Review Article

The challenge of diagnosing acute pulmonary thromboembolism in patients with chronic obstructive pulmonary disease*

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ABSTRACT

Pulmonary thromboembolism and exacerbation of chronic obstructive pulmonary disease are common conditions. Chronic obstructive pulmonary disease is a clinical risk factor for pulmonary thromboembolism. The presentation of acute pulmonary thromboembolism and acute exacerbation of chronic obstructive pulmonary disease often mimic each other so closely that they cannot be distinguished clinically. The structural abnormalities of the lungs in chronic obstructive pulmonary disease make also difficult to interpret the results of noninvasive tests like ventilation-perfusion lung scans. Therefore, diagnosing acute pulmonary thromboembolism in patients with underlying chronic obstructive pulmonary disease is a challenging task. In order to update knowledge of the subject and offer suggestions regarding conduct, we evaluated various studies addressing this theme, including case reports and case series. In addition, we reviewed diagnostic approaches to acute pulmonary thromboembolism, and we reflect upon that topic. The clinical probability of pulmonary thromboembolism concomitant to chronic obstructive pulmonary disease is typically intermediate, as is positivity on the ventilation-perfusion lung scan. Diagnostic algorithms should take that into consideration.

Keywords: Pulmonary disease, chronic obstructive/complications; Pulmonary embolism/diagnosis; Pulmonary embolism/epidemiology; Ventilation-perfusion ratio

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PULMONARY THROMBOEMBOLISM

The incidence rates of initial manifestation of venous thromboembolism (VTE), in its deep vein thrombosis (DVT) and acute pulmonary thromboembolism (PTE) forms, are quite difficult to established for various reasons, among which are underdiagnosis, lack of confidence in the case registries, inconsistent autopsy services and lack of accuracy on death certificates.

In some epidemiologic studies, it has been estimated that the incidence of VTE is approximately 100 cases per 100,000 people, with less than five cases per 100,000 among people under fifteen years of age, and approximately 500 cases per 100,000 among people in their eighties. The incidence of VTE increases with age, approximately doubling every decade after forty years of age. In hospitalized patients, PTE is considered the most frequent acute pulmonary complication. Manifestations of VTE are seen in up to 1% of hospitalized patients in general hospitals. Approximately 10% of all in-hospital deaths are attributed to PTE.[1-5]

A common condition, PTE is potentially fatal within the first hours after the occurrence of the acute event and has been correlated with high mortality if not promptly diagnosed and treated. Approximately 10% of all acute PTE events rapidly evolve to death, which typically occurs within the first two and a half hours after the onset of symptoms. Even when promptly diagnosed and treated, approximately 5% of patients die from PTE. General mortality has stabilized at approximately 30%, encompassing PTE as the determining, contributing or associated cause of death. Half of the deaths resulting from acute PTE occur in patients who have already survived the acute phase of a life-threatening underlying disease. In patients who survive the acute event and are treated for at least three months with anticoagulants, fatal recurrence of PTE is rare. Clinically, acute VTE expresses itself as PTE in one-third of all patients, and as DVT in two-thirds.[5-8]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a condition of increasing prevalence and a significant cause of morbidity and mortality worldwide. In 1990, the prevalence of COPD per 100,000 inhabitants was 698 for males and 379 for females in developed countries, compared with 934 for males and 733 for females worldwide.[9-12]

In the USA, COPD has become the fourth leading cause of death, affecting approximately 20% of the adult population, and, among the ten leading causes of death, it is the only one that is still on the rise. In the United Kingdom, 15% to 20% of males over 45 years of age and approximately 10% of females in the same age bracket present chronic cough and expectoration. In addition, approximately 4% of males and 2% of females are diagnosed with COPD. These rates increase after the age of 45.[12] In Western Europe, 3 million people suffer from COPD in Spain, compared with 2.7 million in the United Kingdom, 2.6 million in Germany, 2.6 million in Italy and 2.6 million in France.[9-12] Worldwide, approximately 44 million people suffer from COPD, which is considered the sixth leading cause of death.[10]

According to the International Classification of Diseases, Tenth Revision, COPD mortality was approximately 50 per 100,000 white males in the USA. Mortality rates were lower for black males, white females and black females.[11] In the United Kingdom, COPD is implicated in approximately 6% of all deaths among males over 45 years of age and 4% of all deaths among females in the same age bracket. Overall COPD mortality is 200 to 300 per 100,000 people in the 45 to 64 age bracket.[10,12]

ACUTE COPD EXACERBATIONS

First and foremost, it has to be taken into consideration that there is a tendency to use the word "exacerbation" to describe a situation in which symptom worsening (exacerbation) occurs on a particular time scale (acute).

