Understanding Pulmonary Vein Thrombosis: Etiology, Risk Factors and Management

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Abstract

Pulmonary vein thrombosis (PVT) is an uncommon and potentially fatal condition that is often misdiagnosed due to its nonspecific symptoms such as cough, haemoptysis, and dyspnoea. The true prevalence of PVT is difficult to determine and is mainly derived from case reports, influenced by the lung's robust venous collateral network. Specific clinical situations, including post-lobectomy, lung transplantation, and metastatic cancer, can precipitate PVT. Accurate and prompt diagnosis, which requires a high index of suspicion and advanced imaging techniques like CT, MRI, and echocardiography, is crucial to prevent severe complications such as peripheral embolization and acute stroke. Risk factors include surgical procedures, cancers, and potentially atrial fibrillation, with a high post-surgical thrombosis risk, especially after left upper lobectomy. Management must be tailored to the underlying pathology and can include antibiotics, anticoagulation, thrombectomy, and lung resection. This review underscores the need for increased clinical awareness and comprehensive diagnostic approaches to mitigate the severe consequences of PVT.

Keywords: Pulmonary Vein; Haemoptysis; Thrombosis.

Introduction

Pulmonary vein thrombosis (PVT) is an uncommon and potentially life-threatening condition often overlooked in clinical practice, posing a significant threat.[1] Onuigbo's autopsy series emphasizes the significance of increased awareness while drawing attention to the historical underdetection of PVT.[1] The true incidence of PVT is still difficult to ascertain and is primarily dependent on case reports found in the literature. PVT is uncommon because of a strong network of venous collateral vessels that drain the lung, yet obstructive episodes might occur under certain clinical circumstances.[2]

PVT has been reported in several clinical settings, including lung transplants, post-lobectomy cases, and associations to metastatic cancer, some of which are classified as idiopathic. Recognizing these associations is crucial for a comprehensive understanding.[3,4] Symptoms of PVT, such as dyspnea, cough, or hemoptysis, are nonspecific, making diagnosis challenging and accurate diagnosis requires a high level of suspicion, as the condition can be easily missed. The diagnostic difficulties emphasize the need for heightened awareness among healthcare professionals. Neglecting timely identification and treatment of PVT may lead to catastrophic consequences, including peripheral embolization and acute stroke.

Given its rarity and severe complications, a comprehensive review of the literature is essential to establish a foundational understanding of PVT. This paper is an invaluable tool that provides crucial background information for future research and clinical awareness.

Clinical Presentation

Individuals diagnosed with PVT often present with either no apparent symptoms or experience nonspecific indications such as cough, hemoptysis, and dyspnea, which are commonly attributed to pulmonary edema or infarction.[1-8] The hemodynamic manifestations of PVT lack specificity and can mimic conditions like acute graft rejection, showing hypoxemia and interstitial infiltrate in the transplanted lung. They also resemble symptoms of right ventricular failure or reperfusion injury.[9]

In most instances of PVT, there is a simultaneous elevation in pulmonary artery pressure alongside systemic hypotension and diminished cardiac output. Additionally, respiratory parameters undergo a decline, characterized by a reduction in oxygenation levels, an increase in carbon dioxide levels (hypercapnia), and a decrease in pulmonary compliance.[10]

It is noteworthy that the clinical presentation of PVT can vary, as illustrated by a case where persistent fever was the sole symptom.[11] Moreover, Schiller and Madge noted systolic murmurs in various locations in three out of 16 patients, though the significance of this observation remains unclear.[1] Furthermore, neurologic deficits resulting from cerebral emboli may manifest as the exclusive symptom in certain instances.[5,12]

This diverse array of symptoms and their varying severity underscores the complexity of diagnosing PVT. Recognition of these diverse clinical presentations is crucial for healthcare professionals to enhance the accuracy and timeliness of diagnosis, enabling prompt intervention in patients with PVT.

