

reviews

The Impact of Right Ventricular Dysfunction on the Prognosis and Therapy of Normotensive Patients With Pulmonary Embolism*

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The prognosis and optimal therapy of patients with pulmonary embolism (PE) are strongly influenced by the presence or absence of associated hemodynamic derangements. Patients with normal systemic arterial pressure have a relatively low risk of recurrent PE and death when treated promptly with therapeutic anticoagulation. Those who present with hypotension, shock, or cardiac arrest, however, have a much higher mortality rate and often receive thrombolytic therapy. Recent evidence indicates that the presence of right ventricular (RV) dysfunction identifies a subgroup of normotensive patients with a much more guarded prognosis who may benefit from more intensive therapy with thrombolytic agents. This article reviews our current understanding of the pathophysiology and diagnosis of RV dysfunction and its impact on the prognosis and therapy of normotensive patients with PE. (CHEST 2004; 125:1539–1545)

Key words: echocardiography; pulmonary embolism; right ventricular dysfunction; thrombolytic therapy; tissue plasminogen activator; venous thrombosis

Abbreviations: ICH = intracranial hemorrhage; LV = left ventricle, ventricular; PE = pulmonary embolism; PVR = pulmonary vascular resistance; rt-PA = recombinant tissue-type plasminogen activator; RV = right ventricle, ventricular

Pulmonary embolism (PE) is a common disorder and an important cause of morbidity and mortality. Epidemiologic studies^{1–3} indicate that PE is diagnosed in 55,000 to 94,000 patients each year in the United States, and data from a large international registry⁴ have demonstrated a mortality rate of 7.3%. Although daunting, these figures almost certainly represent a significant underestimate of the true impact of this disease. PE is notoriously difficult to diagnose, because it is usually accompanied by non-specific clinical manifestations and because diagnostic studies lack sufficient sensitivity and specificity.

In fact, autopsy series^{5,6} indicate that as many as two thirds of all clinically significant pulmonary emboli are undiagnosed prior to death. Such data have led to the estimate that PE occurs in 600,000 patients each year in this country and may cause as many as 60,000 deaths.⁷

With regard to prognosis and therapy, patients with PE have traditionally been classified into two groups based on BP measurements at the time of presentation. Those with normal BP are expected to have relatively low morbidity and mortality if treated promptly with therapeutic anticoagulation. Patients with hypotension, however, are known to have a much more guarded prognosis and are often considered for thrombolytic therapy. Increasing evidence suggests, however, that this classification scheme is too broad.^{8–10} Instead, it has been proposed that prognosis and therapy are best defined by placing patients into one of four groups based on both hemodynamic and echocardiographic parameters^{11–13}: (1) normal BP and right ventricular (RV) function, (2) normal BP with RV dysfunction, (3) hypotension without hypoperfusion, and (4) hypotension with hypoperfusion (shock) or

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cardiac arrest. The latter three groups, in which PE causes increasingly severe hemodynamic alterations, have been termed *major PE*.¹¹⁻¹³ This article will focus on normotensive patients with PE-induced RV dysfunction and will review our current knowledge about the prognosis and optimal therapy of this common and very important group of patients.

PATHOPHYSIOLOGY

As illustrated in Figure 1, major PE initiates a cascade of events that begins with an increase in pulmonary vascular resistance (PVR).^{14,15} The degree to which PVR increases depends largely, of course, on the extent of pulmonary vascular obstruction. There is, however, substantial evidence that vasoconstriction, caused by the release of thromboxane A₂, serotonin, and several other mediators by activated platelets on the surface of the embolized clot, may also play an important role.¹⁶ A significant increase in PVR leads to pulmonary hypertension and to an acute rise in RV afterload. This, in turn, increases RV wall tension and may lead to impaired systolic function, RV dilatation (often with acute tricuspid regurgitation), and elevated RV end-diastolic pressure and volume. Since the heart is contained within the pericardium, RV pressure and volume overload causes a shift of the interventricular septum, thereby reducing both left ventricular (LV) chamber size and compliance. The combination of

impaired RV systolic function and tricuspid regurgitation decreases RV output, and this, combined with a fall in LV compliance, reduces LV filling (preload) and stroke volume. A significant fall in stroke volume may, in turn, lead to a decrease in cardiac output, hypotension, and systemic hypoperfusion.

