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A REVIEW ON VENOUS THROMBOEMBOLISM

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ABSTRACT

Venous thromboembolism is a broad term for deep vein thrombosis and pulmonary embolism. It is a condition in which blood clots form in the deep veins of the legs, pelvis, or arms and travel to the heart and lungs. It is the third most cardiovascular illness after acute coronary syndrome and stroke. Deep vein thrombosis is the clotting of blood in deep veins of the body. Deep vein thrombosis is not, in itself, life-threatening, the condition can become deadly if the clot travel to the lungs and become pulmonary embolism. Pulmonary embolism is the occlusion of pulmonary arteries by the clot that is formed in the deep veins of the body that dislodges from the veins and travels through the heart to pulmonary arteries. It is a fatal condition if untreated immediately. Thrombus is formed mainly due to blood stasis, hypercoagulability, vessel wall injury. Symptoms mainly include erythema, pain, swelling at the site of deep vein thrombosis and dyspnea, tachypnea, pleuritic chest pain, cough, electrocardiography changes for pulmonary embolism. Treatment is mainly anticoagulation using heparin and other anticoagulants. Surgical options like embolectomy and inferior vena cava filters are also preferred.

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INTRODUCTION

The heart pumps oxygenated blood through the aorta to smaller arteries. When the blood supplies nutrients to organs, it returns through veins for oxygenation in the lungs. Blood clots called thrombi often develop in the deep veins of the body. Pulmonary embolism occurs when clots break off from walls of the veins and travel to the heart, then to the pulmonary arteries. The broader term venous thromboembolism (VTE) refers to deep vein thrombosis (DVT), pulmonary embolism (PE), or to a combination of both [1].

Prevalence

Venous thromboembolism is the third most common cardiovascular illness after acute coronary syndrome and stroke [2].Venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism, afflicts an estimated 71 per 100,000 persons yearly. Approximately one-third of patients with venous thromboembolism have a pulmonary embolism, whereas two-thirds have deep vein thrombosis alone[3].

Risk Factors of Venous thrombo embolism

A large number of baseline characteristics were tested as potential risk factors for deep vein thrombosis and pulmonary embolism in a multivariate conditional logistic regression model, as previously reported.Independent risk factors for venous thromboembolism include age at incident venous thromboembolism event, male sex, calendar year, institutionalized at onset (example: hospitalized or in a nursing home or hospitalized within the previous 90 days [with and without surgery]), active malignant neoplasm (with and without chemotherapy), congestive heart failure; serious neurological disease resulting in lower extremity paresis, major fracture or severe soft tissue injury, central vein catheterization or transvenous pacemaker placement, prior superficial vein thrombosis, varicose veins, and serious liver disease [4].

Major risk factors for pulmonary embolism.
Idiopathic, primary, and unprovoked.

- No apparent cause.
- Old age (>65 years).
- Long-haul travel.
- Associated with thrombophilia (example: factor V Leiden orprothrombin gene mutation).
- Obesity.
- Cigarette smoking.
- Hypertension.
- Metabolic syndrome.
- Air pollution.

Secondary and provoked

- Immobilization.
- Postoperative.
- Trauma.

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- Oral contraceptives, pregnancy, postmenopausal hormonal replacement.
- Cancer.
- Acute medical illness (example: pneumonia, congestive heart failure) [5, 6, 7, 8, 9, 10].

Definitions

Deep vein thrombosis

Deep vein thrombosis means clotting of blood in deep veins of the body. The lower extremities of the body like lower limbsare the most common site for deep vein thrombosis, but other affected locations include the upper extremities called upper limbs and the mesenteric veins and pelvic veins, as well as the cerebral veins. A proximal lower-extremity deep vein thrombosis (defined as occurring in the popliteal vein and above of popliteal vein) is prone to an estimation of 50% risk of pulmonary embolism if not treated; while approximately 20% to 25% of calf vein thrombi propagate (in the absence of treatment) to involve the popliteal vein or above. Approximately 10% of all deep vein thrombosis cases involve the upper extremities. Complications are more common following deep vein thrombosis in the upper extremities than in the lower. Pulmonary embolism occurs in between 6% and 10% of cases following deep vein thrombosis in an upper extremity and in 15% to 32% of cases following deep vein thrombosis in a lower extremity[11].