Risk Factors

Case reports meticulously outline a range of risk factors associated with PVT as illustrated in Figure 1. These include vein-related surgical procedures such lobectomies or lung transplants, atrial fibrillation treated with radiofrequency catheter ablation (RFCA), sclerosing mediastinitis, and certain primary or secondary lung tumors. Atrial myxoma, congenital pulmonary venous stenosis, and mitral stenosis with an obstructive left atrial clot are other less common risk factors.[2]

The earliest documented case of non-surgical PVT, dating back to 1925, emerged from the autopsy of a young male with testicular cancer who tragically succumbed to an acute collapse during hospitalization.[13]

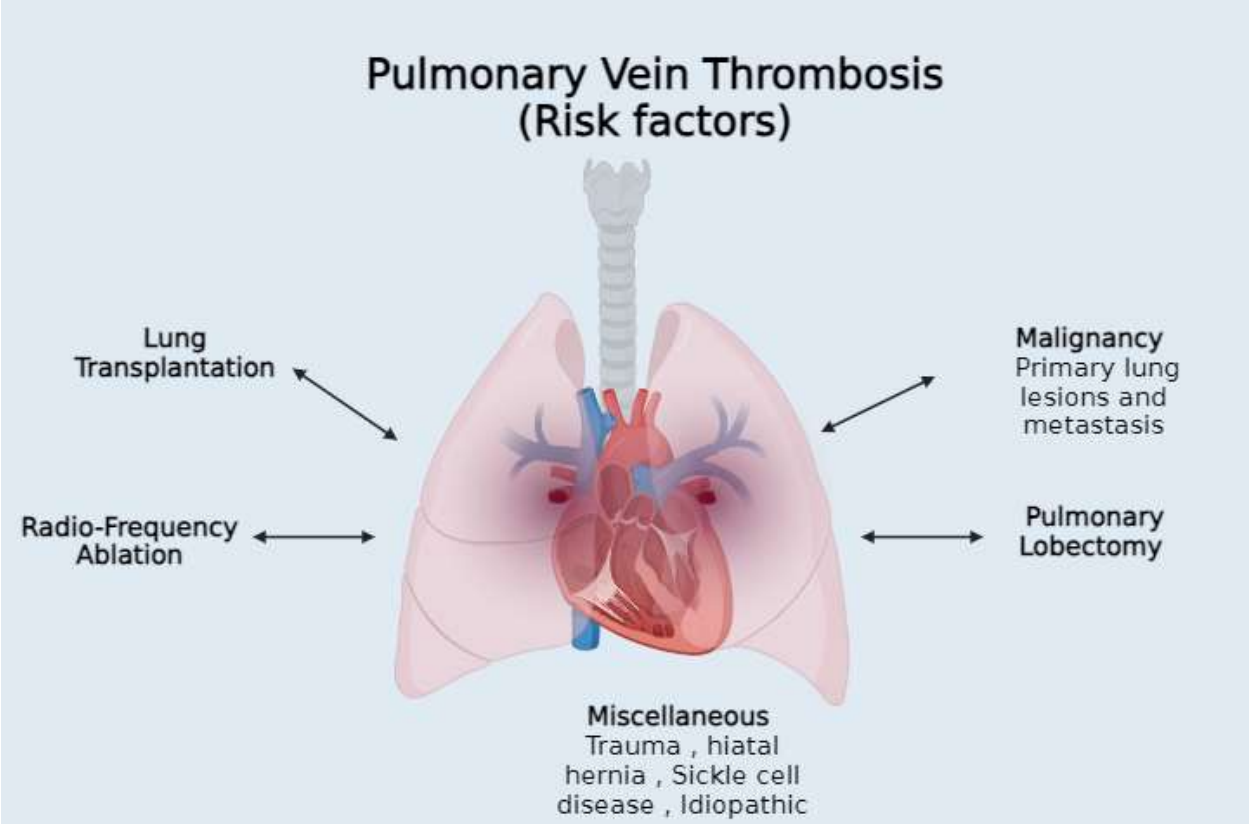

Figure 1: Pulmonary vein thrombosis risk factors.