In general, COPD is a progressive disease presenting gradual worsening of symptoms and physiopathological manifestations. The acute exacerbations reduce quality of life, and the results of studies evaluating their impact on overall deterioration remain inconclusive.[13-14]

Exacerbations of COPD constitute a quite common cause of hospitalization. In-hospital mortality for patients admitted with acute COPD exacerbation and hypercapnia is 11%, and mortality within a year after discharge is 43%.[15]

The main physiopathological abnormality in acute exacerbations is the worsening of gas exchange,

principally resulting from increased imbalance of the alveolar ventilation/perfusion (V/Q) ratio. As a result, hypoxemia increases, there is a need to increase the minute volume to compensate for the extension of the alveolar dead space, respiratory effort increases, respiratory muscle stress can occur, and hypercapnia can develop. Depending on the cardiac index, there might be an increase in the arteriovenous oxygen difference and reduction of the mixed venous blood oxygen saturation, thereby contributing to hypoxemia.[16] The most common causes of acute COPD exacerbation are tracheobronchial infection and air pollution, followed by pneumonia, pulmonary embolism, pneumothorax, broken ribs, right or left ventricular failure and arrhythmia, as well as inappropriate use of sedatives, narcotics or beta blockers.[17]

PTE DIAGNOSIS

The diagnosis of PTE requires that the embolus be identified through objective tests. There is no clinical means of diagnosing PTE, since its occurrence cannot be confirmed or excluded through signs or symptoms. However, a clinical suspicion based on the use of criteria to establish levels of probability and including clinical scores, with or without supporting tests, is essential for the advancement of the diagnostic process.[18-20] In cases of suspicion with high or moderate (intermediate) clinical probability, it is imperative that treatment with heparin be initiated, thereby protecting the patient during the hours preceding the definition of the diagnosis.[21-22] In general terms, it can be said that PTE should be suspected when there are compatible signs and symptoms, together with risk factors, and there is no more likely diagnosis.[18-20, 23-25]

The clinical presentation of PTE encompasses a wide spectrum of variations: from the silent, virtually asymptomatic, event to the sudden death profile. The principal clinical manifestations are tachypnea, pleuritic chest pain, tachycardia, anxiety, cough and hemoptysis.[23-25] Clinical manifestations of DVT might also be observed, and risk factors might be identified. More than the isolated symptoms themselves, combinations of symptoms have been more expressive for the development of clinical suspicion.[24]

The clinical risk factors for VTE are those that provide the basic conditions for venous thrombogenesis. There are various medical conditions that predispose a patient to developing venous thrombosis. Independent risk factors for VTE include surgery, trauma, cancer chemotherapy, being over 40 years of age, decompensated congestive heart failure, chronic diseases that limit movement, thrombophilia, heterozygosity, thrombophilic/heterozygotic status and antiphospholipid antibody syndrome. Oral contraceptive use, hormone replacement and puerperal pregnancy constitute acquired risk factors in women.[1-2,4] Tests used for diagnostic confirmation have evolved as a result of new imaging resources and the greater value now assigned to D-dimers.

The confirmation of a diagnosis of PTE is based on the following criteria: scintigraphic V/Q mapping of the lung resulting in a high probability; perfusion scintigraphy of the lung consistent with PTE when chest X-rays are normal in the areas affected by perfusion defects; mapping revealing inconclusive abnormalities together with objective identification of DVT; positive spiral computed tomographic angiography (CTA); and positive pulmonary arteriogram.[20-21,26] Criteria for excluding a diagnosis of PTE include normal or quasi-normal perfusion scan, normal pulmonary arteriogram (despite a 3% rate of false-negative results and interobserver discrepancy for subsegmental emboli), inconclusive V/Q mapping results accompanied by negative DVT studies, negative multidetector-row CTA (to be confirmed); and normal levels of the D-dimers associated with low clinical probability.[20-21,26-28] Developing pretest suspicion based on an accurate clinical evaluation is an essential stage in the diagnostic process, facilitating the posttest definition and resulting in a better cost-effectiveness ratio. However, as evidence of the difficulties of developing a solid suspicion, various quite well-delineated prospective studies have demonstrated that objective confirmation of PTE is below 40% among suspected cases,(27-29) and that approximately 70% of PTE cases diagnosed during autopsies were not previously suspected by the attending physicians.[30]