Pulmonary embolism

A pulmonary embolism is categorized as definite when confirmed by pulmonary angiography, computed tomographic scan, magnetic resonance imaging scan, or the findings of the pathologic examination of a thrombus that had been removed at surgery or autopsy[4].

Relationship between deep vein thrombosis and acute pulmonary emboli.

Patients with deep vein thrombi are ten times more likely to have a lower extremity thrombus than an upper extremity thrombus. The more proximal the thrombus within the extremity, the more likely it is to embolize into the lungs as a pulmonary embolus leading to pulmonary embolism. When a thrombus breaks from a deep vein within the venous system, it travels towards the venous cava and then it progresses to the right atrium, then goes through the tricuspid valve into the right ventricle. From the right ventricle, it passes through the pulmonary valve (pulmonic valve) to the lungs. An extremely large clot may get lodged at the bifurcation between the right and left pulmonary arteries; this is known as a “saddle” pulmonary embolus [12].

Recurrence

Many individuals who have the first episode of deep vein thrombosis and pulmonary embolism will have a recurrent event. For some, the first event of venous thromboembolism is not diagnosed, whereas for other venous thromboembolism recurs after anticoagulation therapy is stopped. There are two associated illnesses that arise after pulmonary embolism and deep vein thrombosis they are chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome [13].

Pathophysiology

Venous thrombi, composed predominately of red blood cells but also platelets and leukocytes bound together by fibrin, form in sites of vessel damage and areas of stagnant blood flow such as the value of the deep veins of the calf or thigh. Thrombi either remain in the peripheral veins, and undergo endogenous fibrinolysis and recanalization, or they embolize to the pulmonary arteries and cause pulmonary embolism [14]. Thrombus formation and propagation depend on the presence of abnormalities of blood flow, blood vessel wall, and blood clotting components, known collectively as Virchow's triad [15]. Deep vein thrombosis and pulmonary embolism are different, but common aspects of the same dynamic disease process known as venous thromboembolism (VTE). Pulmonary embolism results from sudden occlusion of pulmonary arteries by thromboembolic originating in the deep veins of the calf or pelvis in the majority of cases. This occlusion has variable and transient clinical and pathophysiologic consequences, involving both mechanical and reflex effects of vascular occlusion with a consecutive perfusion defect as well asthe release of vasoactive and other inflammatory mediators[16]. The pathogenesis of venous thromboembolism is associated with the triad of interdependent factors described by Virchow more than 100 years ago, consisting of,

- Hemodynamic imbalance (blood stasis),
- Endothelial vessel wall damage, and
- A local or systemic state of hypercoagulability.

Accordingly, venous thrombosis develops when stasis in the deep veins of the legs occurs at times of increased blood coagulability and when vessel wall injury is present simultaneously [17].

Blood stasis

Venous stasis represents an important pathogenic factor in the development of pulmonary embolism. The role of venous stasis has been investigated in patients with spinal cord injuryand other forms of paralysis. These studies show that the majority of venous thrombi originate in regions of slow blood flow, e.g., the large venous sinuses of the calf and thigh or in valve cusp pockets or bifurcations of the venous system. This becomes particularly apparent in situations of physical inactivity such as bed rest and during air travel, where a lacking pumping action of the large muscles causes decreased blood flow or even stasis. It has been suggested that blood pooling leads to activation of the coagulation system, thus resulting in a state of local hypercoagulability. In addition, possible endothelial damage from distension of the vessel walls by the pooling blood leads to further activation of the homeostasis system. The activation products of clotting and fibrinolysis can also induce endothelial damage which, in turn, promotes a local state of hypercoagulability.