Malignancy

The predominant malignant trigger for PVT is a primary lung neoplasm, particularly bronchogenic carcinoma.[1] However, PVT can also appear after metastatic tumors,[14] such as but not exclusive to liposarcoma,[14] small cell lung cancer,[15] mantle cell lymphoma that starts in the small intestine[6] and metastatic sarcoma.[6] Predisposing factors that increase the likelihood of malignant PVT include stagnation from mechanical compression related to tumor size and a paraneoplastic hypercoagulable state. The endothelium lining may subsequently sustain damage as a result of this compression.[16]

Atrial Fibrillation

Uncertainty persists regarding whether atrial fibrillation, leading to blood stasis, constitutes a risk factor for thrombus development.[17] There is also a lack of clarity concerning the thromboembolic risk linked to left upper pulmonary vein thrombus in atrial fibrillation, particularly in the post-cardioversion period. Given the increasing prevalence of atrial fibrillation, catheter procedures for ablation have emerged as a novel treatment for drug-refractory cases, but complications from radiofrequency ablation can manifest significantly in the pulmonary system.

Various series indicate a wide prevalence range of pulmonary vein stenosis after radiofrequency ablation, spanning from three to 42%, influenced by the method of assessing venous stenosis and the ablation technique employed.[18] Saad et al., in the largest consecutive series available, reported severe pulmonary vein stenosis (defined as 70% luminal narrowing) in five percent of 335 patients, with 2.1% experiencing total occlusion of at least one pulmonary vein.[18] In a different series, Ernst et al. documented total pulmonary vein occlusion in 1.3% of 229 patients.[18] Lastly, Robbins

et al. detailed severe pulmonary hypertension in two patients who encountered substantial narrowing of all four pulmonary veins near the left atrial junction three months after successful radiofrequency ablation.[18]

Raquel López-Reyes et al. reported another case of PVT post radiofrequency ablation of the pulmonary veins, where pulmonary resection was performed due to hemorrhagic recurrence.[19]

Post Lung Transplantation

PVT has been reported to develop in 15% of patients in the first 48 hours after lung transplantation and to the risk last for up to two years.[6,7,13,16] Improved surgical methods are thought to be the reason for the reported incidence's declining tendency over time.[4] Patients experiencing PVT in this context may exhibit symptoms and findings resulting from pulmonary venous flow obstruction, coupled with thromboembolic events. Thrombus formation is likely linked to endothelial injury during surgery, coupled with blood stasis in the resultant blind pulmonary vein stump.[16]

Interestingly, no specific risk factors have been identified for donors or recipients, such as a history of deep vein thrombosis or prothrombotic disorders.[4,20] While some patients received perioperative bovine pancreatic trypsin inhibitor (aprotinin), the thrombotic risk associated with this agent remains uncertain.[20] An analysis of 153 lung transplant recipients revealed that 45 patients developed upper or lower extremity deep vein thrombosis. This occurrence showed a strong association with factors such as the presence of an indwelling catheter, infections, and the use of prednisone with mycophenolate mofetil plus either cyclosporine or tacrolimus.[20]

Post Lobectomy

As of the latest updates, there have been only six documented instances of Pulmonary Vein Thrombosis (PVT) following lobectomy.[21-25] In all reported cases, the involvement was exclusive to resection of the left upper lobe, resulting in thrombus formation within the left upper pulmonary vein stump. The actual frequency of PVT occurrences post-lobectomy remains elusive, likely underestimated, particularly among asymptomatic individuals who forego postoperative imaging using Transesophageal Echocardiography (TEE) or Computed Tomography (CT).[16] Despite its potential underdiagnosis, PVT after lobectomy is not benign, posing risks of thromboembolic complications, including transient ischemic attacks and strokes.

Ohtaka et al. conducted a retrospective study, revealing that thrombosis in the pulmonary vein stump occurred in 3.3% of patients who underwent lobectomy and 17.9% of those who specifically underwent left upper lobectomy (LUL).[17] Clinically, thrombi in the systemic circulation usually arise from atrial fibrillation. While left lobectomy is suggested as a potential risk factor for atrial fibrillation, the 18 patients in the Ohtaka study exhibited no signs of atrial fibrillation when the thrombosis was diagnosed.[17] This underscores the unique association of PVT with left upper lobe resection, emphasizing the importance of vigilant monitoring and thorough diagnostic approaches in such cases.

