ABSTRACT

Pulmonary embolism is a potentially lethal disorder, consequent to thrombi formed in the deep venous system that, once detached, cross the right chambers of the heart, thus obstructing the pulmonary artery or one of its branches. Mortality rate associated to untreated embolism is approximately 30%. A quick diagnosis is crucial, since treatment reduces mortality and morbidity, and improves the quality of life for reducing the likelihood of thromboembolic pulmonary hypertension and post-thrombotic syndrome. The objective of this article is to present a literature review on this condition, divided into two parts. On the first part we approach the practical aspects of its epidemiology, pathophysiology, identification of risk factors, clinical, laboratorial and imaging diagnostic methods. On the second, the main aspects of its medical and surgical treatments are addressed.

Keywords: Pulmonary embolism/diagnosis; Pulmonary embolism/epidemiology; Venous thrombosis; Thromboembolism; Angiography; Radionuclide imaging

INTRODUCTION

There is little data available on the incidence of pulmonary embolism in our country. National studies show that thromboembolism is found in 3% to 5% of autopsies; in those, 68% were considered the cause of death[1-2]. According to data from DATASUS[3], the approximate number of hospital admissions in Brazil due to pulmonary embolism was of 6,700 cases in 2004. However, it is estimated that around 75% of cases are not diagnosed[2]. In the US, over 500 thousand cases of pulmonary embolism are diagnosed each year, leading to approximately 200 thousand deaths[4-5].

Mortality associated to untreated pulmonary embolism is of approximately 30%. A quick diagnosis is crucial, once treatment reduces mortality by 2% to 8% and improves the quality of life, reducing the possibility of thromboembolic pulmonary hypertension and post-thrombotic syndrome[4-6-7].

PATHOPHYSIOLOGY

Pulmonary emboli usually result from thrombi originated in the lower limb deep venous system. They may also originate from pelvic or renal veins, upper limbs or right heart.

Ileofemoral thrombi seem to be the cause of most pulmonary embolism[8-9]. On the other hand, most thrombi that originate below the popliteal vein (calf vein thrombi) seem to resolve spontaneously and do not usually embolize to the lungs. Around 20% of thrombi originated in calf veins migrate to proximal veins.

After migrating to the lungs, larger thrombi may impact in the pulmonary artery bifurcation or in lobar
branches, leading to hemodynamic impairment. Smaller thrombi that settle distally will more frequently lead to pleuritic pain, consequent to the inflammatory response adjacent to the parietal pleura. Approximately 10% of thrombi will cause pulmonary infarction, usually in patients with pre-existing cardiopulmonary diseases. In most cases there are multiple emboli, with a predominant involvement of the lower lobes\(^{(10)}\).

The gas exchange modifications seen in patients with pulmonary embolism can not be explained by the mechanical obstruction of pulmonary vessels and by increased ventilation-perfusion rate in some pulmonary portions alone. Some phenomena, such as release of inflammatory mediators resulting in altered surfactant production, changes in vascular permeability and intrapulmonary shunts, are probably responsible for the blood gas changes\(^{(11)}\).

**RISK FACTORS**

Patients with pulmonary embolism usually present risk factors for the development of venous thrombosis. The most important risk factors are:

- Immobilization/paralysis
- Surgery in the last three months
- Stroke
- Cancer
- Previous history of venous thromboembolism
- Obesity
- Smoking (especially 25 or more cigarettes a day)
- Arterial hypertension
- Hip fracture
- Congestive heart failure
- Pregnancy and post-parum
- Oral contraceptives and hormone replacement therapy

In patients with pulmonary thromboembolism without an initially identified risk factor, one should suspect of the following causes:

- Occult neoplasms: the neoplasms most commonly associated with thromboembolism are pancreatic and prostate cancer.
- Factor V Leiden – present in up to 40% of cases with no other identifiable risk factors.
- High concentrations of factor VIII – present in 11% of population and associated with a six-fold increase in the risk of venous thromboembolism.
- G2010A polymorphism of the prothrombin gene.
- Hereditary disorders: deficiencies of protein C, protein S, anti-thrombin III, dysfibrinogenia, plasminogen disorders and increased factor XI.
- Acquired conditions: antiphospholipid antibody syndrome (lupic anticoagulant and anticardiolipin antibody).

### CLINICAL MANIFESTATIONS

The diagnosis of pulmonary embolism is extremely difficult due to unspecific clinical picture. Moreover, the clinical presentation varies according to quantity and size of the emboli, associated to the previous cardiopulmonary status of the patient. The possibility of pulmonary embolism should always be considered when there is sudden dyspnea or non-explained pleuritic pain.

