HERE IS NO CLINICAL controversy about patients with massive pulmonary embolism (PE) and hemodynamic collapse. These patients warrant thrombolytic therapy unless contraindications preclude this management strategy. It is also clear that patients with PE who present with normal blood pressure and heart rate as well as normal right ventricular (RV) function will have excellent outcomes with anticoagulation therapy alone. The debate centers on patients with submassive PE who have RV dilatation and hypokinesis despite normal blood pressure. I will make the case for thrombolysis based on the available evidence to support this position. However, I advocate and am helping to organize an international trial of these patients, who fall between the 2 extremes, to provide a definitive answer to this ongoing issue.

Patients with PE who have moderate or severe RV dysfunction are not really hemodynamically stable. Their clinical course may lead to either recovery or crisis. Right ventricular dilatation and hypokinesis will either resolve with supportive care or will evolve to hemodynamic collapse requiring high-dose pressors, mechanical ventilation, or cardiopulmonary resuscitation and possibly death. The overall prognosis of patients with normal systemic arterial pressure plus moderate or severe RV hypokinesis is grave compared with patients who have normal systemic arterial pressure plus normal RV size and function. The presence of RV dysfunction is a warning sign that escalation of therapy might be required during the hospitalization or that death may ensue with a conservative “hands off” approach. When we evaluate such patients, we must remind ourselves that even if they appear stable, they may develop cardiopulmonary instability over the ensuing 48 hours.

The fundamental triad that I use to determine accurate prognosis relies on (1) the clinical evaluation (Does the patient look sick? Are there signs of tachypnea, tachycardia, or elevated pulmonary arterial pressure such as a left parasternal lift?), (2) cardiac biomarkers (Is there elevation in the level of troponin or B-type natriuretic peptide [BNP]?), and (3) RV dilatation or hypokinesis observed on an imaging test such as echocardiography or chest computed tomography or deduced by new abnormalities on electrocardiography.

Anticoagulation therapy alone will result in excellent clinical outcomes among patients with PE who have normal RV size and function. These individuals and their families can be reassured that adequate anticoagulation will result in a low rate of adverse clinical events. These patients can also be triaged to a non-intensive care setting for hospitalization, benefit from a shortened length of hospital stay using low-molecular-weight heparin or fondaparinux sodium as a bridge to oral anticoagulation, and in some centers, such as the University Hospital in Geneva, Switzerland, even receive care on a completely outpatient basis in selected low-risk patients. In the presence of hemodynamic stability and normal cardiopulmonary function and oxygenation, these patients should generally not receive thrombolytic therapy, even if they have an anatomically large PE.

Conversely, for patients with PE and RV dysfunction, thrombolytic therapy is not universally appropriate. Outside of a clinical research setting, the presence and degree of RV function are assessed qualitatively, not quantitatively. Those with “normal/near normal” RV function will have excellent clinical outcomes with adequate anticoagulation. About half of patients with moderate or severe RV dysfunction will have contraindications to thrombolysis, such as recent major surgery, active bleeding problems, prior stroke, or old age. These high-risk individuals, especially those with severe RV dysfunction, may be suitable for catheter or surgical embolectomy. Another option is placement of an inferior vena caval filter to prevent recurrent PE. If a bleeding problem is considered temporary, a retrievable rather than permanent filter should be considered.

Hemodynamic stability is multifactorial and cannot be determined merely by assessing systemic arte-
rial pressure and heart rate. Often, a fall in the systolic blood pressure is the last parameter to deteriorate because patients with PE will defend vascular tone by responding with vasoconstriction and increased systemic vascular resistance. With hypoxia and poor gas exchange, venous blood enters the systemic circulation, and right-to-left shunting ensues. As RV wall stress increases, cardiac ischemia may develop with release of troponin, and myocardial “stretch” may lead to release of BNP and pro-BNP. Hypoxia also causes increased pulmonary vascular resistance, which can exacerbate RV dysfunction and lead to progressively more severe RV dilatation, hypokinesis, and thromboembolic pulmonary hypertension. A dilated, hypokinetic right ventricle serves as an additional source for thrombus formation and propagation, even in the presence of adequate anticoagulation.

Among 162 normotensive patients with PE, 65 (31%) had RV dysfunction, and 3 (5%) of the 65 died during hospitalization; in contrast, none died in the group with baseline preserved RV function. This difference in survival was not statistically significant, and the positive predictive value of RV dysfunction for PE-related death among normotensive patients was only 5%. In 126 consecutive patients from another PE study, RV dysfunction was found in 56%, and all 10 in-hospital deaths occurred in patients with RV dysfunction. In a very recently completed analysis of the largest prospective registry of acute PE, the International Cooperative Pulmonary Embolism Registry, those patients who presented with normal systemic arterial pressure and RV hypokinesis on echocardiography were at a 2-fold increased risk of death. Overall, 2454 patients were enrolled in this registry, and 1035 underwent baseline echocardiography. The 30-day survival rates were much lower among “hemodynamically stable” patients with RV hypokinesis.

Right ventricular enlargement on chest computed tomography also predicts an increased mortality rate in patients presenting with acute PE. We evaluated 431 consecutive patients with acute PE confirmed by multidetector-row chest computed tomography. With multiplanar reformats of axial computed tomographic data, computed tomographic 4-chamber views were reconstructed. We detected RV enlargement (defined as RV diameter: left ventricular diameter ratio >0.9) in 64% of our patients with PE. Thirty-day mortality was 15.6% in patients with RV enlargement vs 7.7% in those without (P = .02). The hazard ratio of a RV diameter–left ventricular diameter ratio greater than 0.9 for predicting 30-day death was 5.17 (P = .005) after adjusting for pneumonia, cancer, chronic lung disease, and age.

