

Review Article

Massive pulmonary embolism: the predisposing and complicating factors, its current diagnostic approaches and critical importance of early diagnostic physical exam

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Abstract

Massive pulmonary embolism (MPE) often leads to circulation collapse, a form of shock. The process is set off by thrombus or multiple thrombi dislodgement followed by a rapid perfusion insufficiency of pulmonary arterial system. Patients experience severe hypotension with diastolic and systolic failure with an acute tricuspid regurgitation. On many occasions, release of an obstruction is unattainable and death is occurring frequently within one hour of presentation.

A key reported source of MPE is its occurrence as a complication of deep vein thrombosis (DVT). While long-term immobilization and surgery are both directly associated with MPE, others such as previous DVT, malignancy, infectious lung and heart diseases, family thrombophilia, lower limb paralysis and pregnancy have to be considered as risk factors mainly due to its silent nature. Predisposing and complicating risks should be addressed by an early diagnostic physical exam. The clinician might offer a wide variety of diagnostic approaches, combining techniques into algorithms to better deal with the embolism severity. Multiple patient life-style changes and decisions to adhere to the proposed plan should be built up on patient-physician team effort.

KEY WORDS: Massive pulmonary embolism, predisposing factors, current diagnostic approaches.

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Massive pulmonary embolism (MPE) can lead to circulation collapse, a form of shock. Shock is manifested by critical tissue hypoperfusion and hypoxia followed on a cellular level by toxic metabolic cell deterioration. The key conditions for categorizing pulmonary embolism (PE) as massive are arterial hypotension and cardiogenic shock. Arterial hypotension is described as a systolic arterial pressure <90 mm Hg or a drop in systolic arterial pressure of at least 40 mmHg for at least 15 minutes¹. The right heart ventricle (RV) must then generate higher pulmonary arterial pressure to maintain its normal cardiac output. If pulmonary emboli occlude more than 30-50% of pulmonary arterial

tree, RV will be restricted from such generation. This leads to a severe hypotension^{2,3} where thin walled RV is further not capable to respond to an immediate increase of after-load, and experiences diastolic and systolic failure with an acute tricuspid regurgitation. Coronary perfusion of the RV decreases below 30 mmHg, and RV myocardial blood flow drop off significantly. This leads to an ischemia of RV myocardium and ischemia-induced RV failure.

Pulmonary artery constriction could increase RV myocardial blood flow, compromising LV myocardial flow, which leads to left ventricle (LV) ischemia. LV edema due to

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acute pulmonary hypertension compromises further LV performance by decreasing its contractility. Promoted pericardial constriction increases LV dysfunction leading to LV failure. Patients die because their heart cannot drive blood from the systemic circulation into the pulmonary circulation, since it is obstructed by an embolus or multiple emboli. In many cases, release of an obstruction is impossible and thus PE is fatal. Every year about 10% of patients diagnosed with PE die⁴. About 75% die within one hour of onset of symptoms⁵.

Because of silent nature of this disease the majority of PE is asymptomatic, thus goes undiagnosed. In some cases physician may observe abnormalities. These include for instance: sudden chest pain, dyspnea, intermittent hyperpnea with tachypnea, hypotension, tachycardia, and occasionally unexplained apprehension.

Clinicians and surgeons should be aware that once released into venous circulation, distribution of thromboemboli to both lungs is about 65%, to the right lung is 25%, and to the left lung is 10%. Lower lobes are involved four times more often than the upper lobes⁶. Most thromboemboli lodge in large or intermediate (elastic or muscular) pulmonary arteries, 35% or fewer reach the smaller arteries⁶. It is often the size of an embolus and its physical obstruction capacity that creates an abrupt change in circulation. In most instances however, blood flow alteration in massive PE is undiagnosed or omitted and treated as acute myocardial infarction or ventricular arrhythmia.

Furthermore, as a response on presence of microemboli in the lungs, intermittent hyperpnea with tachypnea usually occurs. Stimulation of juxtacapillary receptors in alveolar capillary membrane by swelling of the alveolar interstitial space increases vagal activity, which stimulates medullar respiratory neurons and causes chest pain⁶. Hyperventilation is manifested by lowered PCO₂ and respiratory and respectively metabolic alkalosis will be observed. Further depletion of alveolar surfactant results in diminished lung volume capacity and compliance. Areas in lungs are then venti-

lated but not perfused. Reduced lung volume leads to an atelectasis, with severe cases, manifested by an elevation of the diaphragm⁶.

