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Pulmonary embolism: The clot stops here

By JOHN GRANTON, MD

In the face of advances in prophylaxis, therapy, and diagnostic strategies/methods, acute pulmonary embolism (aPE) remains a common cause of morbidity and mortality in Canada. This fact has not gone unnoticed. The *Medical Malpractice News*¹ advises its readers:

- *In cases of lethal or disabling pulmonary embolism following major surgery, look for specific risk disclosure preceding consent.*
- *The general intent to anticipate and prevent venous thrombosis should be documented, even though the blood thinner heparin may be too hazardous in exceptional cases.*
- *Consider whether this might be a case for a Supreme Court of Canada ruling on the appropriateness of community standards.*
- *Even though appropriately administered post-operatively, anticoagulation may have been discontinued prematurely.*

This issue of *Critical Care Rounds* will focus on patients presenting with a massive or a so-called sub-massive pulmonary embolism. Massive pulmonary embolism is defined as an embolic event that leads to sudden death, cardiac arrest, systemic hypotension (in general, a systemic blood pressure <90 mm Hg), or shock. Sub-massive aPE is reserved for instances where an aPE produces evidence of right ventricular dysfunction without significant hypotension. This latter group has been the focus of several studies evaluating prognosis and is an area of active debate regarding the role of thrombolysis. This review will provide the reader with:

- an understanding of the pathophysiology and acute hemodynamic consequences of aPE
- an approach to the treatment of aPE
- a review of the factors that may influence the decision to admit a patient with aPE to the ICU
- a review of the controversy surrounding the rationale for giving thrombolytic therapy for aPE.

Hemodynamic effects

In a given patient, the hemodynamic consequences of an aPE are dependent on the degree of mechanical obstruction (clot burden), the effect on right ventricular function, and comorbidities that reduce the patient's ability to tolerate the hemodynamic consequences.

Most pulmonary emboli arise from a proximal venous thrombosis. The initial effect is a mechanical obstruction of the pulmonary vasculature and any attendant vasoconstrictor effects of vasoactive substances released by the clot, and secondary endothelial



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Correspondence:

John Granton, MD
The Toronto General Hospital
10 EN-220
200 Elizabeth Street
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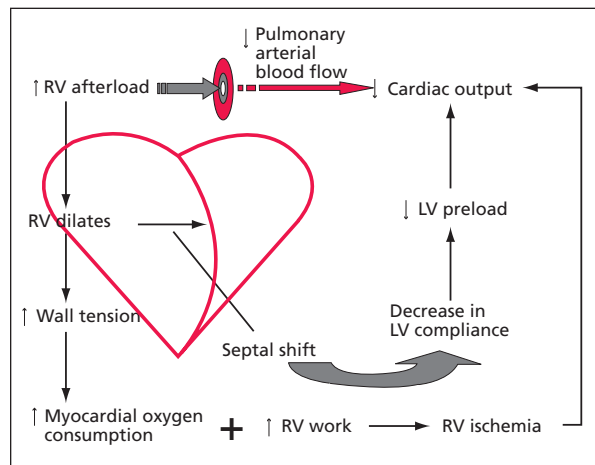
injury, although this is not well-defined. In the healthy individual, the pulmonary arterial circuit is a high capacitance/low resistance system that can accommodate large increases in flow without changes in pressure. However, in the setting of aPE, the cross-sectional area of the pulmonary vasculature is reduced and the ability of the circuit to vasodilate may also be reduced. Right ventricular cardiac output is impaired, leading to a reduction in exercise capacity, breathlessness, tachycardia, or hypotension. The increase in right ventricular afterload in turn leads to right ventricular dilation and an increase in right ventricular pressure.² These effects are summarized in Figure 1.

As a result of the reduction in cardiac output, the heart rate increases (leading to a further increase in cardiac work) and adrenergic tone increases in an attempt to preserve organ and coronary perfusion. If the unconditioned right ventricle cannot generate sufficient pressure to overcome the resistance, it will fail. Patients may present with syncope, hemodynamic instability, shock, or cardiac arrest. In the setting of recurrent or chronic aPE, the right ventricle may have had sufficient time to remodel and overcome the increase in afterload. However, pre-existing pulmonary vascular disease may limit the hemodynamic reserve and render the individual less able to cope with an increase in myocardial work or cause further reductions in the cross-sectional area of the pulmonary circuit. Consequently, in marginal patients, the hemodynamic consequences of an aPE may not be predictable, based on size of the defect alone.