A decline in stroke volume and cardiac output may further impair cardiac function by decreasing coronary blood flow and precipitating myocardial ischemia. The RV is particularly at risk, since increased wall tension both reduces myocardial perfusion and increases oxygen demand. In fact, two studies^{17,18} have demonstrated that elevated serum concentrations of cardiac troponin I and troponin T are common in patients with PE-induced RV dysfunction. Since most of the patients in these studies^{17,18} had no signs of significant coronary disease, these data suggest that the pathophysiologic alterations produced by major PE are, by themselves, sufficient to cause minor myocardial necrosis.

The severity of the hemodynamic alterations produced by PE depends on the level to which PVR rises, the presence or absence of underlying cardiac or pulmonary disease, and the effectiveness of compensatory mechanisms, which increase sympathetic tone in an attempt to maintain cardiac output, BP, and systemic perfusion.

PREVALENCE AND PROGNOSIS

Approximately 80% of patients with PE have normal systemic arterial pressure at the time of presentation,¹¹ and between 27% and 55% of normotensive patients have echocardiographic evidence of RV dysfunction.^{11,19-22} This finding appears to significantly alter patient prognosis. Table 1 displays information from four studies that have prospectively evaluated the relationship between RV dysfunction and PE-related mortality. Goldhaber and colleagues²⁰ performed baseline echocardiography on 101 normotensive patients with PE, and 46 patients were found to have RV dysfunction. During the 14-day follow-up period, five patients with RV dysfunction had recurrent PE, and two patients died.

Table 1—The Effect of RV Dysfunction on Short-term Mortality

Source	Patients, No.	Mortality, %	
		RV Dysfunction	Normal RV Function
Goldhaber et al ²⁰	101	4.3	0
Kasper et al ¹⁹	317	12.6	0.9
Ribeiro et al ²¹	126	12.8	0
Grifoni et al ¹¹	162	4.6	0
Total	706	9.3	0.4

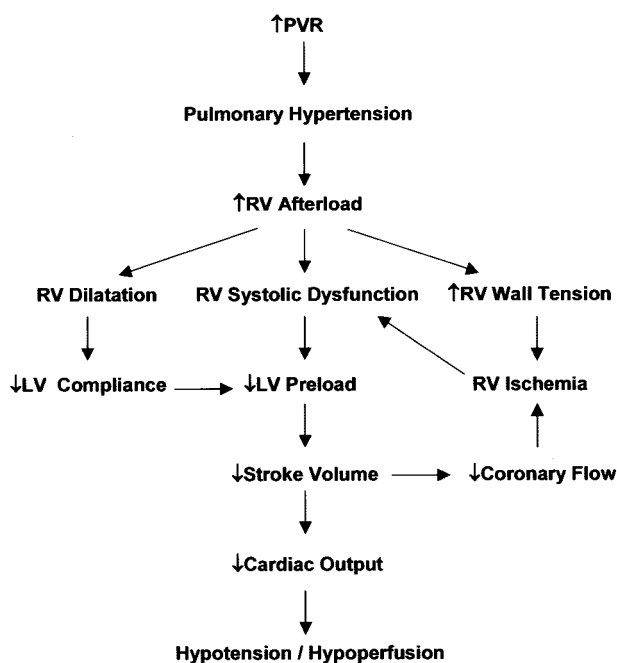


FIGURE 1. Pathophysiology of hemodynamic derangements caused by major PE.

