



## Patients with acute pulmonary embolism should have an echocardiogram to guide treatment decisions

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*A 62-YEAR-OLD MAN with a past medical history notable for hypertension, osteoarthritis, and calf deep vein thrombosis at age 55 following a total hip arthroplasty presents to the emergency department with acute-onset dyspnea and right-sided pleuritic chest pains. His medications consist of a calcium channel blocker and a COX-2 inhibitor. Pretest clinical suspicion for pulmonary embolism (PE) is high. Ventilation and perfusion lung scintigraphy are interpreted as being high-probability for PE. The nurse asks if a stat transthoracic echocardiogram should be ordered.*

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### A PROTAGONIST'S PERSPECTIVE

Despite major advances in thromboprophylaxis, diagnosis, and management, acute PE (APE) continues to cause and contributes to an estimated 200,000 deaths annually in the United States [1]. Over the past 40 years, the incidence of PE in autopsy studies remains essentially unchanged at 10% to 15% [1–6]. APE frequently presents with nonspecific symptoms, such as chest pain, dyspnea, hypoxia, syncope, acute right ventricular dysfunction (RVD), or unexplained hemodynamic instability. Establishing the diagnosis of APE requires objective confirmatory tests, such as lung scintigraphy, chest helical CT scan, or pulmonary angiography. In certain cases, such as critically ill patients and those presenting with sudden cardiac death, transeophageal echocardiogram may allow direct visualization of the thrombus in the proximal pulmonary vasculature.

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Since the inception of effective anticoagulation therapy more than 60 years ago, variants of anticoagulant medications remain the dominant form of treatment for venous thromboembolic disease [7]. Anticoagulation therapy is believed to arrest thrombus propagation and limits further embolization, allowing for effective endogenous fibrinolytic activity. Patients with APE can present with, or later develop, hemodynamic instability followed by rapid clinical deterioration and death despite adequate anticoagulation. It has long been noted that death from APE usually occurs within the first few hours of the onset of symptoms. Right ventricular (RV) failure (despite the presence of an intrinsically normal left ventricle) and RV ischemia are the primary etiology by which early death from APE occurs [8–11]. Although acute severe RVD can be detected readily by physical examination, echocardiography is the most sensitive tool for diagnosing acute RVD in APE. Rigorous and proactive risk stratification of APE patients may allow for early identification of those at such risk and, subsequently, prompt application of measures targeted at decreasing the thrombus burden and re-establishing blood flow to the obstructed vasculature before overt failure of the compensatory mechanisms (ie, reaching the point of no return) ensues.

### **Pathophysiology of acute pulmonary embolism–induced right ventricular dysfunction**

Acute pulmonary embolism–induced RVD is the end product of a series of events that are triggered by the abrupt increase in pulmonary artery pressure. The hemodynamic response to APE depends on the size of the embolus, coexistent cardiopulmonary disease, and various neurohumoral effects. In the case of significant APE, atrial natriuretic peptide and brain-type natriuretic peptide levels increase acutely in response to the elevated pulmonary artery pressure. The vasodilatory and anti–rennin-angiotensin system effect of these peptides in the setting of APE is believed to decrease the pulmonary artery pressure (counterregulatory mechanisms) [12]. When the compensatory mechanisms fall short, however, the increase in RV pressure and pulmonary artery (PA) pressure lead to RV dilatation; hypokinesia; ischemia; and, if the cycle goes uninterrupted, the RV ultimately fails. The acute increases in RV pressure can cause left ventricle dysfunction because of the anatomic juxtaposition of the two ventricles and ventricular interdependency. With underfilling of the left ventricle, both systemic cardiac output and pressure decrease, potentially compromising coronary perfusion and producing more myocardial ischemia [8–10,13–15].

### **Echocardiography for the assessment of physiologic response to acute pulmonary embolism**

Echocardiography, a rapid, noninvasive, and widely available test, provides a window that looks at the previously mentioned cycle, frequently

capturing one or more of these abnormalities before the end results of cardiac failure or ischemia become clinically manifest.