Prognosis

In general, the observed mortality and death from aPE is higher in registries than that observed in clinical trials. In the largest aPE registry – the International Cooperative Pulmonary Embolism Registry (ICOPER) – the course of 2454 consecutive patients from 52 hospitals across Europe and the United States was reported.³ The diagnosis of aPE was made using accepted diagnostic testing in 2110 (86%) of the patients. The crude 3-month mortality was 17.4%, with 45% of the deaths being attributed to the aPE. In contrast, the mortality in the Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire (THÉSÉ) study was appreciably lower.⁴ In the THÉSÉ trial, 612 patients were randomized to receive either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Twenty-six of the 612 (4.3%) patients died in the first 3 months. Of the patients who died, one-third died from aPE.

Figure 1: The hemodynamic effects of a pulmonary embolism



There are several potential explanations for the higher mortality rates in registries than in clinical trials:

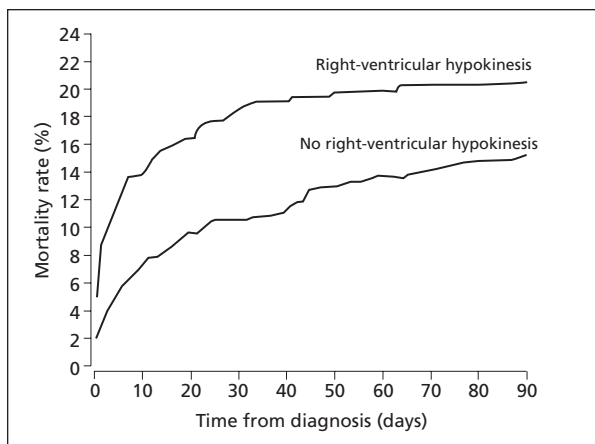
- First, clinical trials often exclude patients with massive aPE who require embolectomy or thrombolysis. In general, these patients have higher mortality rates.
- Second, patients with poor immediate prognosis from their underlying disease are excluded from clinical trials. In particular, patients with an underlying malignancy have a very poor prognosis after aPE.
- Third, owing to less stringent diagnostic entry criteria, patients with conditions other than aPE may have been enrolled in the registries.
- Fourth, many registries include patients who died shortly after admission or who were diagnosed at autopsy (generally associated with 100% mortality).

The impact of these factors on reported mortality rates was emphasized in a recent retrospective registry of venous thromboembolism in 2218 patients.⁵ In that study, the 1-week mortality was 29%. This contrasts sharply with the observed 5% 1-week mortality in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study. However, when immediately fatal and post-mortem discovered aPEs were excluded, mortality rates approached those of PIOPED. In practice, however, clinicians must deal with potentially fatal aPE, which will be the focus of further discussion.

Right ventricular dysfunction

The prognosis of aPE is dependent on both the hemodynamic consequences of the clot and underlying disease(s) in the patient. Age >70 years, malignancy, co-existing obstructive lung disease, or cardiac disease are associated independently with worse outcomes.³ The presence of more severe clinical signs (syncope or

Figure 2: Comparison of mortality rates between patients with RV dysfunction on echocardiography compared to those without RV dysfunction.³



severe breathlessness) and systemic hypotension are also poor prognostic indicators.