Hypercoagulability

The risk of venous thrombosis is increased when the homeostatic balance between pro- and anticoagulant forces is shifted in favor of coagulation. When this imbalance is due to an inherited defect, the resulting hypercoagulable state remains a life-long risk factor for thrombosis. In contrast, hypercoagulability due to a transient factor should be treated only as long as the risk factor is present. In most cases, disturbances in the coagulation cascade arise in inherited thrombophilias [17].

Vessel wall injury

Since the combination of local vascular stasis and systemic hypercoagulability has been shown experimentally to produce thrombi within a few minutes, vessel wall damage is believed to be another essential component of venous thrombogenesis. Damage to the vascular endothelium is a particularly important predisposing factor to venous thrombosis after major hip or knee surgery. Next to an injury, sudden changes develop in the clotting system, particularly an increase in components of the Von Willebrand factor macromolecular complex and platelet aggregability which could further contribute to the state of hypercoagulability [18].

Pathogenesis of pulmonary embolism

Origin of the thrombus

Pulmonary emboli usually arise from thrombi originating in the deep venous system of the lower extremities when hemodynamic instability, a hypercoagulable state and vessel wall damage are present. Occasionally they may also originate in the pelvis, renal, or upper extremity veins and in the right heart. Iliofemoral thrombi are believed to be the source of most clinically recognized venous thromboembolism. Approximately 20% of calf vein thrombi propagate to the popliteal, femoral, or iliac veins (proximal venous thrombosis).

Thrombogenesis

There are fundamental differences between thrombi originating in arteries and those arising in veins. Whereas arterial thrombi are predominantly composed of platelets, venous thrombi consist mainly of fibrin and red blood cells. As mentioned above, venous thrombi prefer lowflowconditions and usually originate in the muscular veins of the calf or in the valve cusp pockets of the deepcalf veins. Coagulation at these sites is initiated by vascular intimal trauma and is augmented by both venous stasisand local or systemic perturbations of the coagulation cascade.

Emboli in transit

Right atrial or ventricular thrombi in patients with pulmonary embolism are emboli in transit and as such is a medical emergency due to their association with a high mortality rate [20]. The European Cooperative Study classified emboli in transit into two major categories according to sonomorphology, etiology, and clinical significance[21]. Type A thromboembolic are more prevalent in a subgroup of patients who have experienced a first embolic event [22]. Patients with type A thrombi were considered to comprise a high-risk group that was characterized by severe PEs of which one third were fatal within 24 h of the diagnosis [23 24].Type B thrombi, which shows partial organization. Moreover, type B thrombi showed higher resistance to thrombolytic treatment [25, 26, 27].

Feature/property	Type A thrombi	Type B thrombi
Shape	Long and thin	Round to oval
Size	2-10 cms	<5cm
Morphology	Hypoechoic and heterogeneous	Hyperechoic and homogenous
Sonomobility	high	Low to immobile
Association	Pulmonary embolism	Right ventricular thrombogenetic abnormalities such as congestive heart failure, heart failure, etc.
Origin	Peripheral deep vein thrombosis	Right ventricular
Preferential location	Right atrial with prolapse into the right ventricle	Right ventricular
Prognosis	Serious/poor	Good

Characteristics of intracardial type A and type B thrombi detected using echocardiography or transesophageal sonography [23, 28, 29, 30].

The pathophysiology of pulmonary embolism is extremely complex. The pathophysiologic consequences of pulmonary embolism result from both the direct effects of artery occlusion on the function of the heart, pulmonary vessels, lung parenchyma, and pleura. The alterations are further modified indirectly by various cardiopulmonary reflexes.