No episodes of recurrent PE and no deaths occurred in patients with normal RV function. In another cohort of 317 patients,¹⁹ the 87 patients with echocardiographic evidence of RV dysfunction had a 12.6% PE-related in-hospital mortality rate, whereas only 0.9% of those with normal RV function died from PE prior to discharge. Similarly, in a study²¹ of 126 normotensive patients with PE, 9 of 70 patients with moderate or severe hypokinesia died from PE. No deaths occurred in the group with normal or mildly impaired RV function. Finally, Grifoni and colleagues¹¹ performed echocardiography on 162 normotensive patients with PE. Three of 65 patients with RV dysfunction died prior to discharge, whereas no deaths occurred in patients with normal RV function. When data from these four prospective trials are combined, patients with normal BP and impaired RV function had an average PE-related short-term mortality of 9.3%. In marked contrast, patients with normal RV function had a mortality rate of only 0.4%.

The prognostic importance of RV dysfunction has been further validated by data from two large multicenter patient registries. The International Cooperative Pulmonary Embolism Registry⁴ collected data on 2,454 consecutive patients with PE from 52 hospitals in Europe and North America. Echocardiography was performed on 1,135 normotensive patients, and RV hypokinesia was noted in 40%. Using a multivariate analysis, the presence of RV dysfunction was found to double all-cause mortality during the 3 months following diagnosis. The Management Strategy and Prognosis of Pulmonary Embolism Registry¹² compiled information about 1,001 consecutive patients with PE from 204 hospitals in Germany. To be enrolled, patients were required to be either normotensive with RV dysfunction or hypotensive with or without shock or cardiac arrest. Patients with normal BP but impaired RV function had an in-hospital mortality of 7.1%, and 14% had recurrent PE. Patients with hypotension, shock, and cardiac arrest had observed mortality rates of 14%, 23%, and 65%, respectively.

To summarize, there is compelling evidence that the presence of RV dysfunction identifies normotensive patients who have a significantly higher risk of recurrent PE and death. In terms of prognosis, this group can be thought of as part of the continuum between patients with normal BP and RV function and those presenting with hypotension, shock, or cardiac arrest.

DIAGNOSIS OF RV DYSFUNCTION

As shown in Table 2, published studies have based the diagnosis of PE-induced RV dysfunction on a

Table 2—Diagnostic Criteria for RV Dysfunction

Qualitative	RV hypokinesia (mild, moderate, severe)
Quantitative	RV dilatation
	RV:LV end-diastolic diameter > 1
	RV end-diastolic diameter > 30 mm
	Pulmonary hypertension
	Pulmonary artery systolic pressure > 30 mm Hg
	Tricuspid regurgitant velocity > 2.8 m/s
	Pulmonary artery mean pressure > 20 mm Hg

wide variety of criteria. The most common is the qualitative echocardiographic assessment of RV wall motion,^{4,20–22} which is judged to be normal or mildly, moderately, or severely hypokinetic. The principal quantitative criterion is the presence of RV dilatation, diagnosed either when RV exceeds LV end-diastolic diameter (RV:LV > 1),^{11,12,19} or when RV end-diastolic diameter is > 30 mm^{11,19} (Fig 2). The presence of pulmonary hypertension, demonstrated either by echocardiography or right-heart catheterization, has also been used as a diagnostic criterion.^{11,12,19,21} To complicate matters further, many authors have based the diagnosis of RV dysfunction on various combinations of these findings. It is unknown which of these criteria is the most sensitive