The most common symptoms are dyspnea (73%), ventilation-dependent chest pain (66%), cough (37%), hemoptysis (13%). Symptoms such as palpitation or angina-like pain may appear less frequently. The most frequent signs are tachypnea (70%), rales (51%), tachycardia (30%), a fourth heart sound (24%), hyperphonesis of the second heart sound pulmonary component (23%) and temperature ≥ 37.5°C (14%). Temperatures above 39°C are not usually observed\(^{(12)}\).

Although most pulmonary emboli originate in the lower limbs, the presence of signs and symptoms of deep venous thrombosis occurs in only 30% of cases.

Medical scores may be useful for an objective determination of the risk of pulmonary embolism\(^{(13)}\). They will not confirm or exclude the diagnosis, but help the physician estimate the likelihood of pulmonary embolism and thus efficiently define the subsequent diagnostic tests. The Geneva score (Table 1) enables classifying patients as low (10% risk), intermediate (38%), and high (81%) risk for pulmonary embolism.

**Table 1. Geneva score for clinical estimation of pulmonary embolism risk\(^{(13)}\)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>+ 1</td>
</tr>
<tr>
<td>≥ 80</td>
<td>+ 2</td>
</tr>
<tr>
<td>Previous DVT or PTE</td>
<td>+ 2</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>+ 3</td>
</tr>
<tr>
<td>Heart rate &gt; 100 bpm</td>
<td>+ 1</td>
</tr>
<tr>
<td>PaCO(_2) &lt; 36.0</td>
<td>+ 2</td>
</tr>
<tr>
<td>36.0-39.0</td>
<td>+ 1</td>
</tr>
<tr>
<td>PaO(_2) &lt; 48.8</td>
<td>+ 4</td>
</tr>
<tr>
<td>48.8-59.9</td>
<td>+ 3</td>
</tr>
<tr>
<td>60.0-71.2</td>
<td>+ 2</td>
</tr>
<tr>
<td>71.3-82.4</td>
<td>+ 1</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>+ 1</td>
</tr>
<tr>
<td>Laminar atelectasia</td>
<td>+ 1</td>
</tr>
<tr>
<td>Elevation of the hemidiaphragm</td>
<td>+ 1</td>
</tr>
</tbody>
</table>

| Total score:                              | Probability of developing pulmonary embolism |
| 0-4                                       | 10% – Low                                  |
| 5-8                                       | 38% – Moderate                             |
| 9-12                                      | 81% – High                                 |

### LABORATORY EXAMS AND GRAPHIC METHODS

Besides history and physical exam, the assessment of patients with dyspnea or chest pain possibly due to
pulmonary embolism should include a twelve-lead electrocardiogram, chest radiography and blood gases. These simple and low cost exams are usually altered in most patients with pulmonary embolism, albeit it is well known that they are not specific. Therefore, additional diagnostic methods are always necessary.

**ELECTROCARDIOGRAM**

The electrocardiogram is abnormal in 70% of cases of pulmonary embolism but the changes are unspecific. The most common findings are alterations in the ST-segment and T wave. The presence of negative T waves in the precordial leads is a frequent finding in patients with pulmonary embolism and is associated to poorer prognosis(14). Likewise, the presence of atrial arrhythmias, right bundle branch block, pseudoinfarction pattern (Q waves in DII, DIII, and aVF) or changes in the ST segment in precordial leads are predictors of greater mortality risk(15). The classic cor pulmonale pattern with S1 Q3 T3, P-pulmonale or right bundle branch block, is rarely seen in patients with pulmonary embolism(16).

**CHEST RADIOGRAPH**

Only 12% of cases of pulmonary embolism have a normal chest X-ray(12). The most common findings include laminar atelectasis, pleural effusion, pulmonary infiltrate, and a slight elevation of the hemidiaphragm. The frequency of such findings is not very different from that observed in patients whose final diagnosis is not pulmonary embolism.

Classic changes, such as Hampton hump (wedge-shaped pulmonary infiltrate with a pleural base representing intraparenchymal hemorrhage), or Westermark sign (oligemia area with prominent pulmonary artery) are highly suggestive of pulmonary embolism, although infrequent.

In any case, the chest radiograph is important to assess the presence of other diagnoses, such as pneumonia or pulmonary congestion, but pulmonary embolism is frequently concomitant with other pulmonary problems.

A normal or slightly changed chest X-ray in a patient with dyspnea and/or hypoxemia is highly suggestive of pulmonary embolism.