The risk factors of MPE

The risk factors of MPE have not been fully evaluated in any study to date. The study by Stein et al pointed out the two factors that represent the highest risk factor; long-term immobilization and surgery (within ten weeks) were both directly associated with PE⁷. Others, such as previous deep vein thrombosis (DVT), malignancy, infectious lung and heart diseases, family thrombophilia, lower limb paralysis and pregnancy does not have similar importance, but have to be considered as risk factors because of the sudden and mainly unexpected onset of embolism. Mortality is age dependent, but the causes of this relation have not been determined⁸. Older patients primarily present with different complaints than younger ones, and usually the collapse is their particular symptom of MPE⁸.

Surgeries⁹⁻¹² activate the coagulation cascade causing generation and growth of microthrombi. Surgery induced inflammation reduces the natural anticoagulant effect of protein C and S. Role of inflammation in activation of endothelial cells by cytokines (interleukin-1, TNF) is mutually interconnected with the coagulation pathway. Cytokines stimulate endothelial cells to synthesize plasminogen, tissue factor, and plasminogen activator inhibitor. Those activated factors then produce acute hypercoagulable environment, with chronic consequences. For example, a chronically implanted long-term indwelling central venous catheter due to post-surgical hypercoagulable state tend to develop a fibrin sheath¹³ that more likely sloughs off from the catheter and catheter tip and generates microthrombi. These pathologically developed microthrombi are then observed postmortem in bronchial arteries and capillaries.

After surgery, especially the orthopedic hip replacement, blood loss can be prevented by its monitoring or monitoring of packed cell volume (PCV). A recent study examined the role

of autologous blood donation prior to an orthopedic surgery and its impact on the level of PE. Authors found that preoperative blood donation lowered the incidence of PE¹⁴. Study further concluded that preoperative blood donation reduces the incidence of DVT postoperatively and that lower preoperative level of hemoglobin was associated with lower incidence of DVT¹⁴. As prevention for PE in orthopedic surgery, they recommended routine hemodilution via blood donation prior to surgery¹⁴. This study showed strong association between lower incidence of DVT and lower incidence of symptoms of PE in those who donated autologous blood before surgery. The protective effect may not be only due to the decreasing PCV, red blood cells counts and hemoglobin concentration, but other factors such as platelet-platelet contact and platelet vessel wall contact may play role.

Fifty-nine percent of cases of venous thromboembolism are attributed to immobilization that is either recent hospitalization for surgery (24%) or for any medical illness (22%), or for hospitalization in nursing homes (13%)¹⁵. When patient is hospitalized for an elective surgery, it is necessary to explain and encourage him to start to move as soon as possible, in order to promote blood circulation in lower limbs. Patients hospitalized in the nursing homes have to be taken care of, if immobilized, by frequent body rotation or provided with physiotherapy.

If blood is allowed to stagnate, clots may form in veins. Stagnation may happen by several mechanisms as for example by an inactivity of the muscles of lower leg that used to provide venous compress action. Pressure against a vein by for example the edge of a stiff seat obstructs blood flow and venous return or causes partial compression leading to blood stagnation. Stagnated blood begins to form clots that grow in size. Clot propagates and entire diameter of the vessel will be blocked, forcing blood to bypass the obstruction. Blood tends to become congested below the level of the clot obstruction, without the ability to be returned towards the heart. Partial congestion

causes plasma to escape into the interstitium, which generates leg edema, swelling and pain on muscular contraction. Sedentary life style and obesity in other words puts patient in higher risk in the predisposition to venous stasis and hypertension. Congestion by vasoconstriction in vessels on periphery could be promoted by tobacco smoking¹⁶ or passive smoke inhalation. Moreover, tobacco raises the level of fibrinogen and factor VII in blood, which contribute to a chronic procoagulant state¹⁷.

Diseases such as cancer and end stage liver disease result in inadequate production of coagulation factors II, VII, IX and X¹⁸ and anticoagulation factors such as protein C, S, and Antithrombin III (ATIII)¹⁸. Consequently, neoplasms or tumors destabilize hemostasis in favor of coagulation. Metastasis complications leading to PE occur frequently in patients with lung, uterus, liver, breast and gastrointestinal neoplasms^{19,20}. In case studies^{21,22} cardiac myxomas often cause and obscure signs of PE.

