or during exercise. As stated, survival in this subgroup of patients is related to the degree of elevation of the pulmonary artery pressure. Progressive clinical decline is observed despite the long-term administration of warfarin anticoagulants. The degree to which persistent pulmonary hypertension is related to inadequate or arrested in vivo thrombolysis, recurrent embolic events, in situ thrombosis around areas of previous emboli, remodeling of clot or clots in large and medium-size vessels, or progressive changes in the pulmonary microvasculature, or all of them, is controversial. Many individuals with persistent pulmonary hypertension relate few, if any, episodes of recurrent thromboembolism. There is some evidence, based on lung biopsy results, that changes in the microvasculature, similar to those seen in congenital or acquired cardiac disease with pulmonary hypertension, account for the progressive clinical decline. Either before or concomitant with these small vessel changes, organization and remodeling of the large vessel clots eventuate in what are now recognized both angiographically and angioscopically as webs, abrupt vascular narrowing by organized membranes (sometimes with sievelike fenestrations), laminated intimal irregularities with or without pitting, and vascular pouches.17–19

Therapeutic Interventions to Change Natural History

Attempts to interrupt the natural history by therapeutic interventions, (pharmacological, interventional, and surgical) have been vigorous since the early 1970s. For acute pulmonary thromboembolism anticoagulation (intravenous heparinization followed by oral doses of warfarin sodium) remains unchallenged as a primary component of treatment. The use of modern thrombolytic agents, specifically urokinase, streptokinase, and recombinant tissue plasminogen activator (rt-PA), has been more controversial. Most authorities conclude that thrombolytic agents are indicated in the patient with hypotension secondary to a massive pulmonary thromboembolism. Beyond their use in that patient subset, however, there is little concurrence in the indication or indications for the use of thrombolytic agents. Four randomized trials demonstrate that there is more rapid (yet incomplete) resolution of pulmonary thromboemboli during the first 2 to 24 hours after treatment with rt-PA compared with treatment with heparin alone. However, these same trials failed to find a difference between rt-PA and heparin alone in the extent of embolic resolution at 7 or 30 days after treatment. In contrast, a European multicenter registry, designed to investigate current management strategies, suggested that thrombolytic agents favorably affect the clinical outcome, including survival, of hemodynamically stable patients with a major pulmonary thromboembolism.21 Trials in which thrombolytic agents were compared reported no substantive differences in the effects of rt-PA compared with urokinase. It is accepted that many patients with acute massive pulmonary thromboembolism die before a thrombolytic agent can be considered for administration. Thus, the influence of thrombolytic agents on the universe of patients with acute pulmonary thromboembolism remains undefined.

In selected cases in which thrombolytic therapy is contraindicated, transvenous catheter approaches to thrombolysis of pulmonary thromboemboli have been reported. In several instances, successful therapy depended on suction of the clot after it had been previously fragmented through mechanical manipulation of a relatively large guiding catheter. Other reports involve the use of much more sophisticated devices, such as a rheolytic thrombectomy catheter, that depends on high-pressure saline jets located at the tip to create a low-pressure zone into which the thrombus is drawn and then mechanically lysed by mixing forces. Although promising, all of these catheter approaches require broader and more numerous applications before their impact on natural history can be determined.

Surgical interventions for both acute and chronic pulmonary thromboembolic hypertension, particularly the latter category, have been much more promising. In patients with acute massive pulmonary embolism, particularly in patients unresponsive to thrombolytic therapy and in whom a cardiac arrest with associated neurological damage has not occurred, an emergent institution of cardiopulmonary bypass (either percutaneous or open chest) followed by embolectomy has produced more promising outcomes than those reported in the 1970s and 1980s.25–24

Pulmonary thromboendarterectomy has been performed in many individuals to relieve chronic pulmonary thromboembolic pulmonary hypertension. At the University of California, San Diego, Medical Center, the operation has been performed in >1000 patients since 1970. Considering their deteriorated quality of life and hemodynamic compromise, patient candidates have readily accepted the mortality risk of 5% to 10% for undergoing the operation. As with many surgical procedures, a comprehensive preoperative assessment of the pathoanatomy and pathophysiology of the disease process and associated conditions is crucial to ultimate surgical success. Both short- and long-term follow-up hemodynamic and imaging studies have confirmed the success of the procedure in improving clinical status, reducing pulmonary artery pressure and vascular resistance, and reversing right ventricular dilation and dysfunction. However, as with most successful surgical procedures, no randomized trial has been carried out in which operated and nonoperated cohorts were compared.