**BLOOD GASES**

The typical result of blood gas analysis is hypoxemia associated with hypocapnia. Nevertheless, PaO₂ is normal (> 85 mmHg) in 18% of patients. Additionally, PaCO₂ may be normal or even increased if there is massive embolism with hemodynamic instability.

**D-DIMER**

D-dimer is the sub-product of fibrin degradation that is elevated when thrombi are formed in the body. Almost all patients (97%) with pulmonary embolism present levels above 500 ng/mL. Normal results (< 500 ng/ml) are thus extremely useful, since the diagnosis of pulmonary embolism is then highly unlikely. On the other hand, the D-dimer levels rise in different situations, and high levels are not enough to indicate pulmonary embolism.

Many studies have demonstrated that D-dimer levels <500ng/mL rule out, with high safety level, possible pulmonary embolism in patients with a low or moderate clinical likelihood of having the condition, so that additional imaging exams are not necessary(17-20). It is important to bear in mind that the exam should not be ordered for patients with a high clinical likelihood of pulmonary embolism, since a normal result will not rule out the possibility of suffering the disease (Figure 1).

Different methods have been used to measure D-dimer, with different results. The greater sensitivity techniques are fast quantitative ELISA and quantitative ELISA(18). Other techniques provide inferior results, especially those that use latex and whole blood agglutination. It is mandatory to know which technique is used at one’s place of work.
OTHER LABORATORY TESTS

Higher troponin I or T levels are found in 30% to 50% of patients with pulmonary embolism\(^{(21-24)}\). The finding of high levels of troponin I or T is associated to a poor prognosis: higher frequency of right ventricular dysfunction, prolonged hypotension, and a higher hospital mortality rate\(^{(21-24)}\).

The brain natriuretic peptide (BNP) is produced by the ventricular myocardiun when subject to high diastolic pressures\(^{(25-26)}\). It has been mostly used to establish the diagnosis of heart failure in patients with dyspnea. BNP is also increased in patients with right ventricular dysfunction secondary to pulmonary embolism\(^{(27)}\). In patients with pulmonary embolism, the presence of high levels of BNP is a marker of worse progression, although some patients with adverse outcomes have levels lower than 90 pg/ml\(^{(28-29)}\). Values lower than 50 pg/ml would better indicate patients with benign course\(^{(20)}\).

CHEST COMPUTED TOMOGRAPHY

The interest on helical chest computed tomography (CT) as a diagnostic tool for pulmonary embolism is growing, due to advantages over ventilation-perfusion scintigraphy. It is a faster method, capable of assessing other concurrent diagnoses and it is widely available.

Nevertheless, single-slice helical chest CT will not diagnose pulmonary embolism in roughly 30% of cases\(^{(30)}\), and there is reasonable discrepancy among observers\(^{(31)}\). The procedure is thus not sufficient at all to rule out the presence of pulmonary embolism; in such cases, other tests, such as lower limbs ultrasound should be performed.

New multislice CT scanners have enabled a much better view of segmental and subsegmental branches. Studies using multislice CT scanners have demonstrated a high negative predictive value, that is, the method allows “ruling out” the diagnosis of pulmonary embolism, with no need for lower limbs ultrasound\(^{(30-31)}\).

In a study with 756 patients suspected of having pulmonary embolism, using helical chest CT along with D-dimer, the risk of embolism in three months in patients whose tests were negative was 1.5%\(^{(18)}\). Additionally, the diagnosis of pulmonary embolism using multislice CT is less dependent on the observer. Patel et al., for instance, found an excellent inter-observer agreement\(^{(32)}\).

It is important to point out that intravenous contrast has to be administered for helical CT. The amount is similar to that used in pulmonary angiography; hence, in patients with renal function impairment, the kidneys should be prepared with acetylcysteine and volume expansion using a sodium bicarbonate solution\(^{(33-35)}\).

VENTILATION-PERFUSION SCINTIGRAPHY

The ventilation-perfusion scintigraphy is one of the most frequently used methods to assess patients with suspected pulmonary embolism; nonetheless, it has been recently replaced by multislice helical CT.

In patients suspected of having pulmonary embolism, a normal pulmonary scintigraphy virtually excludes this diagnosis, whereas a “high probability” result is associated to the presence of pulmonary embolism in about 90% of cases\(^{(36)}\).

The great limitation of the method is the high frequency of intermediate results (low or moderate probability). On the PIOPED\(^{(36)}\) study, only 42% of patients with a confirmed diagnosis of pulmonary embolism had a “high probability” result in the scintigraphy. The remaining results were low or intermediate probability. On the other hand, pulmonary embolism was present in 14% and 30% of patients with low and intermediate probability on pulmonary scintigraphy. Such results are therefore non-conclusive, and do not allow confirming or ruling out the diagnosis, and demand additional tests, such as pulmonary arteriography.