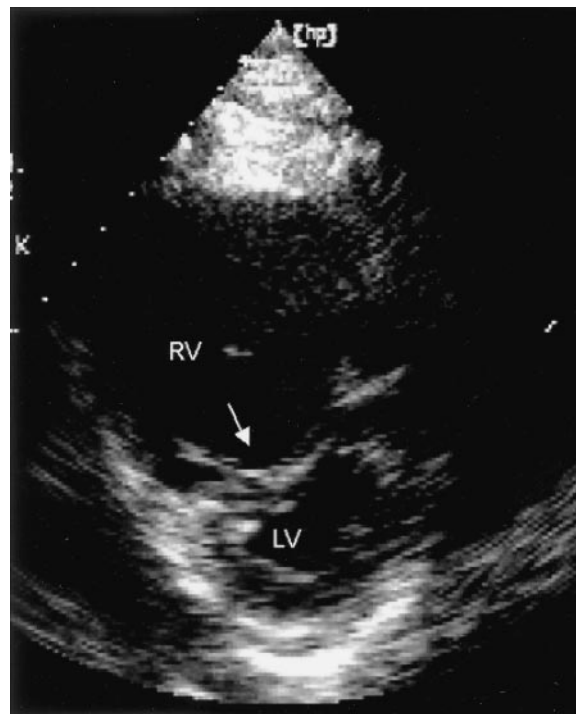


FIGURE 2. Echocardiogram demonstrating RV dysfunction in a patient with major PE. Note that the RV exceeds the LV chamber size and that the interventricular septum (arrow) is shifted toward the LV.

indicator of PE-induced RV dysfunction and which, if any, correlates best with patient prognosis.

Several investigators have examined the relationship between the extent of vascular obstruction and the presence of RV dysfunction. In 90 normotensive patients with PE, Wolfe and associates²² found that a lung scan with a perfusion score > 0.3 (reflecting loss of perfusion to $> 30\%$ of the lungs) accurately discriminated between patients with and without echocardiographic evidence of RV dysfunction. A virtually identical study²³ confirmed that a perfusion score of 0.3 best separated patients with and without RV dysfunction. In this trial,²³ however, a large amount of overlap existed between the two groups, and almost one third of the patients with RV dysfunction would have been missed by relying on the perfusion score. Most recently, a study by Miller et al²⁴ found no significant correlation between the extent of perfusion defects and the presence of RV dysfunction. Thus, there is insufficient evidence that the perfusion scan, or any other diagnostic test, can be used to accurately predict which patients are likely to have echocardiographic evidence of RV dysfunction.

THERAPEUTIC CONSIDERATIONS

Anticoagulation with heparin has long been the standard treatment for normotensive patients with PE. By preventing clot propagation, heparin allows endogenous fibrinolysis to occur, with eventual resolution of thromboemboli. Presumably through this mechanism, heparin therapy has been shown to significantly reduce both the incidence of recurrent PE and patient mortality.^{25,26} However, in the absence of an absolute contraindication, patients with PE-induced hypotension or shock are usually treated with thrombolytic agents. These drugs directly or indirectly convert plasminogen to plasmin, which breaks down cross-linked fibrin to produce clot lysis.²⁷ The US Food and Drug Administration has approved three thrombolytic agents for the treatment of PE: streptokinase, urokinase, and recombinant tissue-type plasminogen activator (rt-PA).

The use of thrombolysis in critically ill patients with PE is based on the results of nine prospective, randomized trials that compared heparin and thrombolytic therapy.²⁸ Interestingly, eight of these studies^{20,29–35} were limited largely or entirely to patients with normal BP. These trials consistently demonstrated that thrombolytic therapy produces more rapid clot lysis, improvement in pulmonary perfusion, and decrease in RV and pulmonary artery pressures than anticoagulation alone. Although no decrease in mortality was demonstrated, these re-

sults suggest that thrombolytic therapy should be beneficial in patients with severe hemodynamic compromise. Only one randomized trial³⁶ has compared thrombolytic therapy with anticoagulation alone in patients with shock. In this small study (eight patients), thrombolysis was associated with a significant survival advantage.