Incidence of Chronic Pulmonary Thromboembolic Hypertension

The success of pulmonary thromboendarterectomy prompts interest in a more precise estimate of the percentage of patients with acute thromboembolism who develop chronic pulmonary thromboembolic pulmonary hypertension. Based on the growing caseload in San Diego, it can be surmised that either the incidence is higher than formerly suggested or detection rates have significantly improved, or both.
Echocardiography Doppler allows serial estimation of pulmonary artery pressure and right ventricular function, during both the acute and follow-up phases of pulmonary thromboembolism. In this issue of Circulation, Ribeiro and colleagues from the Karolinska Hospital in Stockholm report an exacting 1-year follow-up by serial echocardiography Doppler and a 5-year clinical follow-up of 78 consecutive patients available from an original screened population of 128 potential subjects who had been hospitalized with the diagnosis of acute pulmonary thromboembolism. In 37 of 78 patients for whom there were ≥5 echocardiographic assessments, the authors were able to define an early exponential phase, followed by a much more protracted linear or stable phase, of pulmonary artery pressure decline after the acute pulmonary thromboembolic event. The time to achieve the stable phase was 38 days. The acute administration of neither a thrombolytic agent nor heparin affected the time to development of the stable phase. Fifty-six of 78 patients also had successful serial assessment of right ventricular function. Of the studied patients, 5.1% developed chronic pulmonary hypertension, a significantly higher percentage than previously estimated by investigators in this field. Three of 4 patients with persistent pulmonary hypertension and right ventricular dysfunction were referred for and underwent successful pulmonary thromboendarterectomy. A pulmonary artery systolic pressure of >50 mm Hg at the time of the initial diagnostic echocardiogram conferred an odds ratio (albeit with a wide 95% CI) of 3.3 for persistent pulmonary hypertension, right ventricular dysfunction, or both.

Several caveats about this new insight into the natural history of acute pulmonary embolism should be heeded. First, only 78 of 128 consecutive candidates ultimately could be assigned to a long-term analysis of morbidity and mortality rates. Of these 78 patients, 70 had successful serial measurements of pulmonary artery pressure out to 1 year. A minority of 37 patients could be subjected to a mathematical model of the repeated measurements of pulmonary artery systolic pressure (early monoeXponential, followed by stable linear, phases). The remaining patients either had inadequate observations or failed to meet an arbitrary constraint on an observed change in pulmonary artery pressure. In fact, several patients did not show a pressure decline at all but instead showed a progressive increase with time. The observations raise the question of whether these individuals had experienced thromboembolic events before being enrolled in the protocol. Second, the percentage of patients categorized within their 5-year follow-up as having persistent pulmonary hypertension/right ventricular dysfunction was augmented conceivably by use of the principle of “pragmatic approach,” in which patients who withdrew or died were classified as having persistent pulmonary hypertension/right ventricular dysfunction. Although this approach may minimize the chance of underestimating the long-term adverse effects of acute pulmonary thromboembolism, it also creates a risk of overstating the true incidence of chronic pulmonary thromboembolic hypertension. Notwithstanding these caveats, the Karolinska data support the previously reported suspicion that acute pulmonary thromboembolism more frequently leads to persistent pulmonary hypertension and right heart dysfunction than was previously estimated.

The report by Ribeiro and colleagues also highlights the importance and usefulness of follow-up echocardiography in detection of the chronic pulmonary thromboembolic state. If, in fact, 1 of 20 patients with acute pulmonary thromboembolism is at risk for persistent cardiorespiratory disability and chronic cor pulmonale, then early detection of this compromised state is desirable. The Karolinska analysis suggests that a follow-up echocardiogram, performed at 6 weeks after an acute embolic event, can be supported as a practice standard that will serve to identify patients at risk of further hemodynamic deterioration and potential candidates for treatment with pulmonary thromboendarterectomy.

References

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