Grifoni et al evaluated the influence of hemodynamics at baseline and clinical outcome in a study of 209 cases of proven aPE from a series of 388 consecutive patients with suspected aPE.⁶ Patients presenting with shock had an in-hospital mortality of 32%, compared to no mortality in those without hemodynamic impairment or evidence of right ventricular (RV) dysfunction. The importance of RV function on clinical outcome has been emphasized in several observational studies and clinical trials.⁷⁻¹⁰ Indeed, in the study by Grifoni et al, patients with normal systemic pressures and echocardiography (ECHO) evidence of RV dysfunction had a mortality rate of 5% (3 of 65 patients). Furthermore, 10% of these patients had clinical deterioration as compared to those without evidence of RV strain. Ribero, in an earlier study, also found that the presence of RV dysfunction was associated with a lower chance of survival (relative risk of death 2.3; 95% confidence interval, 1.2 to 4.5).¹¹ The ICOPER trial also reported a higher risk of death in patients who had evidence of RV dysfunction (Figure 2).³ However, only 963 of 2454 evaluable patients had an ECHO performed.

Based on these observations, it would seem reasonable to perform an ECHO to evaluate RV dysfunction in patients presenting with advanced symptoms (eg, syncope, hypotension, severe breathlessness, or tachycardia, or a large embolism). RV dysfunction would seem to mandate closer observation of these patients who are at increased risk of deteriorating. In addition, ECHO may also identify patients who are at extreme risk of death if a free RV clot or a patent foramen ovale is/are identified.^{12,13} Thrombolysis should likely be offered to such patients. The role of thrombolysis in the setting of RV dysfunction alone remains controversial – *vide infra*.

A potential surrogate for echocardiographic evidence of RV dysfunction is the presence of biochemical markers of cardiac ischemia. In a study of 106 consecutive patients with aPE, Konstantinides et al evaluated the association between elevated troponin I and T measurements and a complicated clinical course.¹⁴ A complicated course was defined as death or >1 of the following: need for thrombolytic treatment, catecholamine support of blood pressure (other than <5mcg/kg/min of dopamine), endotracheal intubation, or cardiopulmonary resuscitation. Elevation of troponin levels was more frequent in patients with RV dysfunction and was associated with a higher risk of death or complicated clinical course. Using their assay, a troponin I level >1.5 ng/ml had an odds ratio for death or complicated course of 16.9 (95% CI, 1.6–178) and 15.5 (95% CI, 3.8–62.6), respectively. Similarly, a troponin T level >0.1 ng/ml had an odds ratio for death or complicated course of 6.5 (95% CI, 1.1 to 38.2) and 8.7 (95% CI, 2.6–29.5), respectively.

Initial management

The goals of therapy are to support the circulation and improve RV function.

Fluids are administered to improve RV preload. However, it must be cautioned that aggressive fluid administration may worsen RV dilation and septal shift, increase left ventricular end-diastolic pressure, and worsen left ventricular preload. Consequently, this situation differs from acute myocardial infarction of the right ventricle where, in general, there is no increase in RV afterload.

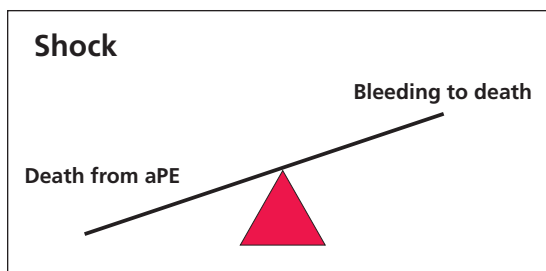
Catecholamines are administered to improve contractility;¹⁵ however, given the small muscle mass of the RV relative to the LV, the precise benefit of this strategy could be questioned. Indeed, most inotropes may lead to systemic vasodilation and worsened systemic hypotension.

Experimental evidence in animal models of aPE supports the use of noradrenaline.^{16,17} The proposed mechanism centers on its alpha effects leading to systemic vasoconstriction with potentially improved coronary perfusion and venous vasoconstriction with improved venous return and RV preload. Efforts should also concentrate on reducing RV afterload.

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator and, in one case, series was reported to lead to a reduction in pulmonary arterial pressure, improved cardiac output, and improved oxygenation.¹⁸ However, this series also emphasized that interruption in NO therapy (which occurred in 2 patients) can lead to precipitous and poorly tolerated effects.

The most common strategy to reduce RV afterload is clot lysis.

Figure 3a: Perceived benefit of thrombolysis on survival from massive aPE in patients with shock vs. the risk of clinically significant bleeding.



