CARDIOLOGY Rounds®

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The Role of Echocardiography in the Diagnosis and Management of Acute Pulmonary Embolism

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The diagnosis of an acute pulmonary embolism is often difficult to make since many of the clinical symptoms can be confused with other acute pulmonary or cardiac disorders. Echocardiography is frequently performed on individuals with suspected pulmonary emboli, either to rule-out other suspected cardiac diseases or determine the hemodynamic consequences of the embolism, which may warrant more aggressive management. This issue of *Cardiology Rounds* reviews the echocardiographic features of pulmonary embolism and discusses the utility of this modality for both diagnosis and management.

Pulmonary embolism (PE) is a common medical problem that is associated with significant morbidity and mortality. In the United States alone, there are >600,000 new cases of PE each year, resulting in >50,000 deaths.[1] Making a diagnosis of PE can be difficult since the clinical presentation, such as symptoms of chest pain and dyspnea, can be confused with other pulmonary or cardiac pathology. It is estimated that up to two-thirds of all cases of clinically significant pulmonary embolism go undiagnosed prior to death. With an average mortality rate of 7.3%,[2] which increases to as high as 50% in patients presenting in shock,[1] it is important to make an accurate diagnosis of PE. Echocardiography is a test that is frequently performed on individuals with either *suspected* pulmonary emboli (to diagnose PE and rule-out potential acute cardiac causes for symptoms) or *confirmed* pulmonary emboli (to further risk-stratify patients and guide therapy).

Echocardiographic features of acute pulmonary embolism

Echocardiographic imaging can definitively establish a diagnosis of PE only in rare circumstances. In these cases, a thrombus is seen either in the main pulmonary artery (PA) or proximal branch PA ("saddle" embolus), or within the right-sided cardiac chambers (pulmonary embolus "in-transit"). In the International Cooperative Pulmonary Embolism Registry (ICOPER),[3] 4% of patients presenting with acute PE had an intracardiac thrombus identified on echocardiography.

On the other hand, it is much more common for echocardiography to detect the hemodynamic consequences of acute PE on the cardiac chambers. With the sudden occlusion of portions of the pulmonary vascular bed with a thrombus, acute pressure overload of the right ventricle can occur with subsequent changes in right-sided pressures and right ventricular (RV) function (Figure 1). Findings on echocardiography that are suggestive, but not diagnostic, of pulmonary embolus include:

- RV dilatation and hypokinesis
- elevated pulmonary systolic pressures
- ventricular septal flattening and paradoxical septal motion
- patent foramen ovale, with right-to-left shunting
- diastolic left ventricular impairment

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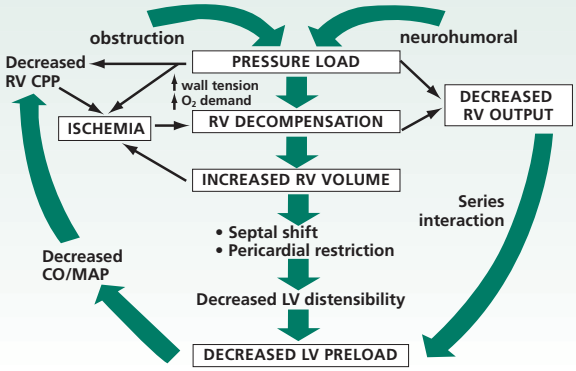
Figure 1: Physiologic effect of pulmonary embolism on the heart[1]



CO/MAP = cardiac output/mean arterial pressure
CPP = coronary perfusion pressure

The most commonly identified abnormalities on echocardiography include RV dilatation and hypokinesis, and elevation of RV systolic pressure (RVSP). These findings are seen in 40% to 60% of all cases of acute PE.[4-8] With transthoracic imaging, the right ventricle loses its triangular shape and takes on a more rounded appearance in the apical views. Similarly, in the parasternal short-axis view, the RV loses its crescentic shape and takes on a more oval appearance (Figure 2). Finally, evidence of pulmonary hypertension, with tricuspid regurgitant velocity of >2.8 m/s, can be detected in patients with pulmonary embolism.