Others

PVT incidents have been sporadically documented following blunt chest trauma.[5,26] Additionally, a case has been reported in a patient with sickle cell disease, where vascular stasis due to hypoxia and sickling was hypothesized as the underlying cause.[16] Another reported case identified a large hiatal hernia as a potential contributor to PVT, attributing it to compression of intrathoracic structures.[5]

In the realm of idiopathic causes, PVT has been associated with hemoglobinopathy.[7,27] Remarkably, only two previous instances of spontaneous idiopathic PVT have been documented.[28,29]

Diagnosis

Clinical diagnosis of PVT poses challenges due to nonspecific signs and symptoms reported. Previous cases have relied on either pulmonary angiogram or pathological examination for accurate diagnosis.[3] The discovery of

unsuspected PVT during surgery carries a grim prognosis due to the high likelihood of massive embolization. Therefore, preoperative diagnosis becomes crucial, with alternative techniques of pulmonary venous clamping and cardiopulmonary bypass being potential strategies to minimize the risk of embolization.[1]

Postoperative diagnosis of PVT after lobectomy or lung transplantation does not typically present specific difficulties. It often manifests a few days post-surgery with sudden-onset dyspnea, and chest X-ray studies reveal unilateral airspace disease without volume loss.[5] Notably, physical examination and plain chest radiography lack diagnostic utility.[4] The identification of PVT requires a comprehensive approach, involving conventional imaging modalities such as pulmonary angiography, transthoracic echocardiography (TTE), and Transesophageal Echocardiography (TEE), which can differentiate between tumor and thrombus. Additionally, late-phase CT with intravenous contrast material injection is employed to reduce flow artifacts. More recently, MRI has also emerged as a diagnostic tool.[1,2,7,16]

Complications

PVT is frequently linked to complications such as pulmonary infarction, pulmonary edema, right ventricular failure, and allograft failure as summarized in Figure 2.[4,30] Despite being less frequently documented, peripheral embolism poses a potential complication, leading to incidents of limb ischemia, stroke and renal infarction.[31-34]