Life-threatening APE has conventionally been equated with anatomically massive PE [15]. Such classification has limitations:

1. Only a minority of patients with anatomically massive APE have hemodynamic instability at presentation [5,16,17].
2. It ignores the impact of the patients' physiologic response, which depends on the integrity and adequacy of cardiopulmonary compensatory mechanisms, on outcome. Although radiographically small emboli, for example, may prove fatal in patients lacking adequate physiologic response, others with efficient compensatory mechanisms can tolerate radiographically large emboli. Physiologic correlation, when integrated in risk stratification strategies, adds another dimension to the course and outcome of APE.
3. Because the concept of anatomic sizing of APE evolved from studies that evaluated lung perfusion-ventilation scans by angiographic findings [18] one cannot generalize this methodology to the large group of patients diagnosed with APE by helical chest CT.

Traditionally, hemodynamic instability, defined as hypotension on presentation, has been used as the clinical discriminator between massive and nonmassive APE. Up to 30% to 50% of normotensive patients presenting with APE are found to have RVD by transthoracic echocardiographic assessment [1–5]. Normotensive patients with echocardiographically detected moderate-to-severe RVD are commonly referred to as having submassive PE, APE with impending hemodynamic compromise, or APE with associated latent hemodynamic impairment. Echocardiographic RVD is commonly encountered in patients with APE who have approximately one third or more of the lung nonperfused on lung scintigraphy [19,20]. In these instances, RVD provides an indirect evidence of severe pulmonary artery obstruction and, perhaps, impending hemodynamic failure [10,11,20–22]. Latent hemodynamic impairment is prevalent in a substantive group of unselected patients with APE and it represents the gray area between mild (small) and severe (large) APE [19,21–24].

The accuracy of echocardiography in APE is further improved in the presence of an intermediate or high clinical probability of APE [25,26]. Despite the fact that echocardiography is the standard imaging modality for accurate diagnosis of the abnormalities commonly encountered in patients with APE, such as RVD, RV hypokinesis, RV dilatation, intraventricular septal flattening, right pulmonary artery dilatation, decreased inferior vena cava inspiratory collapse, and tricuspid regurgitation, opponents to using echocardiography in this population argue that these are nonspecific signs for APE and could be found in a myriad of other conditions. To improve the specificity of transthoracic echocardiogram in detecting APE-related RVD, McConnell et al [8,27] elegantly identified a useful sign, widely known

as the “McConnell sign,” where they noted that in patients with moderate-to-severe RV free-wall hypokinesis secondary to PE there seems to be relative sparing of the RV apex. In their model, the McConnell sign had a specificity of 94% and a negative predictive value of 96% for APE.

### **Acute right ventricular dysfunction as a criterion in risk stratification of acute pulmonary embolism**

The absence of intraventricular septal hypertrophy (thickness < 7 mm) is the most important finding that differentiates acute from chronic RVD [18,28,29]. Generally, it is agreed that the presence of APE-associated cardiogenic shock warrants aggressive therapy despite the risks such strategies may incur. The fact that only 10% of APE patients present with hemodynamic instability may explain the limited use of fibrinolytic therapy in APE patients. The current available evidence supports the position that relying merely on the clinical hemodynamic status of patients presenting with APE could be deceiving. Although an important finding when present, clinicians should not wait for overt clinical hemodynamic compromise to develop. Rather, they should be proactive in seeking subtle and early signs predictive of adverse outcomes. Timely detection of RVD in normotensive APE patients is an important event (a marker) that signifies impending hemodynamic compromise, a precursor of death (an outcome).

Several clinical studies have reported a correlation between echocardiographic RVD and clinical outcome in patients with objectively confirmed APE [10,23–27,30–37]. The degree of RVD may help stratify patients into categories of increased risk for either recurrent PE or death and also provide complementary information and enable clinicians to manage these patients more effectively by using aggressive therapies, beyond anticoagulation, such as the use of fibrinolytic agents [23] or mechanical or surgical declotting interventions. In reality, however, only the sickest patients are evaluated and a minute minority of those evaluated receives such treatments.