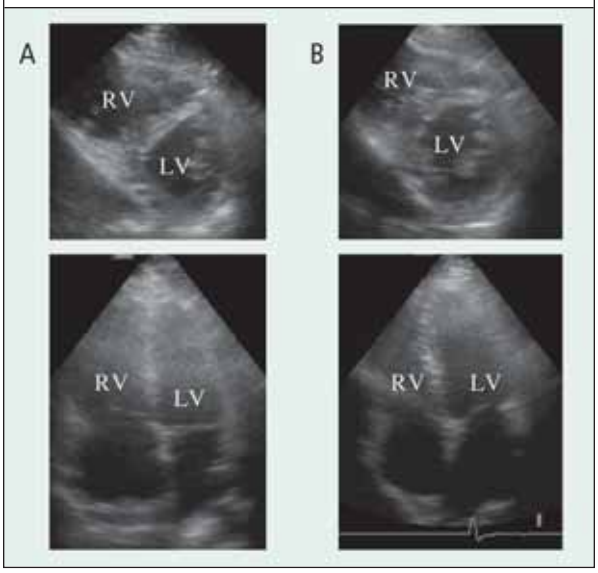
Diagnostic utility of echocardiography

The use of transthoracic echocardiography (TTE) for the diagnosis of pulmonary embolism is attractive because it is widely available, portable, and completely non-invasive. Several studies have found TTE to be a fairly specific test for the diagnosis of PE (specificity ranging from 87% to 96%), but relatively insensitive (sensitivities 29%-51%).[9,10] However, there are several problems associated with relying on TTE to make a diagnosis of acute PE. As previously mentioned, only 40% of patients with confirmed PE have abnormal echocardiograms. Given that >30% of the pulmonary vascular bed has to be affected on lung perfusion imaging to reveal any echocardiographic abnormality,[3] TTE is not useful in the setting of small pulmonary emboli.

Although the specificity of TTE has been reported to be good, there remains the potential for false positive tests. Similar to patients with PE, those with primary pulmonary hypertension (PPH), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and RV infarction may also have RV dilatation and hypokinesis on echocardiography.

In an effort to help differentiate patients with acute PE from other conditions with RV systolic dysfunction, McConnell et al[11] described a wall motion pattern of

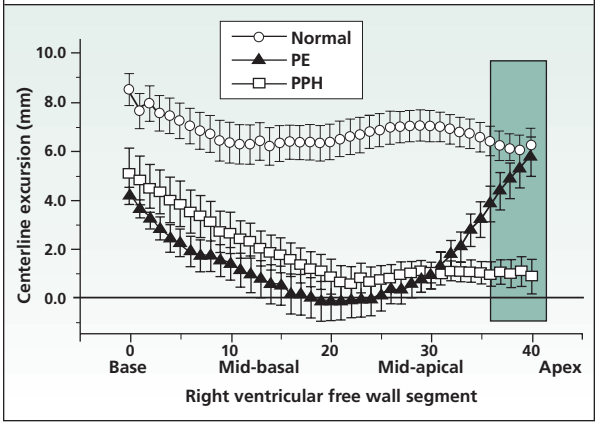
Figure 2: Echocardiographic images before (A), and after (B) thrombolytic therapy in a patient with acute PE. Prior to lytic therapy, RV dilatation is seen with deviation of the ventricular septum towards the left ventricle (LV). After therapy, the RV size returns to normal, with a normal septal configuration.



the right ventricular free wall seen in PE. Termed the "McConnell sign," this finding identifies a hypokinetic midportion of the free wall with relative sparing of the apex. Conversely, patients with PPH are less likely to have apical sparing and, thus, have a more diffusely hypokinetic RV (Figure 3). Using the McConnell sign, these authors found that echocardiography performed better as a diagnostic test, with a sensitivity of 77% and a specificity of 94%.[11]

Transesophageal echocardiography (TEE) has many potential benefits over TTE in the diagnosis of PE. In sicker patients in an intensive care setting, where limited

Figure 3: Graphical representation of RV regional wall motion in patients with PE and PPH, demonstrating preserved RV apical excursion in patients with PE[11]



PE = pulmonary embolism; PPH = primary pulmonary hypertension

transthoracic views are available, it can provide more reliable imaging. As well, it allows for more direct visualization of the proximal pulmonary arteries and the potential for identification of thrombus in these areas. Pruszczyk et al[12] examined the diagnostic value of TEE in 113 consecutive patients with suspected PE and RV overload on TTE imaging. Using the combination of computed tomography (CT) scanning, ventilation perfusion imaging, and pulmonary angiography as the gold standard for diagnosis, the sensitivity of TEE in diagnosing *severe* PE was 80.5%, and the specificity was 97.2%. Cases where the diagnosis was missed were those with more distal thrombi in the pulmonary bed. The authors also reported some technical difficulty in viewing parts of the left PA due to shielding by the left main bronchus. Regardless, they concluded that TEE was a reliable and safe method to definitively confirm hemodynamically significant PE. Particularly in unstable patients in an intensive care setting, where transfer for diagnostic radiologic imaging may be problematic, TEE may help establish a bedside diagnosis and facilitate prompt treatment.