OCCURRENCE OF PTE IN PATIENTS WITH COPD: EVIDENCE

The prevalence of COPD as a clinical risk factor for PTE has varied in some epidemiological studies. In the Worcester study, which involved 450 patients with initial VTE episodes, COPD was found in 18%

of the patients with PTE and in 34% of the patients with DVT.[1] In the ICOPER study, 12.4% of the patients with PTE presented COPD.(25) In the Olmsted study (Minnesota, USA), the univariate logistic analysis of VTE potential risk factors showed that the odds ratio for patients with COPD was 1.2 (95% confidence interval: 0.89 - 1.70), using a population-based objective diagnosis for a first manifestation of VTE in comparison to community controls.[2,4] In the multivariate analysis, COPD was not found to be an independent risk factor for VTE.[2,4]

Among the authors referred to in our study, there is a consensus that the significance of COPD as a clinical risk factor for PTE results from related factors such as age, sedentary lifestyle, immobility, decompensated congestive heart failure, asymptomatic malignancy, and, possibly, hypoxemia-related polyglobulia. Venous thrombosis can be the cause or the consequence of acute exacerbations, since they increase VTE risk factors, especially accentuating dyspnea upon exertion.

It is known that approximately 90% of venous thromboses occur in the deep venous system of the lower limbs. The predominant origin are the veins of the calf of the leg, where the thrombus formed may suffer lysis, remain in place or extend to proximal veins (in approximately 20% of cases). As it reaches the deep proximal venous system, the thrombus increases its potential to cause pulmonary embolism (in approximately 45% of cases).[31]

In one study, the authors investigated DVT in 45 hospitalized patients with acute decompensated COPD, using iodine 125-labeled fibrinogen V/Q mapping, contrast phlebography, ultrasound and impedance plethysmography.[32] They found 4 patients (8.9%) with DVT (2 with thrombosis limited to the calf and 2 with distal and proximal thrombosis). In 2 patients, DVT was detected upon admission. Out of the 33 patients evaluated with iodine 125-labeled fibrinogen, only 2 (6%) were diagnosed with DVT during hospitalization, and that was considered a complication of COPD exacerbation.

Another study involved 196 patients with acute COPD exacerbation, from moderate to severe intensity, hospitalized in a respiratory intensive care unit, through lower limb compression ultrasonography.[33] The authors found DVT in 21 patients (10.7%), 18 of whom were asymptomatic. All of the cases were unilateral.

Another group of authors studied 223 patients maintained on mechanic ventilation due to acute decompensated COPD.(34) One group received nadroparin, a low molecular weight heparin, and the other received a placebo. Compression ultrasonography and color Doppler ultrasonography were used to identify DVT, which was found in 15% (13/84) of the nadroparin group patients and in 28.2% (24/85) of the placebo group patients ($p = 0.045$). Regarding location, 3 cases in the nadroparin group were proximal, and 10 were distal, whereas the control group presented 7 cases of proximal DVT and 17 cases of distal DVT. The use of subcutaneous nadroparin resulted in a 45% reduction in DVT incidence.

Another study evaluated the presence of DVT in 56 hospitalized patients with acute COPD exacerbation from moderate to severe intensity.(35) The authors used compression ultrasonography/color Doppler ultrasonography in all cases and contrast phlebography in 2 patients. The results of the contrast phlebography were inconclusive, but the ultrasonography identified DVT in six patients (10.7%).In eight patients suspected of having PTE based on symptoms, hypocapnia or suggestive chest X-ray, V/Q mapping was performed. Five patients presented a V/Q with a high probability of PTE. Of the patients studied, 16% were diagnosed with VTE. There was no indication of the location of DVT in this study.