Since isolated RV dysfunction is associated with significant morbidity and mortality and may be thought of as one end of the spectrum of hemodynamic derangements caused by PE, there has recently been a great deal of interest in expanding the use of thrombolytic therapy to this group of patients.^{9,10} Come and associates³⁷ performed echocardiography before and an average of 9 h after thrombolysis in seven normotensive patients with PE-induced RV dysfunction. They demonstrated a decrease in RV end-diastolic diameter, decreased severity or resolution of tricuspid regurgitation and pulmonary hypertension, and improvement or resolution of RV hypokinesis and septal flattening. In another prospective trial³⁸ of 14 patients with PE who presented with normal BP and RV dysfunction, significant decreases in RV end-diastolic area, the end-diastolic RV:LV ratio, tricuspid regurgitant flow, and pulmonary hypertension were noted 1 h after PE thrombolysis. Nass and colleagues³⁹ retrospectively reviewed the echocardiograms of 18 patients with PE and RV dysfunction, who had been evaluated before and a median of 7 days after the administration of thrombolytic therapy. In agreement with previous studies, they found significant improvements in RV systolic wall motion and RV end-diastolic area. In the only randomized trial to assess the effect of thrombolysis on RV function, Goldhaber and associates²⁰ performed echocardiography before and 3 h and 24 h after the initiation of either rt-PA or heparin therapy in 101 normotensive patients with PE. Within the first 24 h, qualitative RV systolic function was much more likely to improve in patients who had received rt-PA and was much more likely to worsen in those treated with heparin alone. Patients receiving rt-PA were also noted to have a significant decrease in RV end-diastolic area.

Although RV dysfunction adversely impacts prognosis and is rapidly improved by thrombolysis, the essential question is whether normotensive patients with PE-induced RV dysfunction actually benefit from thrombolytic therapy. The first attempt to answer this question was made by analyzing data from the Management Strategy and Prognosis of Pulmonary Embolism Registry registry.¹³ In 719 patients, baseline evaluation demonstrated normal systemic arterial pressure with echocardiographic evidence of RV dysfunction. Most of these patients

(n = 550) were treated with heparin alone, while 169 patients also received thrombolytic therapy. Subgroup analysis demonstrated that patients undergoing thrombolysis had significantly lower in-hospital mortality and PE recurrence (4.1% and 7.7%, respectively) than those treated with anticoagulation alone (10.5% and 18.7%). Despite several important baseline differences between the two patient groups, multivariate logistic regression analysis demonstrated that thrombolytic therapy remained an independent predictor of survival. As stressed by the authors,¹³ however, interpretation of these results is limited by the nonrandomized nature of the study, which generated an unavoidable selection bias.

Subsequently, Hamel and colleagues⁴⁰ performed a retrospective analysis of normotensive PE patients with RV dysfunction. In an attempt to match the treatment groups, 64 patients who had received thrombolysis were paired, based on the echocardiographic end-diastolic RV:LV ratio, with 64 others who had been treated with heparin alone. In each group, recurrent PE was diagnosed in three patients, and in-hospital mortality was significantly higher in those receiving thrombolytic therapy (6.3% vs 0%). Given the retrospective nature of this study and its inherent selection bias, these results must, of course, also be interpreted with a great deal of caution.

In an effort to finally determine whether normotensive patients with PE-induced RV dysfunction should receive thrombolytic therapy, Konstantinides and colleagues⁴¹ published a prospective trial in which 256 patients with PE were randomized to receive heparin plus either rt-PA or placebo. The primary end point was in-hospital death or clinical deterioration that required an escalation of therapy. The authors defined treatment escalation as the requirement for either a catecholamine infusion to treat hypotension or shock, secondary or “rescue” thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency catheter or surgical embolectomy.

At first glance, the results of this study seem to strongly support the use of thrombolytic therapy. Patients treated with anticoagulation alone were much more likely to die or require treatment escalation than those who received rt-PA (24.6% vs 11.0%; $p = 0.006$), and there was no difference in the incidence of major bleeding or intracranial hemorrhage (ICH) between the two treatment arms.