Overall, in most circumstances, echocardiography should not be relied on for the diagnosis of PE due to its poor sensitivity. With the advancement of CT angiography, magnetic resonance imaging (MRI), and ventilation perfusion lung imaging, there are more reliable tests available. Echocardiography can be useful in conjunction with these tests since it provides useful information regarding the hemodynamic impact of pulmonary emboli, which can help identify patients at higher risk of complications or death.

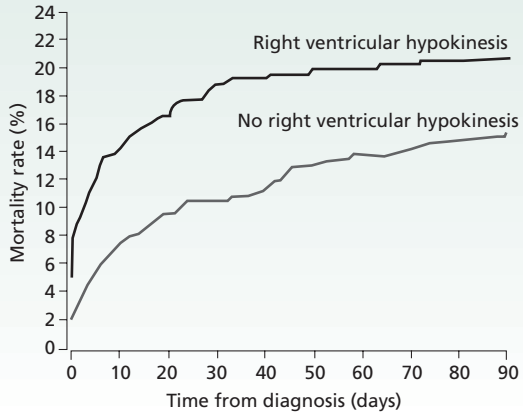
RV dysfunction and prognosis in acute PE

While echocardiography has limited diagnostic utility, it is generally accepted that echocardiographic evidence of RV systolic dysfunction is associated with a poorer prognosis. There have been at least 4 prospective studies examining the impact of RV dysfunction on prognosis in patients with PE.[4-6,13] The findings of these studies were recently summarized in a review[8] and the results are illustrated in Table 1. Combining these results, it was determined that short-term mortality in patients with RV dysfunction on echocardiograhy was 9.3% compared to only 0.4% in patients with normal echocardiograms.[8]

Table 1: The effect of RV dysfunction on short-term mortality in patients presenting with acute pulmonary embolism[8]

Source	Patients, No.	Mortality, %	
		RV dysfunction	Normal RV function
Goldhaber et al	101	4.3	0
Kasper et al	317	12.6	0.9
Ribeiro et al	126	12.8	0
Grifoni et al	162	4.6	0
Total	706	9.3	0.4

Figure 4: Cumulative mortality in patients with acute pulmonary embolism, stratified by the presence or absence of RV dysfunction[2]



Registry data also exist to support the prognostic implications of RV dysfunction and PE. The ICOPER[2] collected information on 2454 patients with PE and found that all-cause mortality at 3 months was 15.3%; 45% of these deaths were felt to be secondary to PE. After multivariate analysis of the 1135 patients who underwent echocardiography in this registry, it was observed that individuals with RV dysfunction had a 2-fold increased risk of death at 3 months (Figure 4).[2]

Overall, there is good evidence that RV dysfunction is a marker for a worse prognosis in PE. As a result, echocardiography may play a role in risk-stratifying these patients. For example, patients with normal RV function may be able to be managed conservatively, potentially in an outpatient setting. Patients with RV hypokinesis likely warrant closer monitoring in a hospital setting, along with consideration of more aggressive therapy, including thrombolysis and surgical embolectomy.

Management of PE and the role of echocardiography

The mainstay of treatment for PE has been anticoagulation with either low-molecular weight or unfractionated heparin and long-term treatment with coumadin. Prior to the use of heparins in PE, this condition was associated with mortality as high as 35%.[1] While more contemporary treatment has led to a reduction in mortality in acute PE, there are certain patients in whom mortality remains quite high. In these patients, more aggressive therapy with either thrombolytics or surgical embolectomy should be considered. Particularly when patients present with shock, the general consensus is that they should be strongly considered for thrombolytic therapy.[15] What remains unclear is whether individuals without hypotension, but with poor prognostic

Table 2: Predictors of 30-day mortality in patients presenting with acute pulmonary embolism[25]