Yet another group of authors presented three cases of patients with severe COPD with angiographically-documented PTE, emphasizing that clinical and scintigraphic studies were not very useful in making a diagnosis.[36] The clinical manifestations were a sudden worsening of dyspnea and reduced exercise tolerance. The three patients presented sharp increases in alveolar ventilation and reduced arterial carbon dioxide tension ($PaCO_2$), as well as hypoxemia. These changes in arterial gases in patients with severe COPD should suggest PTE rather than exacerbation of bronchial obstruction. The V/Q mapping revealed discordant multiple bilateral segmental defects in one case and concordant defects in another case. No V/Q mapping was performed in the third case. The authors contended that inactivity and right cardiac insufficiency were the predisposing factors for VTE, and recommended the following: PTE should be suspected in any patient with COPD and cor pulmonale whose dyspnea presents rapid worsening and does not respond to conventional bronchodilator

treatment; in previously hypercapnic patients, PTE diagnosis should be supported by a finding of reduced $PaCO_2$; clinical and scintigraphic signs should not be considered useful in the differentiation between PTE and acute COPD exacerbation; and angiography should be performed to confirm PTE diagnosis in patients with severe COPD.

Another study involved two patients with acute massive PTE (obliteration of pulmonary circulation > 50% seen on the angiogram).[37] Both patients had pronounced alveolar-arterial oxygen gradient (one patient presenting arterial oxygen tension of 62 mmHg with a 100% fraction of inspired oxygen; and another, who was receiving oxygen via face mask, presenting arterial oxygen tension of 45 mmHg with a 40% fraction of inspired oxygen). The multiple inert gases elimination technique was used to determine the distribution of the V/Q ratio. An increased imbalance of the V/Q ratio was found in both patients, resulting entirely from the greater ventilation of units presenting high V/Q ratios (> 1.0). No blood flow perfusion was found in areas with V/Q ratios below 1.0. Both patients presented considerable blood flow (20% to 39% of the cardiac index) perfusing nonventilated lung units (shunt). In addition, the percentage of minute volume redirected to underperfused lung units, as well as the dead space/tidal volume ratio (as determined by the Bohr equation), increased. The fact that 82% of the minute volume was driven to the dead space area, together with the observation that there were regions presenting high V/Q ratios, can explain the $PaCO_2$ of 42 mmHg, despite a minute volume of 17 liters (dead space/tidal volume ratio of 78%), seen in one of the patients. The other patient presented a $PaCO_2$ of 24 mmHg (minute volume of 13 liters and dead space/tidal volume ratio of 54%). The authors concluded that, regarding these two patients with massive PTE, V/Q imbalance did not play a predominant role in hypoxemia, and that the increase in the alveolar-arterial oxygen gradient could be attributed to the large short-circuit (shunt) that was found.

The most probable causes of large shunts in the acute PTE scenario are pulmonary edema and atelectasis (with or without pulmonary infarction). The mechanism of formation of pulmonary edema might be the release of mediators that produce increased permeability and elevated pulmonary capillary hydrostatic pressure, both accompanied by increased fluid infiltration into the lung parenchyma.

The mechanisms proposed for hypoxemia in acute PTE include right-left shunt, diffusion impairment, V/Q imbalance and desaturation of the mixed venous blood through the increased arteriovenous oxygen gradient.

One case of refractory hypercapnia secondary to massive PTE was reported in a patient without any underlying heart or lung disease.(38) The authors of that report briefly reviewed various case reports of patients with massive PTE and hypercapnia, despite the increase in minute volume with spontaneous or mechanical ventilation.

In another report, the case of an 81-year-old patient with severe COPD, the apparent profile of acute COPD exacerbation and a two-week history of dyspnea and productive cough with purulent sputum was presented.[39] Arterial blood gas analysis on room air revealed arterial oxygen tension of 43 mmHg, $PaCO_2$ of 38 mmHg and pH 7.43. The patient was treated with antibiotics, prednisolone and bronchodilators. His cough and sputum production diminished after one week of treatment, although his dyspnea continued. The spiral CTA revealed PTE involving the right pulmonary artery.

Another study investigated 83 patients with COPD and suspected PTE using V/Q mapping.(40) The mapping results were categorized as high probability, inconclusive or low probability. The authors found PTE in 19 of the 22 cases with high probability mapping results (86%), in none of the 2 cases with inconclusive mapping results (0%) and in 4 of the 59 cases with low probability mapping results (7%). The general sensitivity of the V/Q scintigrams was 83%, and the specificity was 92%. False-negative results were obtained in 3 (19%) of the 16 patients presenting abnormalities in over 50% of the lung fields in the ventilatory study. In the 67 patients who presented ventilatory abnormalities in less than 50% of the lung fields, V/Q mapping presented 95% sensitivity and 94% specificity for PTE diagnosis. The authors concluded that, regardless of the COPD diagnosis, V/Q mapping constitutes a reliable method of detecting PTE if the abnormalities in the ventilatory component are limited.