Diseases of heart and lungs such as pneumonia, tuberculosis, chronic obstructive pulmonary disease²³ asthma, pneumothorax, bronchitis, pericarditis, congestive heart failure, angina, myocardial infarction, pericardial tamponade, sepsis and variety of intoxications, can cause or worsen PE.

During pregnancy the risk of MPE increases by six-fold and PE remains the main common cause of maternal death²⁴. Most cases of PE are the results of thrombophlebitis of femoral or pelvic veins. DVT are 6 times more frequent in pregnant women than in non-pregnant women²⁵. Venous stasis worsens the circulation due to an increase in venous capacitance and compression of the inferior vena cava by the gravid uterus. Within the coagulation system, there are increases in fibrinogen and several other clotting factors (factors I, II, VII, VIII, IX, and XII). The new studies suggest that the risk of DVT is greater during the antepartum period than is in the late third trimester. Most of PE cases occurring postpartum are strongly associated with cesarean section²⁶. Use of oral contraceptives and hormonal replacement therapy with estrogen plus progestin, increase risk of

DVT and PE²⁷, but data related to the effect of those drugs on blood circulation and stasis is still limited.

Furthermore, the congenital factor such as mutation of factor V (Leiden), has been long time discussed in the research literature as the one of the factors that could lead to PE and MPE because of the imbalance which is in favor of thrombosis that occurred by the inability of activated protein C (APC) to inactivate altered factor V. Study made by Desmarais et al²⁸ showed that there has been low occurrence of PE in patients primarily admitted for activated protein C resistance and in PE-suspicious patients who had been finally ruled out of PE. This study is in sharp contrast with association of the Leiden factor V and PE, which is low, and predisposition to DVT by this factor that is high²⁹. Although, MPE is severe circulation collapse, one can prevent its impact by limitation of the factors that predispose venous stasis and hypercoagulable states. Hypercoagulable states that occur in blood might be divided into congenital and acquired origin. The congenital hypercoagulable states are characterized by the presence of Leyden factor V thrombophilia, resistance to protein C and protein S, inherited mutation of prothrombin gene 20210GA, defect of factors VIII and V, congenital AT III defect, dysfibrinogenemia, fibrinolytic disorders, homocystinuria, hyperhomocysteinemia and, hereditary pulmonary arteriovenous malformation, pulmonary arteriovenous malformation, (Osler-Weber-Rendu) syndrome pulmonary arteriovenous malformation, varicose veins, lower limbs syndrome and cardiac defect, foramen ovale persistence³⁰⁻³⁶. The hypercoagulable acquired factors are associated for example with stress or an inflammation.

Taken together, pathophysiological factors such as low blood flow in leg veins, high packed cell volume and axial red blood cell migration, increase inter-platelet contacts and predispose to DVT and PE¹⁴. High viscosity of blood can be caused by either decrease of the amount of the plasma such as dehydration, severe burn, renal diseases or increase of the

number of cells such as high packed cell volume or hemoglobin seen in polycythemia vera³⁷. One of the consequences of low blood flow is that red blood cell axial migration takes place. This may lead to a change of the plasmatic zone forces (zone between axial flow and vessel wall) of the vessel in which platelets are dispersed, causing increased platelet contact and as well other interactions. Those situations can increase the risk of thrombus formation.

PE diagnosis

PE diagnosis is usually established and confirmed in less than 35% of patients suspected of PE³⁸. As a first and rapid diagnostic tool is the initial chest x-ray. Findings are frequently normal, thus on rare occasions, Westermark sign that is a dilatation of the pulmonary vessels proximal to an embolism along with collapse of distal vessels may be present. In MPE, the most common chest radiographic signs are described as cardiomegaly, pleural effusion and pulmonary artery enlargement. Regrettably, these signs have lack of specificity and sensitivity to establish presence of MPE, which sometimes leads to premature patient discharge from the emergency department.