The value of echocardiography in APE is outlined by the following facts:

- As a predictor of short-term mortality: Patients with moderate-to-severe RVD have a mortality rate as high as 15%, independent of blood pressure [23,38]. Patients with moderate-to-severe RVD who suffer recurrent emboli have a mortality rate of up to 50%. Four recent APE registries have provided echocardiographic data demonstrating that the detection of RV hypokinesis is associated with a twofold to threefold increase in mortality [31,39–41].
- As a predictor of short- and long-term morbidity: In a prospective clinical outcome study, Grifoni et al [23] reported that among normotensive patients, only the subgroup with evidence of RV dysfunction experienced adverse PE-related outcomes. Conversely, normotensive patients without echocardiographic RV dysfunction have a benign short-term

prognosis. Moreover, Ribeiro et al [42] followed 78 patients with APE with serial echocardiography for 1 year. A 5-year survival analysis showed that pulmonary artery systolic pressure of greater than 50 mm Hg at the time of diagnosis was associated with persistent pulmonary hypertension after 1 year. The pulmonary artery systolic pressure decreased exponentially initially, and the RV recovered during the first 38 days after the event but had little change afterward [41–44].

- Echocardiography has the unique ability of uncovering the presence of a patent foramen ovale and right heart thrombi, both of which have been found to predict worse outcome in this population.
- In the case of patients presenting with sudden cardiac arrest and pulseless electrical activity, transesophageal echocardiography may be a better screening test [8,45,46] than transthoracic echocardiography because of its ability to visualize the main pulmonary artery, the right pulmonary artery, and at least a portion of the left pulmonary artery. Although transesophageal echocardiogram has been shown to be a safe test in critically ill patients [47,48] with very high sensitivity and specificity in the detection of APE [35,49–51], one must remember that the usefulness of this test cannot be generalized to all patients with acute cor pulmonale. A negative transesophageal echocardiogram in this case does not necessarily exclude left proximal-to-mid or lobar PE [5,7,35,52].

### **Acute pulmonary embolism and patent foramen ovale**

Large APE can lead to increased pressure in the right side of the heart and pulmonary vasoconstriction, which is triggered by the associated hypoxia, further exacerbates pulmonary hypertension. The end result may be intracardiac shunt perhaps through the reopening of the foramen ovale or worsening of an already present intracardiac shunt through a patent foramen ovale. In a study of 139 patients with large APE, Konstantinides et al [53] found a strikingly high prevalence of patent foramen ovale (35%) and this subgroup of patients had a surprising 33% death rate (compared with 14% in those without patent foramen ovale,  $P = .15$ ). Only arterial hypotension (OR 26.3,  $P < .001$ ) and the presence of patent foramen ovale (OR 11.4,  $P < .001$ ) maintained their independent predictive power of mortality when logistic regression analysis was performed. In addition, patients with patent foramen ovale and APE had a 13% incidence of ischemic stroke believed to be secondary to paradoxical embolism as compared with 2.2% in those without patent foramen ovale ( $P = .02$ ).

### **Acute pulmonary embolism and right heart thrombi**

The ICOPER investigators [54] recently reported the ominous prognosis of right heart thrombi in APE. The overall mortality rate at 14 days and at 3 months in 42 patients with right heart thrombi compared with 1071 patients

without was twice as high (21% versus 11%, and 29% versus 16%, respectively,  $P < .05$ ) and remained so after the exclusion of patients with right heart thrombogenic instruments, such as catheters and electrodes (mortality at 14 days 22% versus 10%,  $P = .026$ ). Interestingly, this difference in mortality was almost entirely observed within the subgroup of patients treated with heparin alone instead of thrombolysis or embolectomy as adjuncts to heparin (25% versus 7.2%,  $P = .007$ ), despite similar clinical severity at presentation (systolic blood pressure  $122.2 \pm 24.2$  versus  $127.8 \pm 24.1$  mm Hg, hypotension in 5.9% versus 3.4%, and right ventricular hypokinesis in 52.5% versus 30.8% patients, respectively, all differences nonsignificant). These findings suggest that patients with APE who have right heart thrombi should be managed with more aggressive therapy than heparin anticoagulation alone, even when hemodynamically stable at the time of presentation.