Thrombolysis

In general, agents that augment the fibrinolytic process are used in aPE. However, mechanical methods have also been reported. Some renewed interest in the use of pulmonary thromboendarterectomy for aPE has emerged with some centres reporting acceptable outcomes.¹⁹ However, these centres have significant expertise in pulmonary thromboendarterectomy – a procedure not for the faint-of-heart that should be reserved for centres with an established program.

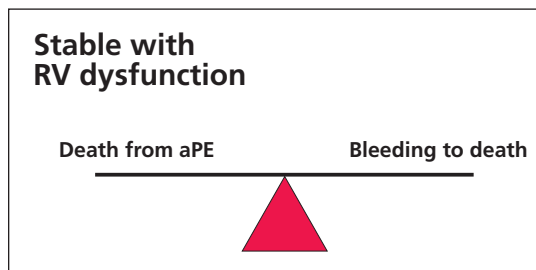
Radiological methods that include clot basket retrieval in the setting of RV thrombi have also been reported. The clot is generally manipulated into the inferior vena cava (IVC), below the level where an IVC filter can be placed above the clot before it is again released. Most mechanical methods are reserved for patients in whom thrombolysis is contraindicated. The general rules for thrombolysis are:

- it doesn't matter which agent is used
- systemic thrombolysis is equivalent to regional thrombolysis
- high doses over prolonged periods are associated with unacceptable risks of bleeding²⁰
- shorter dosing protocols are recommended.

In a recent study comparing a 2-hour infusion of 100 mg alteplase (rTPA) versus 1.5 million units of streptokinase (SK), there was no difference in hemodynamics 2 hours after the infusions. However, more patients experienced a hemodynamic improvement at 1 hour after infusion (33.6 +/- 16% in the rTPA group vs. 19.6 +/- 16% in the SK group, $P=0.006$). There was no significant difference in either pulmonary vascular obstruction at 36 to 48 hours or bleeding complication rates.

The case for systemic thrombolysis stems from the observation that exogenously achieved thrombolysis produces more rapid clot resolution than endogenously achieved thrombolysis.²⁰ The argument follows that this leads to more rapid hemo-

Figure 3b: Absence of clear benefit on survival from massive aPE in patients without shock but having RV dysfunction. The risk of bleeding needs to be weighed against supposed benefit in this setting.



dynamic stability and potentially, a reduction in mortality from massive aPE. It is hoped that this benefit offsets any increase in the risk from major bleeding (Figure 3a). However, no large-scale clinical trial has demonstrated an effect on mortality using this strategy. The largest prospective trial to date – the Urokinase Pulmonary Embolism Trial (UPET) – randomized 160 patients to receive a 12-hour infusion of urokinase (UK) followed by heparin or placebo followed by heparin.²² At 24 hours, the UK group had better hemodynamics and pulmonary blood flow as measured by angiography or perfusion scan. However, by the 5th day this effect was lost, with the placebo group “catching up” such that there was no difference in estimates of pulmonary blood flow at either 3, 6, or 12 months. Importantly, there was no difference in mortality or rate of recurrence of aPE between the two groups.

Only one trial has focused on thrombolytic treatment for massive aPE. This small, randomized, placebo-controlled trial was stopped early after 8 patients were enrolled.²³ Four of the patients who received placebo died, compared to no deaths in the 4 patients who received SK therapy. Based on these observations, thrombolysis is recommended in “unstable” patients with an aPE. An excellent and comprehensive review of thrombolysis, effect of timing, mode of administration, and other aspects are provided in the study by Arcasoy and Kreit.²⁰