Another group of authors evaluated the impact that previous cardiopathy or lung disease has on the usefulness of V/Q mapping in the diagnosis of PTE in patients enrolled in the PIOPED study.[27] Scintigraphies from 365 patients with no history of previous diseases (117 with PTE), were compared

with those from 526 patients with underlying cardiopathies or lung diseases (140 with TEP).[41] The results revealed that the positive predictive value for high probability V/Q was of 83% for cases with underlying diseases and 93% for patients without underlying diseases, a difference that was considered less than significant. The sensitivity of studies of high probability V/Q was 39% for patients with underlying diseases and 43% for those without underlying diseases, also considered a less than significant difference. In V/Q studies of patients with confirmed PTE, intermediate probability was found in 39% of the patients without underlying diseases and in 26% of the patients with underlying diseases ($p < 0.02$). The specificity of a high probability V/Q mapping was 97% in patients with underlying diseases and 98% in those without underlying diseases, also considered a less than significant difference. The authors concluded that the diagnostic utility of V/Q mapping for acute PTE was not impaired by pre-existing heart or lung diseases, although intermediate probability (inconclusive) results were less common in patients with underlying diseases.

In another study,[42] the clinical characteristics and the results of noninvasive tests, including V/Q mapping, were evaluated in 108 patients with COPD and suspected PTE who were part of the general PIOPED study sample.[27] A total of 21 patients (19%) were definitively diagnosed with PTE (20 by angiography and 1 by autopsy), although PTE remained unconfirmed in 87 patients. There were no significant differences among the groups of patients with and without confirmed PTE in terms of clinical manifestations, chest X-ray findings and arterial blood gas analysis results. However, in patients with PTE, pleuritic chest pain was more frequent than in those without PTE, although the difference was less than significant. The alveolar-arterial oxygen gradient in the group with PTE was 64 ± 59 mmHg, compared with 89 ± 116 mmHg in the group without PTE (the fraction of inspired oxygen varied). In the same two groups, $PaCO_2$ was 34 ± 6 mmHg and 38 ± 11 mmHg, respectively. Most V/Q mapping results (65/108 = 60%) were interpreted as indicating an intermediate probability of PTE. Intermediate probability was found in 33% of the 356 PIOPED patients with no history of heart or lung diseases ($p = 0.001$) and in 43% of the 227 patients with previous heart or lung diseases (including COPD) ($p = 0.01$). Only 5% of the results were interpreted as high probability, another 5% were interpreted as normal or quasi-normal, and 30% were interpreted as low probability (inconclusive). In the patients presenting high probability V/Q mapping results (5%), PTE was confirmed, and in the patients with normal or quasi-normal V/Q mapping results (5%), PTE was ruled out. Among the patients presenting intermediate probability V/Q mapping results, PTE was confirmed in 22%, whereas, among those presenting low probability V/Q mapping results, PTE was confirmed in 6%. In summary, in patients with COPD, the V/Q mapping results are predominantly of intermediate probability. However, in 19% of the patients with COPD, the V/Q mapping results were diagnostic (of high or normal probability) or there was concordance among low probabilities, clinical profile and scintigraphy.

In one study,[24] the PIOPED cases(27) were reviewed, and the authors found that the PTE patients with COPD (n = 21) differed from the PTE patients without previous heart or lung diseases (n = 117): in the group with COPD, pleuritic pain was less frequent ($p < 0.005$), whereas cough ($p < 0.05$) and wheezing ($p < 0.001$) were less frequent in the group without previous heart or lung diseases (Table 1).

In another study,[43] PIOPED data(27) was used to study PTE mortality in patients with COPD. Mortality rates were evaluated in 1487 patients submitted to V/Q mapping for PTE diagnosis, and these patients were monitored for up to one year after entering the study. A total of 23.8% of the patients with PTE and 18.9% of those without PTE died (relative risk of 1.34; 95% confidence interval: 1; $p = 0.03$). Among the patients with COPD and PTE, 53.3% died. After adjusting for the characteristics of the patients, the estimated risk of mortality within one year after the thromboembolic event was 1.94 times greater (95% confidence interval: 1.17 - 3.24) for COPD patients with PTE than for COPD patients without PTE, and 1.14 times greater (95% confidence interval: 0.85 - 1.54) for PTE patients without COPD ($p = 0.08$). Pulmonary arterial hypertension might explain the relationships among COPD, PTE and mortality. Pulmonary arterial hypertension has been correlated with mortality ($p = 0.001$), but not with COPD ($p = 0.25$) or PTE ($p = 0.79$). No significant interaction has been found among PTE, COPD and pulmonary arterial hypertension ($p = 0.79$).The estimated relative mortality risk among patients with pulmonary arterial hypertension was of 1.87 (95% confidence interval:

TABLE 1

Symptoms in suspected acute PTE

Symptoms	PTE + COPD n = 21 n (%)	PTE without COPD n = 117 n (%)	COPD without PTE n = 87 n (%)
Dyspnea	19 (90)	85 (73)	80 (92)
Cough	13 (62)	43 (37)*	48 (55)
Pleuritic pain	9 (43)	77 (66)*	32 (37)
Wheezing	8 (39)	10 (9)**	35 (40)
Hemoptysis	4 (19)	15 (13)	7 (8)

Adapted from references 24 and 37

*p < 0.05; **p < 0.001 (other differences were less than significant); PTE: (acute) pulmonary thromboembolism; COPD: chronic obstructive pulmonary disease

1.42 - 2.45). In patients with COPD, the estimated relative mortality risk adjusted for pulmonary arterial hypertension was 1.52 (95% confidence interval: 0.90 - 2.55) in patients with PTE compared to patients without PTE.

One study investigated 627 consecutive patients with suspected PTE at six teaching hospitals in the USA with the objective of evaluating the performance of the D-dimers, V/Q mapping, CTA and conventional angiography for the diagnosis of PTE in COPD patients.[44] The patients were independently categorized as having or not having COPD (based on clinical, radiological and pulmonary function diagnoses). There were 91 patients identified as having COPD (15%). The authors identified PTE in 29% of the patients with COPD and in 31% of the patients without COPD. The V/Q mapping results were inconclusive in 46% of the patients with COPD and in 21% of those without COPD (p = 0.001). The diagnostic performance of high probability V/Q mapping results did not differ significantly between patients with COPD and those without COPD: sensitivity 79% versus 88%; specificity 92% versus 96%; positive predictive value 79% versus 90%; and negative predictive value 92% versus 94%. In these two groups of patients, contrary to what had been expected, the sensitivity, specificity and predictive values (positive and negative) were higher for V/Q mapping than for CTA. The distribution of clinical probability, the diagnostic value of D-dimers, the diagnostic value of CTA and the reproducibility of pulmonary angiography were comparable between patients with COPD and those without CPOD. The presence of COPD did not affect the diagnostic performance of the clinical probability, D-dimers, CTA or pulmonary angiography. Although more inconclusive scintigraphy results can be expected in the presence of COPD, the V/Q study proved to be valuable in patients with COPD and suspected PTE.

COMMENTS

Clinical suspicion of acute PTE (high clinical probability or diagnostic pretest) is based on the presence of one or more risk factors and clinical symptoms consistent with the condition that cannot be explained by another diagnosis. The presence of another possible cause for this profile decreases the probability of PTE occurrence.[46]

Although COPD is not an independent risk factor for PTE, various conditions potentially associated with COPD, such as immobility, old age, uncompensated congestive cardiac insufficiency and adjacent cancer, have been identified as independently correlated clinical risk factors for VTE. Therefore, when confronted with symptoms consistent with PTE, diagnosticians should consider COPD a clinical risk factor, even though airflow limitation is not a thrombogenic factor per se. In addition, in theory, we can say that, since symptoms compatible with PTE, except for the acute pleuritic pain, can be explained by an underlying disease (when present), clinical suspicion of acute PTE in a COPD scenario would signify an intermediate probability of PTE.

It is difficult to identify characteristics of acute PTE in patients who may be experiencing an acute exacerbation of severe COPD. Symptoms, physical signs, X-ray abnormalities and abnormalities in the alveolar-arterial oxygen gradient or in $PaCO_2$ neither permit PTE diagnosis in individuals without underlying heart or lung disease nor help reinforce suspicion in cases of PTE and COPD.