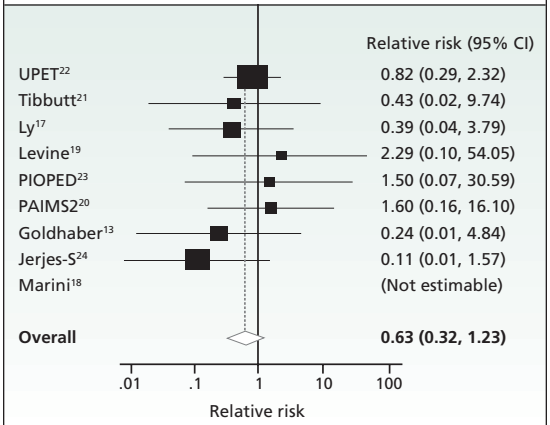
Characteristic	Odds ratio	95% Confidence interval	*P*
Thrombolytic treatment	0.46	0.21-1.00	.051
Age >65 y	1.25	0.71-2.20	.43
Acute symptom onset	1.19	0.67-2.11	.55
Syncope	1.61	0.93-2.80	.092
Tachycardia	1.64	0.87-3.09	.13
Arterial hypotension	1.44	0.85-2.46	.18
Recent major surgery	0.76	0.40-1.43	.39
History of venous thrombosis	0.78	0.43-1.40	.40
Congestive heart failure	1.37	0.77-2.45	.28
Chronic pulmonary disease	1.60	0.77-3.32	.21
History of stroke	1.08	0.35-3.41	.89

features such as RV dysfunction on echocardiography, would also benefit from treatment with thrombolytic therapy.

Two retrospective cohort studies have examined thrombolytic therapy in hemodynamically stable patients with RV dysfunction. Konstantinides et al[25] examined a multicentre registry of patients with massive PE; 719 of these patients had clinical, echocardiographic, or hemodynamic evidence of RV failure without profound hypotension. In this study, the 30-day mortality was significantly lower in the group of patients who underwent primary thrombolysis (n=163) compared to those who were initially treated with heparin alone (4.7% versus 11.1%, p=.016). After adjustment for the influence of other relevant clinical characteristics at presentation, thrombolysis was the only clinical variable that reached statistical significance as an independent predictor of outcome (Table 2).

In another study, Hamel et al reviewed 128 patients with RV dilation admitted to ICU and treated with either heparin alone or thrombolytics.[26] Patients treated with thrombolytic therapy were matched to those with heparin therapy to avoid differences in baseline characteristics seen in the prior study. While greater improvements were seen in lung perfusion scan imaging with thrombolytic therapy, in this registry, the group treated with thrombolytics had higher in-hospital mortality compared to those treated with heparin alone (6.3% versus 0%). Two of the 4 deaths that occurred in the treatment group were due to intracranial bleeding. Overall, these studies present conflicting results and both authors suggest that a large prospective randomized trial is needed to properly identify the merits of thrombolytic therapy in this population.

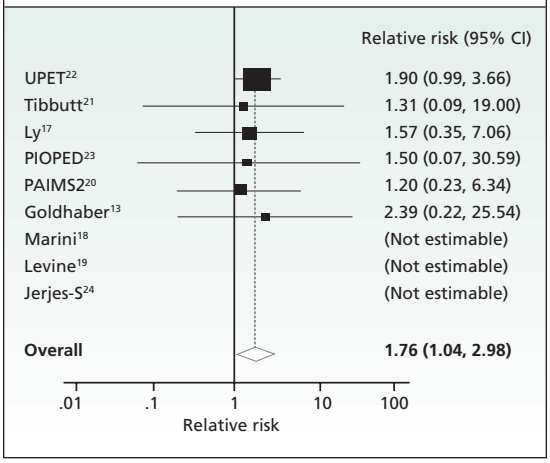
Figure 5: Graphical representation of the relative risk (95% CI) of mortality in thrombolysis versus heparin treated groups[16]



Thabut and colleagues[16] performed a meta-analysis of trials comparing thrombolytic therapy to heparin alone. Inclusion criteria included a prospective, randomized design measuring outcomes of mortality, recurrent PE, or major hemorrhage. A total of 9 trials[13,17-24] were studied, involving a total of 241 patients randomized to thrombolytic therapy (urokinase, streptokinase, or tissue plasminogen activator [TPA]) and 220 patients randomized to heparin. Only 5.2% of the patients in these studies presented in shock. With the exception of one study,[24] none demonstrated that thrombolytic therapy had a significant effect on death, recurrent PE, or major bleeding. The study by Jerjes-Sanchez et al,[24] which did reveal a mortality benefit, included only 8 patients presenting in shock. Combining the results of these studies, the authors found that although there was a trend towards decreased mortality with treatment, the difference did not reach statistical significance (relative risk [RR] 0.63; 95% confidence interval [CI], 0.32-1.23) (Figure 5). There was also a nonsignificant trend toward a lower recurrence of PE with thrombolytic therapy compared to heparin alone (4.9% versus 9.3%). There was, however, a significantly increased rate of major hemorrhage in patients treated with a thrombolytic versus those treated with heparin alone (RR 1.76; 95% CI, 1.04-2.98) (Figure 6). The authors hypothesized that this meta-analysis was underpowered to detect a statistically significant improvement in mortality with thrombolytics. They estimated that a randomized trial with >1000 patients in each treatment arm was needed. It was concluded that thrombolytic therapy did not impact mortality or the incidence of recurrent PE and that it was associated with increased bleeding complications.