Further analysis, however, raises concerns about the design of the study and its conclusions. First, inappropriate inclusion criteria may have been used. Patients with PE were enrolled if they had echocardiographic evidence of RV enlargement, pulmonary hypertension diagnosed by echocardiogram or right-heart catheterization, or new ECG signs of RV strain

(right bundle-branch block, S_1Q_3 , or inverted T waves in V_1 - V_3). To my knowledge, findings on the ECG have not been shown to correlate with the presence of RV dysfunction or pulmonary hypertension or to predict patient outcome. Since only 31% of the patients in each group had RV dilatation, and only 43 patients underwent right-heart catheterization, it appears that many patients may have been enrolled solely on the basis of an abnormal ECG finding. Second, and most important, the large difference in the primary end point resulted solely from the large number of patients in the anticoagulation group who received secondary thrombolysis. There was, in fact, no difference between the treatment groups in the need for catecholamine infusion, endotracheal intubation, cardiopulmonary resuscitation, or embolectomy. There was also no difference in the most important outcome measures, mortality and PE recurrence. Complicating matters further, the indications for secondary thrombolysis were both vague and subjective. For example, patients could be treated if they had “worsening clinical symptoms, particularly dyspnea” or “worsening respiratory failure.” In addition, the investigators were allowed to break the randomization code when clinical deterioration occurred, and this may have led to the disproportionate use of thrombolytic therapy in patients who had not yet received it.

Therefore, despite this large, prospective, randomized trial,⁴¹ the use of thrombolysis in normotensive patients with PE-induced RV dysfunction will remain controversial. In the absence of more definitive data, treatment decisions must be strongly influenced by two important considerations. First, nine prospective, randomized trials^{20,29–35,41} have now examined the effect of thrombolytic therapy in normotensive patients with PE. Although echocardiography was performed in only two studies,^{20,41} all of these trials presumably included a large number of patients with RV dysfunction. Yet, none were able to show that thrombolytic therapy reduced the incidence of recurrent PE or death. It is important to point out, of course, that these trials were insufficiently powered to reliably demonstrate a mortality benefit.

Second, PE thrombolysis is accompanied by a significantly greater risk of major hemorrhage than anticoagulation alone.^{42,43} This risk can be quantified by pooling data from randomized trials that have compared either thrombolytic and heparin therapy^{20,29–35} or different thrombolytic agents.^{44–49} If “major hemorrhage” is defined as fatal bleeding, ICH, or bleeding that requires surgery or transfusion, this analysis yields an average incidence of 11.9% and 1.8% with thrombolytic and heparin therapy, respectively.²⁸ Pooled data also demonstrate

a 1.2% incidence of ICH following PE thrombolysis, which is fatal in about half of the cases.²⁸ In these trials, ICH did not occur in any of the patients treated with heparin alone. Two observational studies^{4,40} have reported an even higher incidence of thrombolysis-induced ICH. In the International Cooperative Pulmonary Embolism Registry study,⁴ 3% of the patients treated with thrombolysis had symptomatic intracranial bleeding, compared with 0.3% of those who received anticoagulation alone. Similarly, Hamel and colleagues⁴⁰ reported ICH rates of 4.7% and 0% in patients receiving thrombolytic and heparin therapy, respectively. It has been proposed⁵⁰ that the higher risk of ICH reported in these series might better reflect “real world” conditions, when thrombolytic therapy is used outside the rigid confines of a prospective, randomized trial.

In conclusion, there is convincing evidence that the presence of RV dysfunction identifies a subgroup of normotensive patients with PE who have substantially increased morbidity and mortality. It is also evident that thrombolytic therapy rapidly improves PE-induced RV dysfunction. What remains far less clear is whether this effect translates into one or more clinically important benefits, and whether these benefits outweigh the substantial risk of major hemorrhage. Given the currently available information, I believe that all normotensive patients with acute PE should be treated with anticoagulation alone and that echocardiography should be used solely to stratify these patients into high- and low-risk subgroups based on the presence or absence of RV dysfunction. This prognostic information can then be factored into certain therapeutic decisions, such as the intensity and duration of patient monitoring. In the absence of an absolute contraindication, patients with hypotension or shock should undergo secondary or “rescue” thrombolysis.

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