Importance of an early diagnostic physical exam

An inspection of the patient along with auscultation in synchronization with taking thorough history helps obtain the first key input in MPE diagnosis. Physician has to carefully look over the signs of RV dysfunction and pulmonary hypertension, such as elevated neck veins, tachypnea, chest pain with dyspnea, and noisy sound near the mitral valve and tricuspid regurgitation murmur. A chest radiograph demonstrates some abnormality in about 90% of patients with MPE. The most common findings are cardiomegaly, pleural effusion and pulmonary artery enlargement¹⁴. If electrocardiographic (ECG) monitoring is used, massive overload of the RV with the manifestation of the right bundle branch block (RBBB) can be seen. Certain correlation between the extent of obstruction of pulmonary artery and the ap-

pearance of the RBBB could be established through the dynamic monitoring of ECG³⁹. Dynamic ECG monitoring of the heart of a PE patient reveals ST-segment depression and T-wave inversion in V1 to V4, or a pseudo-infarction pattern in V1⁴⁰. These signs are significant only in a massive obstruction of main pulmonary trunk and therefore they cannot be used for thrombi detection in the peripheral location³⁹.

In patients that can be stabilized, variety of visualization techniques can be applied to detect presence of MPE. In the fast pacing computerized world, clinician has today an enormous capacity to choose the right equipment and technique to detect MPE. One technique that has become gold standard of MPE diagnostic is pulmonary angiography (PA). It was first developed in 1929 when Forssman successfully introduced catheter into the right atrium and visualized dog pulmonary artery with 20% iodide solution. The subsequent use of safer contrast agents, catheters and guide wires have improved this technique, however contraindications exist that limit this method. PA cannot be used in patients with impaired renal function, left bundle branch block, right-sided endocarditis, congestive heart failure and allergy to iodine containing contrast materials. During the procedure, patient has to be monitored, because total ventricular block may develop due to invasive passage of the catheter through the right heart. Further manipulation of the catheter in the RV may irritate its wall causing ventricular extrasystoles and tachycardia. Reliability of this image technique decreases with lesser vessel caliber where the interpretation becomes much more difficult.

Direct visualization of the lung vessel parenchyma and proper identification of filling defects can be done by traditional Computed Tomography (CT). Without modification, however, this technique cannot be used to evaluate acute PE. CT is unable to capture a lung image within the time required for diagnosis. Scanning time is reduced by using spiral CT, also known as helical or multiple spirals or continuous volume CT. This has become promis-

ing technique for the detection of acute PE because of the better time frame capturing ratio. The fundamental advantage of this method is direct visualization of an embolus inside the vessel wall lumen as filling defect after the injection of the contrast material. Spiral CT works best for the detection of central venous thromboemboli⁴¹. Subsegmental emboli (reported by PIOPED investigators around 6%) can be missed because of poor picture image quality. Peripheral pulmonary emboli can be detected easily with more predilections with ventilation perfusion (V/Q) scan⁴¹.

Magnetic resonance angiography (MRA) provides extremely detailed pictures of body tissues and organs. The electromagnetic energy that is released when exposing patient to a radio waves in a strong magnetic field is measured and analyzed by a computer, which forms two- or three-dimensional images that may be viewed on a TV monitor. The main indication for magnetic resonance in chest was the fact that flowing blood itself offered a natural contrast to mediastinal and hilar structures. MRA is a study of the blood vessels. For the purpose of visualization of the blood vessels, injection of gadolinium is implemented in the protocol. Recent development of MRA technique using the gadolinium-based contrast agent showed improvement in sensitivity and specificity of conventional PA⁴². In 2002, MRA was evaluated by the prospective study made by Oudkerk et al and the results had sensitivity of 40% for subsegmental, 84% for segmental and 100% for lobar or central PE⁴³. Due to the relative noninvasiveness of the procedure and no need of iodinated contrast material or ionizing radiation, this method is safer and lesser contraindicative for the patient suffering with PE. Presence of the subsegmental emboli, however rank this method as a non-sensitive for this type of detection.

Recently, Paterson and Schwartzman⁴⁴ concluded traditional approach of diagnosis of PE, which is V/Q, leg ultrasound and PA as not cost-effective. Spiral CT can replace PA in cases when the patients have negative leg ultrasound, plus non-diagnostic V/Q scan. Per-

rier et al had recently confirmed these results⁴⁵. In the clinical setting, if venous CT is immediately followed by the spiral CT of the chest, (combination of CT angiography and venography - CTPAV) the frequency of thrombi detection in subdiaphragmatic deep vein position, increases the frequency of diagnosis of PE in suspected patients^{46,47}.