The case for the use of thrombolysis in the setting of hemodynamically stable aPE is less compelling. It is unclear if the benefits of rapid and early clot lysis and improved RV function offsets the risk of hemorrhage (Figure 3b). However, several registries have reported improved outcome when thrombolytics were administered in patients with RV dysfunction. The largest of these (MAPPET) enrolled 719 patients with aPE who were hemodynamically stable, with evidence of RV

dysfunction.²⁴ Importantly, the diagnosis of aPE was made on clinical grounds in some patients in this registry. The course of the 169 patients receiving thrombolysis was compared to the 550 who did not. The 30-day mortality was greater in the patients who did not receive thrombolysis (11.1% vs. 4.7%). Interestingly, all but one death was attributable to aPE. The rate of recurrent aPE was also significantly greater (18.7% vs 7.7%) in the group not receiving thrombolysis. It is worth emphasizing that the incidence of clinically significant bleeding was greater (22% versus 8%) in the patients who received thrombolysis; however, only 2 patients in each group had documented cerebral events. There were also clinically and statistically significant baseline differences between the two groups, making interpretation of this registry difficult. The thrombolysis group was younger, had fewer patients with recent surgery, a history of heart failure or obstructive lung disease.

The positive benefits ascribed to thrombolysis have recently been called into question by a sobering observation in a French study.²⁵ In this small registry, the clinical course of 153 consecutive patients with aPE and RV overload was observed. These investigators reported an increase in mortality when thrombolytics were used. There were no deaths in the non-thrombolytic group compared to 4 deaths in the thrombolytic group. All the deaths were related to complications of thrombolysis. Ten patients who received thrombolysis had a major bleeding event (3 cerebral) compared to none of the patients not receiving thrombolysis.

Unfortunately, all these registries represent uncontrolled observations with all of their attendant limitations. To address this question, Konstantinides et al recently completed a randomized controlled study of thrombolysis in 256 patients with acute aPE and RV dysfunction without hypotension or shock.²⁶ Of these, 118 were randomized to rTPA plus heparin, while 139 were randomized to heparin plus placebo. The authors concluded that treatment with placebo was associated with a significant increase in the risk of death or treatment escalation. However, closer evaluation of the results of this study suggests that this conclusion is at best overstated. Death from all causes was very low in both groups. Four (3.4%) and 3 (2.2%) patients died in the thrombolysis and control arms, respectively. Indeed, the sole “benefit” of thrombolysis was related to a reduction in the need to escalate therapy. The only

significant difference between the 2 groups was the greater use of “rescue” thrombolysis in the control group, with 9 (7.6%) versus 32 (23.2%) patients receiving rescue thrombolysis in the treatment versus control groups, respectively ($P < 0.001$). The most common reason for “rescue” thrombolysis was worsening symptoms or “respiratory failure,” neither of which was strictly defined in the study. To compound the problem, the trial protocol permitted breaking the randomization code if additional therapy had to be provided to a patient who was deteriorating, but it is unclear how often this occurred. Clearly, there would have been a risk if physicians were aware of the treatment arm in that they may have been less likely to provide “rescue” thrombolysis to patients who had previously received this therapy.

This trial was also plagued by one of the usual problems experienced in randomized controlled studies, namely that the mortality rate was much lower than anticipated from earlier registry data. Consequently, the trial was likely simply underpowered to demonstrate either a mortality benefit or a detriment from major hemorrhage. Hopefully, the authors will follow-up this cohort to evaluate the potential longer-term benefits of thrombolysis by comparing incidence of chronic pulmonary hypertension, chronic perfusion defects, and response to exercise between the two groups. At present, based on this study, it is unclear if an expectant strategy of early thrombolysis versus a wait-and-see strategy (worsening clinical status) should be adopted in hemodynamically stable patients with RV dysfunction in the setting of aPE. If a wait-and-see strategy is employed, it would seem rational to recommend close monitoring of these patients since they appear to be at greater risk of deteriorating than those without RV dysfunction.

Conclusions

Death from pulmonary embolism remains a common problem. The majority of deaths are ascribed equally to the direct hemodynamic consequences of aPE and underlying disease (particularly cancer). Thrombolysis is recommended for patients who are unstable or are at high risk of chronic pulmonary hypertension. Patients who present with a large perfusion defect, syncope, or significant symptoms should undergo an echocardiographic assessment of RV function. RV dysfunction is associated with a significantly greater risk of clinical deterioration. It is my opinion that these

patients should be monitored closely for changes in clinical status. The role of troponin in risk stratification seems promising. It may represent a cost-effective and timely alternative to echocardiography for most patients. The decision to use thrombolysis in this group of patients should be individualized until more convincing data are available.

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