Pulmonary effects

Pulmonary infarction

Sudden thrombotic occlusion of a vessel due to a thrombus fragment lodged within pulmonary artery results in an increase in pressure proximal to the thrombus and a decrease or cessation of flow distal to it. This leads to a number of consequences including the breakdown of surfactant, increase in protein content, and release of inflammatory mediators[31, 32].

Pulmonary hemorrhage (Incomplete infarction)

Intra-alveolar hemorrhage without necrosis is the most frequent finding in the first 2 days of pulmonary embolism. Characteristically, these lesions disappear completely within 2-4 days, in accordance with the resolution of the intra-alveolar hemorrhage[33].

Bronchoconstriction

Immediately following thrombotic occlusion there is an increase in airway dynamics, a fall in static compliance, and a fall in dynamic compliance[34].

Pulmonary gas exchange abnormalities

A basic pathophysiological dysfunction of pulmonary embolism refers to abnormalities in pulmonary gas exchange. These abnormalities observed in patients with pulmonary embolism are due to multiple causes and are related directly or indirectly to the following factors [35]:

- The size and type of the embolic material,
- The extent of the occlusion,
- The underlying cardiopulmonary status and
- The length of time since embolization.

In addition, hypoxemia resulting from the impaired gas exchange has been attributed to an increase in alveolar dead space, right-to-left shunting, ventilation/perfusion unbalance, and a low mixed venous oxygen level. The two latter mechanisms are believed to account for the majority of hypoxia and hypocapnia observed before and after treatment [36, 37].

Key points

- Virchow's triad aids treatment of venous thromboembolism
- Multiple situations and risk factors can contribute to venous thromboembolism
- Diagnosis of venous thromboembolism depends upon the combination of history, risk factors, and investigations
- Antithrombotic prophylaxis is safe and effective[15].

In hemodynamically critical patients, acutely elevated pulmonary vascular resistance results in decreased right

ventricular (RV) output and hypotension. To maintain healthy pulmonary pressure, the right ventricle must generate systolic pressures in excess of 50 mmHg and mean pulmonary artery pressures greater than 40 mmHg [38]. However the normal right ventricle is unable to generate these pressures, and right heart failure and cardiac collapse ensue. Moreover, elevated right ventricular wall tension can lead to decreased right coronary artery flow and ischemia. Cardiopulmonary collapse from pulmonary embolism is more common in patients with coexisting coronary artery disease or underlying cardiopulmonary disease [39].

Signs and symptoms

Deep vein thrombosis

Common symptoms of deep vein thrombosis in the upper and lower extremities include pain or tenderness and swelling. Signs on physical examination include increased warmth, edema, and erythema, and may also include dilated veins (collaterals) on the chest wall or leg. The clinical presentation of deep vein thrombosis, phlegmasia cerulea dolens, occurs most often in the setting of malignancy, heparin-induced thrombocytopenia (HIT), or other prothrombotic condition in which the thrombus completely occludes venous outflow, causing massive limb swelling, hypertension in the capillary bed, and eventually ischemia and gangrene if untreated [41].

Pulmonary embolism

The typical signs and symptoms of acute pulmonary embolism include dyspnea, tachypnea, and pleuritic chest pain. Other findings include apprehension, hemoptysis, cough, syncope, and tachycardia. Fever, gallop, accentuation of the pulmonary closure sound, or an S_3 and/or S_4 rales, and leg erythema or a palpable cord may also be found[41].

Diagnosis

Clinical probability assessment

Diagnosis of deep vein thrombosis and pulmonary embolism is dependent on several, mainly non-invasive, diagnostic techniques that should be used sequentially. Because the use of a validated diagnostic workup is associated with a substantially diminished risk of complications, the implementation of such standardized approaches is highly recommended[40].