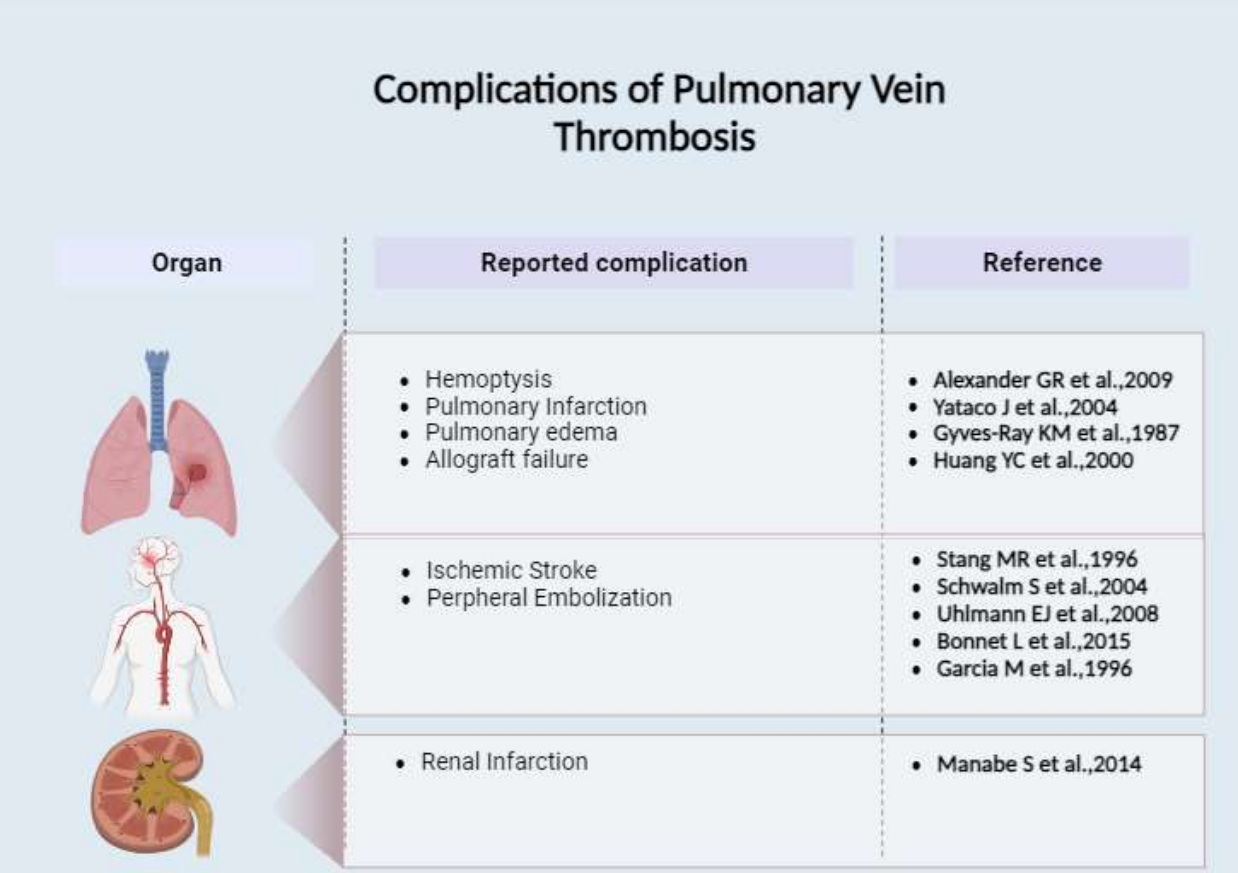

Figure 2: Complications of pulmonary vein thrombosis.

In lung transplant patients, the occurrence of acute PVT can have catastrophic consequences, leading to early allograft failure. This failure is attributed to the obstruction of pulmonary venous flow, causing severe pulmonary edema.[6,10] A prospective study involving 87 consecutive adult lung transplant recipients utilized Transesophageal Echocardiography (TEE) within two days after surgery. During this assessment, PVT was diagnosed in 13 (15%) of

the 87 patients in the early postoperative period. Among these patients, five (38%) succumbed during the perioperative period, with three of the five deaths resulting from graft failure. Another report highlighted a 90-day mortality rate of 38% following lung transplant.[35]

Moreover, PVT has been observed to lead to systemic emboli, resulting in cerebrovascular accidents.[1,6,20,21,23,27] A thorough examination of existing literature reveals a limited number of case reports emphasizing the occurrence of stroke and systemic embolization attributed to PVT. To date, no randomized control trials have been conducted on this specific aspect. In a 2002 study conducted by Grau et al., patients with cryptogenic stroke were scrutinized for PVT using MRV, and the study did not establish PVT as a significant contributor to the etiology of ischemic stroke in these cases.[33] However, the study faced notable limitations, primarily due to frequent inadequate visualization of the left pulmonary veins, stemming from constraints in MRI techniques. With advancements in radiologic techniques over the last 10-15 years, it is conceivable that more cases of PVT, particularly within the left pulmonary venous system, could be identified.[33]

Furthermore, renal infarction has been identified as a complication associated with PVT. To our knowledge, only six instances of renal infarction following lung resections have been documented, and none of these cases exhibited detectable well-known causes for renal infarction.[34] Among the two patients who experienced renal infarction, PVT was visually confirmed. In the remaining four cases of early postoperative renal infarction, the diagnosis was established as idiopathic renal infarction, potentially linked to the postoperative and/or paraneoplastic hypercoagulable state. However, in three cases, the coexistence of thrombus in the pulmonary vein was not examined, and in one case, it was not mentioned, as PVT had not been previously recognized as a risk factor for renal infarction. Furthermore, the frequency of thrombus formation in the stump of the left superior pulmonary vein (LSPV) is more prevalent than previously assumed. Therefore, a history of left upper lobectomy should be considered a potential risk factor for renal infarction, and PVT must be recognized as a potential source of thromboembolism to accurately diagnose the cause of renal infarction.[36]

In addition, other rare complications commonly associated with idiopathic PVT encompass pulmonary gangrene, peripheral embolism, and massive hemoptysis.[7,27,37]

Management

The management of PVT should be put in the context of the underlying disease pathology.[36] At present, there is no randomized controlled trials, evidence-based guideline or expert consensus recommendation for the management of PVT. Management may include the use of antibiotics, systemic anticoagulation, thrombectomy and/or lung resection (36).