LOWER LIMBS VENOUS ULTRASOUND

Approximately 90% of pulmonary emboli come from thrombi originated in the deep venous system of the lower limbs. Patients with pulmonary embolism have a positive ultrasound for deep vein thrombosis in 30% to 50% of cases. The venous thrombus is usually visible, but is not essential for diagnosis. The most sensitive finding for the diagnosis of deep venous thrombosis is decreased compression of the lower limb deep veins.

Ultrasound sensitivity and specificity for diagnosis of deep venous thrombosis in symptomatic patients with decreased compression of the lower limb proximal deep veins is 97%, with a positive predictive value of 94%. Less significant results are found in asymptomatic patients, with sensitivity of 59% and specificity of 98%\(^{(9)}\).

It is highly useful when there is a moderate clinical probability of thrombopulmonary embolism associated with a non-conclusive ventilation-perfusion scintigraphy or a negative single slice helical CT scan\(^{(37)}\).

ANGIOGRAPHY

Pulmonary angiography is the technique capable of establishing or excluding the diagnosis of pulmonary embolism with almost full accuracy. Only 3% of exams are non-diagnostic\(^{(36)}\). The interobserver variability is small, similar to that of multislice helical CT (kappa value: 0.7 to 0.9)\(^{(32)}\).
The angiography is performed injecting contrast in the pulmonary artery branches after percutaneous catheterization. Two views for each lung are performed (anteroposterior and oblique), with a total of four contrast injections.

The pulmonary angiography is a relatively safe procedure, with major complication rates and mortality rate smaller than 1% (36,38). Nevertheless, in patients with moderate to severe pulmonary hypertension, care should be taken due to increased risk of fatal complications (39).

In centers with multislice helical CT scanners available (4 or more slices), the pulmonary angiography is an exam rarely used for diagnosis of pulmonary embolism. When multislice CT is not possible, an arteriography should be ordered when diagnosis of pulmonary embolism can not be confirmed or excluded in less invasive exams. One example of such situation is a non-diagnostic lung scintigraphy and negative lower limb venous ultrasound, associated with an intermediate or high probability of pulmonary embolism.

**ECHOCARDIOGRAM**

It is a valuable exam to assess patients suspected of having pulmonary embolism for the possibility of making an accurate diagnosis and evaluating possible differential diagnoses, such as in cases of acute dyspnea, chest pain, cardiovascular collapse and other clinical situations that mimic pulmonary embolism.

The echocardiogram may suggest or emphasize the suspicion of pulmonary embolism if overload and right ventricle dysfunction are associated to Doppler signs that indicate increased pulmonary artery pressure.

The echographic findings most frequently observed in pulmonary embolism with significant hemodynamic impairment include the presence of a dilated and hypokinetic right ventricle, dilation of pulmonary arteries, intensification of tricuspid regurgitation flow, modifications in velocity of right ventricle outflow, and shift of the interventricular septum from right to left (reverse Bernheim effect). The inferior vena cava is frequently dilated and does not collapse during inspiration.

The presence of a hypokinetic right ventricle in patients with pulmonary embolism with a normal systolic arterial pressure is an independent predictor of early mortality (40).

Transesophageal echocardiogram may be useful to assess the diagnosis of pulmonary embolism in patients with intense hemodynamic instability, in which transportation for other imaging exams (CT or scintigraphy) may be dangerous (41-42).

**CONCLUSIONS**

Pulmonary embolism frequently complicates progression of inpatients. It represents the most preventable cause of death at hospitals and its correct diagnosis and treatment significantly reduce morbidity and mortality associated to this disease.

There are many algorithms for diagnosis of pulmonary embolism. Subsidiary exams should be ordered according to their availability, patient’s hemodynamic status and presence of associated cardiovascular diseases.

D-dimer levels < 500 ng/ml in patients with a low or moderate clinical probability before tests rule out, with a high level of safety, the possibility of pulmonary embolism. Multislice CT has a high negative predictive value. It enables ruling out the diagnosis of pulmonary embolism with no need for lower limb ultrasound.

In patients with a high pre-test clinical probability, a pulmonary arteriography may prove necessary to exclude the diagnosis. A normal pulmonary scintigraphy virtually excludes the diagnosis of pulmonary embolism, while an exam showing a result of “high probability” is associated to the presence of pulmonary embolism in about 90% of cases.

Pulmonary angiography is the technique able to exclude or establish the diagnosis of pulmonary embolism with almost complete accuracy.

**REFERENCES**