	points
Wells score for deep vein thrombosis.*	
Cancer.	+1
Paralysis or recent plaster cast.	+1
Bed rest for>3 days or surgery <4 weeks.	+1
Pain on palpation of deep veins.	+1
Swelling of the entire leg.	+1
Diameter difference on affected calf >3 cm.	+1
Pitting edema (affected side only).	+1
Dilated superficial veins (affected side).	+1
The alternative diagnosis at least as probable as deep vein thrombosis.	-2
Wells score for pulmonary embolism.	+1.5 ·
Previous pulmonary embolism and deep vein thrombosis.	+1.5
Heart rate >100 beats per min.	+1
Recent surgery or immobilization.	+3
Clinical signs of deep vein thrombosis.	+3
The alternative diagnosis is less likely than pulmonary embolism.	+1
Haemoptysis.	+1
Cancer.	+1
Revised Geneva score for pulmonary embolism.‡	+3
Age >65 years.	
Previous deep vein thrombosis and pulmonary embolism.	+2
The surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month.	
Active malignancy (solid or hematological malignancy, currently active or considered as cured since less than 1 year)	+2
Unilateral leg pain.	+3
Haemoptysis.	+2
Heart rate 75-94 beats per min.	+3
Heart rate of ≥95 beats per min.	+5
Pain on deep vein palpation in the leg and unilateral edema.	+4

Scoring systems to assess the probability of suspected DVT or PE on the basis of an item and assigned points. DVT=deep vein thrombosis. PE=pulmonary embolism. *Patients with a score of 0 are low risk, 1-2 are the intermediate risk, and ≥3 are high risk. †For the initial rule, patients with a score of 0-1 are low risk, 2-6 are the intermediate risk, and ≥7 are high risk; for the dichotomized rule, patients are unlikely or likely to have PE if they have scored ≥4 and ≤4, respectively. ‡Patients with a score <2 are low risk, 2-6 are the intermediate risk, and ≥6 are high risk.

Clinical probability assessment.

Revised Geneva criteria for pulmonary embolism

The Revised Geneva criteria is a tool is commonly used as an alternative to the Well's criteria. It is also based on a point system [42].

- Clinical presentations that have a score of 1: Age greater than 65 years.
- Clinical presentations that have a score of 2: Hemoptysis, active malignancy and surgery or fracture within the past 1 month.
- Clinical presentations that have a score of 3: Previous history of pulmonary embolism or deep vein thrombosis, heart rate between 75 -94 beats per minute and unilateral leg pain.
- Clinical presentations that have a score of 4: Pain on leg palpation, unilateral edema.
- Clinical presentations that have a score of 5: Heart rate greater than or equal to 95 beats per minute.

A score of more than 5 implies that a pulmonary embolism is likely. A score less than or equal to 5 makes a pulmonary embolism unlikely [43].

D-dimer measurement for diagnosis of deep vein thrombosis and pulmonary embolism

Several high-quality systematic reviews have recently evaluated the use of D-dimer testing for diagnosis or exclusion of venous thromboembolism[44].D-dimer, a degradation product of cross-linked fibrin, is typically elevated with acute venous thromboembolism [45, 46].D-dimer assays are sensitive but non-specific markers for venous thromboembolism so positive D-dimer results arenotuseful to "rule in" the diagnosis; rather the potential value is for a negative test result to "rule out" the diagnosis[47,48].

Diagnosis of deep vein thrombosis

Duplex Ultrasonography

It is the imaging procedure of choice for the diagnosis of deep vein thrombosis because it is readily available and is less invasive and less costly than other procedures. It is useful for detecting deep vein thrombosis in symptomatic patients; however, it is operator dependent and less sensitive in asymptomatic patients and for detecting calf vein thrombi[52, 53].

Contrast venography

The contrast venography was the gold standard test for the diagnosis of deep vein thrombosis. The presence of a filling defect in the lumen of the vessel is diagnostic, although abrupt cutoffs, non-filling of the deep venous system, or demonstration of collateral flow may raise suspicion for the presence of deep vein thrombosis. It is invasive and requires

the use of potentially harmful contrast agents; therefore, it has largely been replaced by noninvasive tests.