More recently, Konstantinides et al published the results of a prospective, double-blind, randomized

Figure 6: Graphical representation of the relative risk (95% CI) of major hemorrhage in thrombolysis versus heparin treated groups[16]



trial comparing thrombolysis with alteplase to placebo in 256 patients presenting with submassive PE.[27] To be entered into the trial, patients were required to have either RV dysfunction, pulmonary hypertension, or ECG signs of RV strain with a diagnosis of PE. The primary endpoint of the study was a combination of in-hospital death or clinical deterioration requiring an escalation of treatment. Although there was no significant difference in mortality between the alteplase and placebo arms (3.4% versus 2.2%), there was a significant decrease in the combined primary endpoint due to treatment with alteplase compared to placebo (11% versus 24.6%, p=0.006). It is important to note that there was no difference in bleeding complications seen in the 2 groups.

From these results, the authors concluded that treatment of patients with submassive PE with alteplase may improve their clinical course and, in particular, prevent clinical deterioration requiring escalation of treatment. Closer examination of the results of this study raises some concerns regarding the conclusions. For instance, the significant difference in the primary endpoint is driven by the need for repeat thrombolysis. There was, however, no significant difference between the two treatment groups regarding the need for catecholamines, intubation, cardiopulmonary resuscitation, or embolectomy. The exact requirements regarding the need for repeat thrombolysis could be subjective and were not clearly stated. While treatment appeared to be safe, it is still unclear whether patients actually benefit from thrombolytic therapy in this setting.

There is no clear consensus in the literature on the role of thrombolytics in patients with PE and RV dysfunction. At the present time, there is no evidence to suggest a mortality benefit with the use of thrombolytic agents. As a result, physicians must use clinical judgment and consider potential bleeding risks when contemplating thrombolytic agents in this population.

Conclusions

Pulmonary embolism remains both a diagnostic and management challenge for physicians. While echocardiography lacks sensitivity as a diagnostic tool, it can distinguish new pulmonary hypertension and RV dilatation and dysfunction that can aid diagnosis. These are important findings and, when present, are associated with a worse prognosis. As a result, echocardiography can be used to help risk-stratify patients presenting with a diagnosis of PE. The decision to use the presence of RV dysfunction to decide on thrombolytic therapy in patients presenting with acute PE remains unclear and requires further study.

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Abstract of Interest

Heparin plus Alteplase compared with Heparin Alone in Patients with Submassive Pulmonary Embolism

KONSTANTINIDES S, GEIBEL A, HEUSEL G, ET AL, FOR THE MANAGEMENT STRATEGIES AND PROGNOSIS OF PULMONARY EMBOLISM-3 TRIAL INVESTIGATORS

BACKGROUND: The use of thrombolytic agents in the treatment of hemodynamically stable patients with acute submassive pulmonary embolism remains controversial.

METHODS: We conducted a study of patients with acute pulmonary embolism and pulmonary hypertension or right ventricular dysfunction but without arterial hypotension or shock. The patients were randomly assigned in double-blind fashion to receive heparin plus 100 mg of alteplase or heparin plus placebo over a period of two hours. The primary end point was in-hospital death or clinical deterioration requiring an escalation of treatment, which was defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter.

RESULTS: Of 256 patients enrolled, 118 were randomly assigned to receive heparin plus alteplase and 138 to receive heparin plus placebo. The incidence of the primary end point was significantly higher in the heparin-plus-placebo group than in the heparin-plus-alteplase group (P=0.006), and the probability of 30-day event-free survival (according to Kaplan-Meier analysis) was higher in the heparin-plus-alteplase group (P=0.005). This difference was due to the higher incidence of treatment escalation in the heparin-plus-placebo group (24.6 percent vs. 10.2 percent, P=0.004), since mortality was low in both groups (3.4 percent in the heparin-plus-alteplase group and 2.2 percent in the heparin-plus-placebo group, P=0.71). Treatment with heparin plus placebo was associated with almost three times the risk of death or treatment escalation that was associated with heparin plus alteplase (P=0.006). No fatal bleeding or cerebral bleeding occurred in patients receiving heparin plus alteplase.

CONCLUSIONS: When given in conjunction with heparin, alteplase can improve the clinical course of stable patients who have acute submassive pulmonary embolism and can prevent clinical deterioration requiring the escalation of treatment during the hospital stay.

N Engl J Med 2002;347:1143-1150.

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