In Situ Thrombosis of the Pulmonary Arteries: An Emerging New Perspective on Pulmonary Embolism

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INTRODUCTION

he annual incidence of pulmonary embolism (PE) in the United States is reported to be 0.69 per 1,000 persons with mortality of up to 30% depending upon the size of the emboli.¹ PE and deep venous thrombosis (DVT) are both considered manifestations of the same disease of venous thromboembolism. Virchow postulated that dysfunction of vessel walls, alternations in blood flow and hypercoagulability of the blood triggered inappropriate thrombus formation.² DVT most commonly occurs as local clot formation in the deep calf veins. PE arises when clots break off from a peripheral DVT and become lodged within the pulmonary arterial vasculature. PE is routinely diagnosed when filling defects are found in the pulmonary arteries on computed tomography angiogram (CTA). Among the general population of patients presenting to emergency rooms, absence of DVT may occur in up to 57% of those diagnosed with PE.³ A high prevalence of isolated PE may suggest localized thrombus formation in the pulmonary arteries instead of embolization from peripheral clots. In situ thrombosis is not differentiated from emboli on CTA. However, despite evidence for multiple possible origins for clots within the pulmonary arteries, PE is the default diagnosis for filling defects detected by CTA in clinical practice.⁴ The goal of this article is to present a new model suggesting that a subset of what is currently labeled as PE is actually a localized thrombus within the pulmonary arteries. We review the following topics: (1) the unique features of the lung vasculature that contribute to hemostasis, (2) disruption of hemostasis and localized pulmonary

artery thrombosis, (3) a possible role for inflammation in thrombosis, (4) clinical implications of *in situ* pulmonary artery thrombosis, and (5) future directions for research.

HEMOSTASIS IN THE PULMONARY ARTERIES

The pulmonary circulation is a uniquely fibrinolytic environment. Expression of mediators of fibrinolysis are increased in pulmonary arteries when compared to peripheral veins in response to an inflammatory stimulus.⁵ Blood fluidity in the pulmonary arteries and their branches is promoted by a high ratio of tissue plasminogen activator (t-PA) to plasminogen activatorinhibitor 1 (PAI-1) and endogenous heparin-like proteoglycans that provide a non-thrombogenic surface in the vasculature endothelium.^{6,7} One model suggests that the pulmonary vascular system is ideally suited to be a mechanical sieve for venous drainage from the body. With the ubiquitous nature of spiral CT angiography, an increasing incidence of incidental isolated small PEs has been reported.⁸ These small clots may represent the critical role of the pulmonary vasculature in filtering out small emboli from the systemic circulation, which subsequently undergo fibrinolysis.⁹ If the pulmonary vasculature is highly fibrinolytic, how can localized thrombosis occur within the pulmonary arteries?

MECHANISMS OF THROMBUS FORMATION

Systemically, clotting occurs when initiated by a stimulus, which transforms tissue factor from an encrypted FVII cell membrane receptor to a functional receptor.¹⁰ Injury to endothelial cells from trauma, ischemia, inflammation,



or activation of the complement system exposes tissue factor receptor activity. Disruptions to endothelial cell mechanisms that maintain blood fluidity in the pulmonary vasculature may result in localized thrombus formation. Localized thrombosis is the most common type of thrombosis and has been documented throughout the body including cerebral, retinal, upper and lower extremity, and abdominal veins.¹¹ Case studies have described *in situ* pulmonary artery thrombosis in patients who have disruption of hemostasis including patients with pulmonary hypertension, chronic obstructive pulmonary disease (COPD), and with a past history of pulmonary wedge resection surgery.^{12–}

¹⁴ Despite this evidence, local thrombus formation is not routinely considered in patients with obstruction of the pulmonary artery.

The strongest support for a model of *in situ* pulmonary artery thrombosis has come from trauma surgery literature. Several large retrospective studies of patients with chest trauma and PE report that up to 80% of patients have isolated PE without DVT and these authors suggest these findings are due to localized thrombi or 'acute peritraumatic pulmonary thrombus' rather than emboli.^{15,16} In this model, direct damage to the pulmonary vasculature and visceral tissue from chest trauma leads to activation of tissue factor and *de novo* localized thrombus formation.

INFLAMMATION AND THROMBOSIS FORMATION

Local inflammation is associated with a procoagulant state. One proposed explanation for this association is that activated coagulation in acute infection was evolutionarily advantageous to capture circulating microbes in localized thrombi to limit pathogenesis and spread of infection.¹⁷ Infection, inflammation, sepsis, and immune dysregulation cause release of tissue factor receptor activity from macrophages. Alveolar macrophages also express tissue factor.¹⁸ Tissue factor expressed by inflammatory cells promotes conversion of prothrombin to thrombin leading to a shift from a fibrinolytic environment to a thrombotic state.¹⁹ Local inflammation in the lung parenchyma might also be expected to lead to increased thrombosis in the lungs.