Other diagnostic tests

Less frequently used tests to detect deep vein thrombosis include magnetic resonance venography (MRV) imaging and computed axial tomography venography[54].

Diagnosis of pulmonary embolism

Imaging procedures for pulmonary embolism

Pulmonary angiography isregarded as the gold standard test for the diagnosis of pulmonary embolism, and although the procedure is usually well tolerated, it is invasive, expensive and requires a skilled radiologist and a cooperative patient [49,50]. The first imaging test in manycenters is now computerized tomographic pulmonary angiography (CTPA)[51].

Ventilation-Perfusion Scanning

The ventilation-perfusion scanning is now considered a second-line imaging method for the diagnosis of pulmonary embolism. It is useful in patients who have normal chest radiography or who are unable to undergo computerized tomographic pulmonary angiography (patients with renal insufficiency, contrast allergy, obesity, or pregnancy). A normal perfusion scan rules out the diagnosis of pulmonary embolism, whereas a high-probability scan along with a high degree of clinical suspicion is diagnostic. Non-diagnostic lung scans (intermediate or low probability) are the most common, and in the prospective investigation of pulmonary embolism study, they occurred in 72% of patients, thereby limiting the usefulness of this modality[55].

Management

Standard therapy of deep vein thrombosis and pulmonary embolism

Treatment of non-massive venous thromboembolism has three phases: the initial phase, the early maintenance phase, and the long-term secondary prevention phase. Low-molecular-weight heparin and fondaparinux are the choices for initial treatmentfor patients with deep vein thrombosis and pulmonary embolism[56].

Pharmacological prophylaxis for venous.
Thromboembolism.
Low-dose unfractionated heparin twice or thrice a day.
Low-molecular-weight heparins.
Fondaparinux 2 • 5 mg per day for orthopedic surgical or general surgical procedures or, in some countries, for acute and severe medical illness (also often used off label when heparin-induced thrombocytopenia is suspected).
Orthopedics only.
Dabigatran.
Rivaroxaban.
Apixaban.
Warfarin.
Aspirin.
Desirudin.

Anticoagulation

The heparin or low molecular weight heparin such as Lovenox should be initiated until the patient can be bridged to warfarin. Heparin can be administered intravenously or subcutaneously. Lovenox is usually administered subcutaneously. Warfarin usually takes 5-7 days to reach therapeutic levels in the, therefore, a Lovenox bridge is usually required. Systemic fibrinolysis has been traditionally used in patients with a high risk of pulmonary embolism. Fibrinolytic agents are different from anticoagulants. Examples of systemic fibrinolytic include; alteplase, urokinase, and streptokinase. Using intravenous fibrinolytic agents has been shown to be associated with hemodynamic stabilization and the lower rate of recurrent pulmonary embolism. However, these benefits come with an increased risk of bleeding including intracranial hemorrhage [57].

Surgical embolectomy

The surgical embolectomy is considered a last resort for patients with massive pulmonary embolism. This technique was first introduced in the 1960s. Currently, the mortality associated with this procedure is less than 6% which is remarkably low compared to the 50% mortality rate it had when it was first introduced. Patients undergoing surgical embolectomy are put on anticoagulation[58, 59].

Vena cava filter

The placement of an inferior vena cava filter is indicated in patients with acute pulmonary embolism who have an absolute contraindication to anticoagulation or in patients who have recurrent deep vein thrombosis or pulmonary clots despite anticoagulation. The location of the vena cava filter depends on the involvement of the renal vein. In general, retrievable Inferior vena cava filters are associated with fewer complications[60].

CONCLUSION

Venous thromboembolism is a major cause of mortality and morbidity among hospitalized patients. Immediate identification using wells criteria and revised Geneva criteria and adequateprophylaxis can reduce the incidence of venous thromboembolism. Recurrent venous thromboembolism can be prevented by placing the inferior vena cava filters.

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