Latest diagnostic tool in identifying MPE analyzes pulmonary artery pressure (PAP) reflection, by Swan Ganz catheter. Measuring indexes of PAP reflection was found useful in differentiation between the chronic pulmonary thromboembolism and the primary pulmonary hypertension³. PAP hypertension diagnosis can be done non-invasively using transthoracic echocardiography (TEE) method, to detect lesions in pulmonary artery. Moreover, TEE allows visualization of pulmonary arterial thrombi, and can confirm diagnosis in the majority of patients with PE and the RV overload⁴⁸. Results with TEE method indicate that TEE can replace the invasive pulmonary angiography in detection of MPE⁴⁹. Nevertheless, even with the appropriate use of combinations of invasive or noninvasive tests, it is frequently impossible to definitively and early on diagnose or exclude PE.

Despite the fact that most patients can be managed safely without treatment or PA by repeating ultrasound testing of the proximal veins to detect developing DVT, leg venous duplex sonography (VDUS) should be considered, if any signs of symptom related to DVT in legs are observed⁵⁰. The exam is done in two positions that allows observing and measuring venous flow pattern and it's pathological deviations. First, patient is in the supine position with leg externally rotated that allows measure common femoral, superficial femoral, popliteal, posterior tibial, peroneal and greater saphenous veins. Then, patient is in prone or lateral position for viewing the popliteal, peroneal, and soleal veins. VDUS is able to confirm the diagnosis of DVT in 90% of patients with PE⁵⁰. VDUS though should be considered as one of the first tests for the patient sus-

pected having MPE with any signs or symptoms related to DVT in legs⁵⁰.

Recently, laboratory assays have been introduced to measure the serum level of D-dimer (DD) and fibrin monomer and troponin enzymatic values to help diagnose MPE. MPE patients were found to have an elevated concentration of fibrin degradation products (FDPs) and troponin in their serum and plasma. It is clear though that increased levels of FDPs and troponin by itself has a limited diagnostic value. DD is one of the specific fibrin degradation products. Plasma DD levels are increased in patient suspected of PE. Unfortunately, the increased DD levels found in patients with pneumonia makes this test less prognostic⁵¹. DD test has an excellent diagnostic value for a large PE, but limited one for PE in small and sub-segmental vessels⁵². Usually, it is a good idea to use at least two or more types of techniques to confirm diagnosis. Work is underway to further improve the assays of FDPs such as new latex turbidimetric assay, DD PLUS⁵³. Meta-analysis of 52 studies revealed ELISA DD assay technique as a high sensitive (94%) method for detection of DD but not specific (45%) for PE in clinical settings⁵⁴. Normal level of DD concentration (<500 ng/ml), with low clinical probability, appears to be safe method to help exclude PE with a low to moderate suspicion^{55,56}. However, more data is needed to assess the value of this method for a routine diagnosis.

Fibrin monomer (FM) assays have been evaluated to diagnose PE after surgical interventions such as hip arthroplasty⁵⁷. After surgery, FM products rise up immediately, in comparison with DD levels that increase significantly 7 days after the surgery⁵⁷. The FM degradation product assays are in good correlation with DD assay^{58,59} and overall are useful in indicating PE for the immediate purposes; however, other diagnostic method should be considered to make definitive diagnosis.

Lastly, measuring the levels of troponin, an enzyme that increases its presence in failing RV in MPE, could add more tools into laboratory assays. Elevated levels of the enzyme, pre-

dict undesirable outcomes in patients with acute myocardial infarction and in patients without acute coronary syndromes, which are frequently mild and of short duration compared with elevations in patients with acute coronary syndromes ⁶⁰. Failing RV probably plays a major role in the pathogenesis of troponin release.

MPE is life-threatening circulation collapse. The steps to prevent it, starts at the basic physical exam, where trained physician determines the seriousness of the organ system damage and based on the data collected, threats will be fully addressed and possibly partly reduced by patient education. Recent methods used Wells modification criteria point scale to determine if MPE is likely or unlikely

to occur ⁶¹. Patients in the PE-likely group will be investigated directly by chest CT, while those in the PE-unlikely type will undergo DD testing and only patients with abnormal DD will be referred for chest CT. Negative DD results with negative chest CT scans will be considered PE-unlikely.

Prophylactic reduction of MPE can be accomplished by preventing venous stasis, by coupling the use of better inexpensive and preliminary physical diagnostic technique and/or algorithm with an early surgical intervention, to reduce thrombi formation potential, by prophylactic use of antithrombotic surgical drugs and devices, and lastly by encouraging healthy changes in life-style.

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