In summary, although RV dysfunction and enlargement identify an at-risk group of patients with PE, this does not prove that thrombolytic therapy will improve their outcome.

The largest trial of thrombolyis vs anticoagulation alone in patients with PE with initially normal blood pressure and RV dysfunction is the Management Strategies and Prognosis of Pulmonary Embolism-3 (MAPPET-3) Trial. Overall, 256 patients were recruited and randomized to thrombolyis with tissue plasminogen activator vs placebo. During the trial, all patients received continuous infusion intravenous unfractionated heparin. The primary, prespecified end point was defined as in-hospital death or clinical deterioration requiring an escalation of treatment, which included catecholamine infusion, secondary thrombolyis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter. While the end point of “secondary thrombolyis” has stirred controversy because the need for this intervention was determined somewhat subjectively by the attending physician, this parameter was nevertheless prespecified.

In the MAPPET-3 Trial, treatment escalation occurred more than twice as frequently in the heparin-plus-placebo group (24.6% vs 10.2%; P = .004). Mortality was low in both groups (3.4% in the heparin-plus-thrombolyis group vs 2.2% in the heparin-plus-placebo group; P = .71).

The MAPPET-3 Trial, with its small sample size, was not designed as a mortality trial. Nevertheless, treatment with heparin plus placebo was associated with almost 3 times the risk of death or treatment escalation compared with heparin plus tissue plasminogen activator (P = .006). It was surprising that no fatal bleeding or cerebral bleeding occurred in patients receiving heparin plus thrombolyis. The major criticism of the MAPPET-3 Trial is that it permitted physicians to give open-label thrombolyis after initial double-blind treatment with thrombolyis or placebo if they believed their patients were doing poorly from a clinical perspective. The use of open-label thrombolyis by the attending physician was itself part of the end point definition of “escalation of therapy.”

Aside from formal clinical trials, most clinicians who manage PE have witnessed at least several “saves” when patients with hemodynamic collapse were resuscitated with thrombolyis. On the other hand, hardly any data provide long-term follow-up of patients in clinical thrombolyis trials for PE. Because PE often occurs in individuals with chronic disease of the heart and lungs, it is not clear that the detection of RV dysfunction is a result of the PE or secondary to congestive heart failure, chronic obstructive pulmonary disease, or other cardiopulmonary compromising condition. Therefore, uncertainty persists.

Thrombolyis may be risky and lead to fatal intracranial hemorrhage or to stroke with major residual disability. The bleeding rate for PE thrombolyis seems to be higher than for patients with acute myocardial infarction, possibly because patients with PE tend to be older and have more medical comorbid conditions. In the International Cooperative Pulmonary Embolism Trial, the intracranial hemorrhage rate was 3.0%. As physicians, we swear to “first do no harm.” While a catastrophic intracranial bleed is obvious, those lives saved by thrombolyis and those major adverse cardiac events that are averted by thrombolyis cannot be readily detected in patients with nor-
mal blood pressures and heart rates. As a clinician, the “downside” of administering thrombolysis is immediately apparent, but the advantages cannot be detected at the bedside among patients with PE who are clinically and hemodynamically stable.

The clinician wrestling with whether to administer thrombolysis should be aware that this use of potentially life-saving therapy is based on a sound pathophysiologic rationale. Whereas anticoagulation alone merely prevents recurrent PE, thrombolysis removes some of the thrombus, leading to reduced RV afterload, reversal of RV dilatation, and decreased release of adverse humoral factors such as serotonin, thrombin, and histamine.

Based on our global knowledge of acute PE, thrombolysis, and clinical trials and registries, thrombolysis should be considered in patients with so-called hemodynamic stability and RV dysfunction. Treating physicians must consider the safety of thrombolysis and withhold this therapy from patients in whom major bleeding risks are disproportionately high. A note in the medical chart explaining the attending physician’s rationale for administering or withholding thrombolysis serves to document the clinical situation prospectively and to clarify thinking, which will be especially important if adverse outcomes occur despite best efforts. For patients in whom intervention above and beyond anticoagulation seems appropriate but the risks of thrombolysis appear formidable, catheter and surgical embolectomy should be discussed among colleagues and reasons for using or avoiding these primary therapies to remove thrombus should be cited in the medical chart.

We have no single definitive trial proving the utility or futility of thrombolysis in hemodynamically stable patients. Under these circumstances, the next best approach is a methodologically rigorous meta-analysis that includes this controversial subgroup of patients with PE. This approach shows a nonsignificant one-third reduction of the combined end point of recurrent PE and death, but a 42% increase in major bleeding complications. The findings provide evidence to support thrombolysis among patients with massive PE and point us toward its use in selected high-risk patients with hemodynamic stability.

I have championed a large trial of perhaps 1100 patients with acute PE and preserved systemic arterial pressure, increased cardiac biomarker levels, and RV dysfunction to be randomized to thrombolysis plus anticoagulation vs anticoagulation alone. A definitive “yes” or “no” answer in such a trial would be a welcome relief to this persistent clinical controversy. Such a trial is likely to begin in 2006. This ambitious undertaking will have to be international in scope to obtain the required sample size. The project will require a multimillion dollar investment. Randomization might be problematic if many physicians have become entrenched in a strategy of implementing or withholding thrombolysis in patients with preserved blood pressure and RV dysfunction. Debates such as this in “Controversies in Internal Medicine” in the ARCHIVES will help to sustain clinical equipoise, a necessary component of a successful clinical trial.

Correspondence: Samuel Z. Goldhaber, MD, Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115 (sgoldhaber@partners.org).
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REFERENCES