In summary, echocardiography is a valuable test that should be pursued in patients with objectively confirmed APE. The test provides valuable information that may identify patients at risk for adverse events and guide the decision-making process. The controversy about the efficacy of fibrinolytic therapy in improving mortality in APE patients may be related to the fact that clinicians may have been treating the wrong patients: the sickest patients at a late stage of their disease. Using echocardiography in APE population may identify those who qualify for fibrinolytic therapy, yet they are in an early stage of the disease where mortality and morbidity benefit may be demonstrated. It is about time for echocardiography to become at the center of mainstream medicine in risk stratification and management of patients with APE.

## AN ANTAGONIST'S PERSPECTIVE

Patients presenting with suspected APE require prompt identification and treatment. The diagnosis is usually suspected based on clinical findings of shortness of breath and pleuritic chest pain. PE can mimic other disease processes, however, and may present with nonspecific findings. Confirmatory objective diagnostic tests are usually necessary before committing to an extended course of therapy. There are currently a number of tests available to establish this diagnosis including the ventilation-perfusion lung scan, spiral CT, and pulmonary angiography. Additionally, several other ancillary tests may help indirectly to confirm an APE including venous duplex ultrasonography (identifies deep vein thrombosis) and a D-dimer assay.

Over the last decade, the use of echocardiography for diagnosing and managing APE has also gained in acceptance [8,23,55–59]. Echocardiography offers the benefit of widespread availability, relative convenience, and immediate results. It also provides a noninvasive bedside technology that helps to eliminate the need for transporting critically ill patients to other areas of the hospital for diagnostic purposes.

Several basic considerations must be taken into account when using the echocardiogram to determine treatment decisions in patients with an APE. Although some advantages of echocardiography are listed previously, one must also consider its disadvantages. Echocardiography provides evidence of a PE by demonstrating an intracardiac or pulmonary artery thrombus. Unfortunately, direct visualization of thrombi in the pulmonary arteries is infrequent with standard echocardiography, nor is intracardiac thrombus commonly seen. Results are also often critically dependent on the expertise of the echocardiographer.

Perhaps of more concern is that many clinicians believe that the demonstration of RVD or RV dilatation (in the appropriate clinical setting) is sufficient evidence for the diagnosis of APE. Unfortunately, RVD is a nonspecific finding and may be seen in patients with chronic obstructive pulmonary disease, RV myocardial infarction, sarcoidosis of the heart, significant valvular heart disease, or a technical acquisition error. Abnormal motion of the interventricular septum, tricuspid regurgitation, lack of collapse of the inferior vena cava during inspiration, or pulmonary hypertension are other indirect echocardiographic signs of APE, although their specificity is low.

A PE can lead to significant morbidity and mortality. Although most patients are hemodynamically stable and can be managed effectively with standard unfractionated heparin, a small percentage (generally less than 5%) present with hemodynamic instability (hypotension and circulatory collapse). These patients require more aggressive treatment and most clinicians favor thrombolytic therapy over pulmonary embolectomy, assuming no contraindications for its use exists. Thrombolysis accelerates resolution of the pulmonary emboli improving RV function, pulmonary perfusion, and the hemodynamic status of the patient. Unfortunately, no large clinical trials have demonstrated a reduction in mortality with the use of these agents. Earlier trials from the 1970s including the Urokinase Pulmonary Embolism Trial and the Urokinase-Streptokinase PE Trial failed to demonstrate a difference in the rate of death or recurrent PE in either group when compared with heparin therapy [60,61]. More recently Konstantinides et al [62] compared heparin alone with alteplase plus heparin in a randomized, double-blind, placebo-controlled trial. No significant difference was seen in the in-hospital mortality rates between the groups. Only one small clinical trial randomizing patients to thrombolysis versus anticoagulation in massive PE has shown a reduction in mortality. This trial was stopped after enrolling only 8 of a planned 40 patients. All four patients receiving standard anticoagulation died, whereas the four patients receiving thrombolysis all survived [63].