Risk factors for isolated PE differ from the risks of PE with DVT, which may be expected if isolated PE represents *in situ* thrombosis originating from a different pathophysiologic mechanism. PE without DVT is associated with a younger age, recent surgery and hospitalization without being bedridden.²⁰ Mortality for PE without DVT was 4.6% compared to 12.9% in patients with PE and DVT. In a recent retrospective review study,

Van Langevelde et al. examined risk factors for DVT and PE. They found diseases that cause pulmonary inflammation such as COPD, pneumonia, and sickle cell disease were associated with a high incidence of PE but not DVT. In the paper's discussion, they suggest that pulmonary inflammation may contribute to localized *in situ* thrombosis.²¹

Multiple recent studies support a connection between pulmonary inflammation and PEs. New research suggests clotting factors and tissue factor can pass between blood vessels into the airways of patients with asthma.²² In a large population-based study of 31,000 patients, asthma was associated with an increased hazard ratio of 3.24 for PE when compared to patients without asthma.²³ In another recent study of 648 patients with asthma, Majoor et al. found that patients with severe asthma had an increased risk of PE but not DVT.²⁴ Similarly, patients with COPD have an increased incidence of PE; up to 25% of patients have concurrent PE during exacerbations.^{25,26} This evidence suggests physicians can no longer consider diseases of the pulmonary circulation separately from diseases of the airways.²⁷

LIMITATIONS TO A MODEL OF *IN SITU* PULMONARY ARTERY THROMBOSIS

Although recent studies suggest a connection between local pulmonary inflammation and pulmonary thrombus, there are also several significant limitations to the theory of in situ thrombosis. Many of these limitations were first laid out by Velmahos et al. in their 2009 paper introducing a model of in situ thrombus in trauma patients.²⁸ The first limitation is the possibility that when PEs are being detected without peripheral DVTs, the entire clot dislodges instead of a part of the clot breaking off, and so DVTs are not detected on ultrasound scans of the extremities. Another possible explanation is that current compression ultrasound techniques are not sensitive enough to detect all peripheral DVTs in the extremities and so they may be present and contributing to PEs but remain undetected. A third possible explanation is that a subset of PEs originates from clots in the upper extremities or pelvic veins, which are not routinely scanned by compression ultrasound.

To address these limitations, Van Langevelde et al. completed a prospective study of 100 patients with CTA diagnosed PE and used full body MRI scans to look for peripheral thrombosis in the upper extremities, pelvis, and abdomen in addition to the lower extremities. They found that 56% of patients had isolated PE without any peripheral thrombus.²⁹ This study did not



address the possibility that these findings were due to cases where the entire clot dislodged from the peripheral vein. Other limitations include the fact that MRI may not be highly sensitive for thrombus and thus may not be detecting all peripheral clots. Van Langevelde et al. also suggested that thrombi in the pulmonary artery could originate from thrombi right atrium in patients with atrial fibrillation.

CLINICAL IMPLICATIONS

Treatments are not likely to change for in situ thrombosis when compared to those for PE. Current research shows that patients should receive 3 months of anticoagulation for venous thromboembolism with reversible, provoked etiologies and indefinite anticoagulation for patients with unprovoked, or persistent and progressive etiologies.³⁰ Case studies suggest localized thrombus does not undergo fibrinolysis in the 3 months patients with idiopathic PE receive anticoagulation for active disease.¹⁴ Due to ongoing disruption of smooth blood flow and the pulmonary fibrinolytic environment, patients with in situ pulmonary artery thrombosis likely require indefinite anticoagulation. Treatment of patients with placement of inferior vena cava filters (VCFs) is likely to differ in patients with in situ thrombosis as compared with PE. VCFs are placed in patients with PE with contradictions to anticoagulation to prevent recurrent emboli from traveling from the pelvic veins and lower extremities up the inferior vena cava to the pulmonary arteries.³¹ If the thrombosis originates in the lung, VCFs would be unnecessary in patients receiving anticoagulation.

The most serious consequence of *in situ* thrombosis is likely pulmonary hypertension and right heart strain. Chronic thromboembolic pulmonary hypertension (CTEPH) develops in 4.6% of patients with acute PE, resulting in considerable morbidity and mortality.³² Patients with *in situ* pulmonary artery thrombosis are likely at increased risk for development of CTEPH due to retained residual clots and disrupted blood flow. Due to concern for right heart strain and potentially CTEPH, frequent echocardiography may be warranted in patients with *in situ* thrombosis.

FUTURE INVESTIGATIONS

Although there is evidence of localized thrombosis in the pulmonary arteries, there are few studies that investigate the pathophysiology of these phenomena. Currently, research in this area is focused on *in situ* thrombosis in trauma patients. One group, Kumar et al.⁵ recently published a study examining the response of pulmonary artery endothelium to inflammatory mediators to explore the molecular origins of *in situ* thrombosis in trauma patients. Future directions could focus on autopsy studies to determine if *in situ* pulmonary artery thrombosis can be differentiated from pulmonary embolus based on histology. There is no current data available on treatment outcomes for patients with *in situ* thrombosis, and future research should also examine whether treatment for *in situ* thrombosis should include surgical therapy to reduce clot burden in patients with right heart strain or CTEPH.

Thus far, investigations of *in situ* thrombosis have focused on diagnosis by CTA.

Transesophageal echocardiogram (TEE) is also potentially a useful way to examine the pulmonary arteries. Future research should focus on identifying thrombus formation and examining if it is possible to differentiate thrombus from emboli with TEE. Due to increased risk of PE and likely *in situ* thrombosis in patients with COPD and asthma, a study of TEEs in this patient population to screen for PEs, thrombosis, and possible right heart strain may yield additional information about the role of venous thromboembolism in pulmonary diseases.

CONCLUSION

PE is a common disease with significant mortality. When filling defects are found on CTA, they are almost universally assumed to be emboli from a peripheral DVT. However, new studies have found that half of all PEs are found without evidence of a peripheral thrombus. These findings have led to the theory that localized inflammation, endothelial cell damage, and disruption of blood flow cause de novo formation of clots within the pulmonary artery or in situ thrombosis. Although treatment with anticoagulation would likely not change for patients with in situ thrombosis as compared to PE, patients with in situ thrombosis would likely not benefit from placement of VCFs. Patients with COPD and asthma are at increased risk for PE and are also likely at risk for in situ thrombosis. The theory of in situ thrombosis presents a new perspective on the traditional understanding of the pathophysiology of PE. Further research needs to be done to truly understand the clinical implications of this new model in terms of treatment, patient outcomes, and prevention.

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