Antibiotics therapy

Due to increased risk of infection in patients with PVT post lung transplant and post lung resection, antibiotics are usually initiated.[36] In addition, the possible association between infection and thrombosis in patients post lung transplant, makes antibiotics necessary in the management.[20]

However, a thorough review of the literature indicates that no studies have specifically evaluated which antibiotics are most appropriate for PVT in this patient population. As such, the choice of antibiotics becomes a clinical decision that must be tailored to the individual patient's context. Several factors should be considered when selecting an antibiotic regimen: the patient's age, immune status, the specific lung procedure performed, and the overall severity of the patient's illness.

For instance, Immunocompromised patients, particularly those post-lung transplant, may require broader-spectrum antibiotics or prophylaxis against opportunistic infections. The type of lung procedure (e.g., transplant vs. resection) can influence the risk of specific infections, guiding antibiotic choices. Additionally, critically ill patients may necessitate initial broad-spectrum antibiotic coverage, with adjustments based on clinical response and culture results.

Despite these considerations, there is no evidence favoring any specific antibiotic regimen for the treatment or prevention of thrombosis in PVT. Moreover, no studies have compared outcomes between using antibiotics versus not using antibiotics in patients with PVT following lung transplant or resection. Therefore, the use of antibiotics in this context remains empirical, guided by clinical judgment, patient health, and any present signs or risk factors for infection.

Anticoagulation

In systematic review of 28 case-reports, 23 cases were treated with anticoagulation.[38] The anticoagulation management of PVT in the context of malignancy should fall under the umbrella of cancer associated thrombosis (CAT). There are several evidence-based guidelines that address CAT.[38-40] In general, anticoagulation is usually initiated with either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) depending on the renal function and bleeding risk. LMWH used to be standard of care of long term management of CAT, however, there is now enough data to showing the non-inferiority of direct oral anticoagulant (DOAC) in the context of CAT.[39-41]

There are several case reports of successful treatment of PVT using DOACs with different underlying pathologies.[42-45] DOACs have been showed be non-inferior to warfarin or LMWH in several clinical trials in the context of venous thromboembolism, cancer associated thrombosis and in stroke prevention in atrial fibrillation.[46-49] In addition, DOACs are associated with lower major bleeding risk, do not require monitoring and are more convenient. Therefore, DOACs are the prefer oral anticoagulation option in patients with PVT, in the right context.

The duration of anticoagulation in PVT is also depends in the clinical context. For example, PVT in the context of CAT, should probably be treated for at least 6 months.[37-39] Regardless of the underlying pathology, anticoagulation should be given for at least 3-6 months.[36]

Embolectomy and Lung resection

Successful embolectomy was narrated in two case reports. The 1st case was in the context of progression of PVT despite being on anticoagulation and the other was after bilateral lung transplant.[38,50] Lung resection might be needed in selected cases. This may include cases with massive hemoptysis, pulmonary necrosis or gangrene.[8,36]

Thrombolysis

Thrombolysis with recombinant tissue plasminogen activator (rtPA) was successfully utilized in a single case report of a lung transplant recipient with a left atrial thrombus.[51] However, this remains anecdotal and not broadly recommended.

Conclusion

In conclusion, the management of PVT must be tailored to the underlying pathology, with options including antibiotics, anticoagulation, thrombectomy, and lung resection. Antibiotics are essential following lung transplant or resection because of the risk of infection, despite lack of randomized controlled studies. Anticoagulation, particularly with DOACs, is commonly used, offering convenience and lower bleeding risks. Duration of anticoagulation generally spans 3-6 months, contingent on the clinical scenario. In specific cases, embolectomy or lung resection may be necessary. Further research is essential to establish comprehensive guidelines for PVT management.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used [Quillbot] to improve the language used and eliminate grammatical mistakes]. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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