Despite the lack of convincing data using survival as an end point in the unstable patient with APE, thrombolytic therapy is often recommended for the hemodynamically stable patient who demonstrates RVD on echocardiogram [23,38,41,64]. In this subgroup of patients, the goal of therapy is rapid

reversal of right-sided heart failure with an expected reduction in death and fewer recurrent PEs. According to Goldhaber et al [38], Konstantinides et al [41], and Grifoni et al [23], this patient population has “impending hemodynamic instability” and represents up to 40% or 50% of all normotensive patients presenting with PE. They report that recurrence and death rates for PE is higher in this subgroup despite their normotensive presentation, and believe that waiting to use thrombolytic therapy may result in irreversible clinical deterioration. In support of this concept, Grifoni et al [23] reported a 5% death rate in their normotensive patients presenting with RVD, compared with none of their patients without RV strain. Four of their six deaths were in patients over 80 years of age, however, and none occurred in patients who would have been considered eligible for thrombolytic therapy. Goldhaber et al [38] enrolled 101 hemodynamically stable patients in a multicenter trial comparing rt-PA with heparin. No episodes of recurrent PE were seen among rt-PA patients; however, there were five clinically suspected recurrent PEs in the heparin group and all demonstrated RVD by echocardiography. Although two of these patients died, both deaths were a result of recurrent PE and not RVD. In addition, only two of their five patients with suspected recurrent PE had confirmatory studies to document their recurrence. Patients receiving heparin in this study were dosed based on an antiquated regimen and no mention was made about therapeutic levels. Kasper et al [57] enrolled 719 consecutive hemodynamically stable patients with APE and found 30-day mortality to be significantly higher in their population with echocardiographic findings of RV pressure overload (10% as opposed to 4.1%). These authors believed that thrombolysis favorably affected the clinical outcome of their hemodynamically stable population. This study, however, was a multicenter registry, treatment was not randomized, thrombolytic patients had less cardiac and pulmonary disease, and recurrent PE was diagnosed clinically by the on-site physician.

In contrast to the reported benefits of managing the patient with APE based solely on findings of RVD using the echocardiogram, a number of authors have debated this approach. They cite increased costs of the thrombolytic agents, an increased risk for intracranial hemorrhage and major bleeding, and lack of evidence that thrombolytic therapy decreases mortality or reduces recurrent PE [24,65]. For example, Hamel et al [65] found fewer deaths among patients with RV dilation receiving unfractionated heparin or low-molecular-weight heparin compared with those receiving thrombolytic therapy. They reported no deaths in their 64 patients receiving standard therapy compared with 4 of 64 deaths in the thrombolytic group. Three of the patients in the thrombolytic group suffered intracranial bleeds, whereas six other patients had other severe bleeding complications. Dalen et al [24] also reported no knowledge of patients dying with APE who were normotensive when treated with heparin and stress the good prognosis of the hemodynamically stable patient with APE.



Other authors have also reported increased risks of bleeding in patients receiving thrombolysis for APE. Konstantinides et al [41] reported a major bleeding rate of 21.9% in patients receiving thrombolysis compared with 7.8% receiving standard therapy, whereas Levine [66] cited an 8.4% incidence of major bleeding and a fatal hemorrhage rate of 2.2% in a similar group of patients. Goldhaber et al [28,38,67] also reported more major bleeding (including one intracranial bleed) in their patients receiving thrombolytic therapy, whereas Dalen et al [24] reported a 2.1% incidence of intracranial hemorrhage and the International Cooperative of Pulmonary Embolism Registry reported a 3% incidence.

Most studies have demonstrated a favorable outcome for the hemodynamically stable patient presenting with APE [24,62,65]. If recommendations endorsing the use of thrombolytic therapy in patients based on echocardiographic documentation of RVD were followed, one would expect to see a marked increase in their use. This would add greatly to the cost of managing patients with APE and potentially lead to greater morbidity secondary to higher major bleeding rates and deaths caused by intracranial hemorrhage. Although thrombolytic therapy results in more rapid initial resolution of PE, this has not yet translated into a reduction in mortality or reduction in the rate of recurrent PEs [60–62]. In patients with smaller emboli and evidence for RVD that do not produce significant hemodynamic compromise, thrombolytic therapy is not yet warranted in most cases [68]. Managing patients based only on echocardiographic findings of RVD cannot be recommended. Further prospective studies are needed to determine if this patient population benefits from thrombolytic therapy [69].

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