It is usual for patients with severe COPD to present hypoxemia due to the dispersion of the V/Q ratio. Hypoxemia is usually accentuated by acute exacerbations or by PTE episodes. It has been suggested that a diagnosis of PTE should be considered when there is a reduction in $PaCO_2$ in a previously hypercapnic patient. However, in some patients with COPD, due to the inability of the minute volume to compensate for the increased dead space (caused by PTE or by the redistribution of the minute volume to the alveolar dead space), $PaCO_2$ might not be reduced and might even increase. A diagnosis of PTE should be considered in any patient with severe COPD who presents worsening

of dyspnea and decreased exercise tolerance, and who does not respond to conventional treatment with bronchodilators.

Antibiotics can improve occasional cough and purulent expectoration, but the lack of corresponding improvement of dyspnea, or even its worsening, should lead to suspicion of a causative acute COPD exacerbation-related thromboembolic episode.

Once the suspicion has been raised, an additional challenge is to make the diagnostic confirmation within the constraints of the cost-benefit ratio. In recent decades, V/Q mapping has been the principal instrument of PTE diagnosis. Among the COPD patients in the PIOPED study sample,[27] 60% of V/Q mapping results were found to be of intermediate probability, compared with 33% among the patients without previous lung disease.[42] However, in 19% of the patients with COPD, the V/Q mapping results were of high or normal probability or there was concordance between the clinical manifestations and low probability. High or normal probability V/Q mapping results were not affected by the underlying disease. In a previous study,[35] it was demonstrated that, despite the COPD diagnosis, V/Q mapping constitutes a reliable method of detecting PTE if the abnormalities found in the ventilatory study were not very extensive. However, V/Q mapping results of intermediate probability have been more frequently observed in patients with underlying lung diseases.

Among the algorithms used to diagnose VTE, measurement of D-dimer levels has become increasingly more important because of its high negative predictive value (resulting from its high sensitivity). Taken together with the levels of clinical probability, D-dimer levels, when negative and accompanied by low probability or inconclusive imaging exams, can be used to rule out the presence of acute VTE. The D-dimers levels of are elevated in any condition presenting reactional fibrinolysis, in which fibrin is formed and then degraded by plasmin. Levels of D-dimers are also elevated when there is infection, cancer, surgery, heart insufficiency, renal insufficiency, acute coronary syndrome, nonlacunar cerebrovascular accident, pregnancy or sickle cell crisis. Elevated D-dimers levels are seen in 80% to 90% of patients with infection or malignancy. Chronic COPD inflammation does not seem to interfere with the baseline increase in D-dimer levels.[20-21,44-45]

In a comprehensive study, it was found that the presence of COPD did not affect the diagnostic performance of the clinical probabilities of D-dimer levels, CTA or pulmonary catheter angiography.[44] The use of V/Q studies has been considered useful in patients with COPD and suspected PTE, although a greater number of inconclusive results might be expected in the presence of COPD.

It is worth mentioning that the ventilatory studies referred to in the literature were carried out with radioactive gases, first with xenon-133[27-28,40] and, more recently, krypton-81m.[44] Radioactive gases present greater penetration into obstructive processes than does technetium-99m-labeled diethylenetriaminepentaacetic acid aerosol.[47]

In patients with accentuated obstruction of the airways, the aerosol deposition occurs in the bronchi and central carinas, not reaching the alveolar area in sufficient quantity to allow an adequate V/Q comparison. The PISA-PED[28] study demonstrated that perfusion mapping can be sufficient for the diagnosis of PTE probability, with high positive and negative predictive values, when considered together with clinical probabilities.

The clinical probability of acute PTE in patients with severe COPD can, in general, be considered moderate. In such patients, the perfusion mapping results will also most probably be intermediate (inconclusive). Under these conditions, ultrasound of the lower limbs has been proposed as an initial diagnostic test, and, if negative, CTA is indicated (Figure 1).[20-21,29,48-49] Whenever possible, perfusion mapping can be useful for the diagnosis when normal/quasi-normal, or of high probability, even in patients with COPD (Figure 2). In cases of low clinical probability, a negative D-dimer test (which has high sensitivity) can rule out the diagnosis (Figure 3).

One method that can increase the diagnostic power of computed angiography of the chest is the incorporation of venography of the lower limbs. This technique extends the examination of the pulmonary arteries to the deep veins in the thigh and in the popliteal fossa.[50] Considering that VTE is a unique entity, indirect venography can help in its diagnosis through the identification of DVT in the same test. This combined approach economizes contrast medium but increases the exposure to radiation and therefore should follow specific recommendations.[51] This method is only valid for ruling out DVT when technically excellent procedures are employed[52] and is still awaiting more ample validation within the criteria that have guided the validation of other

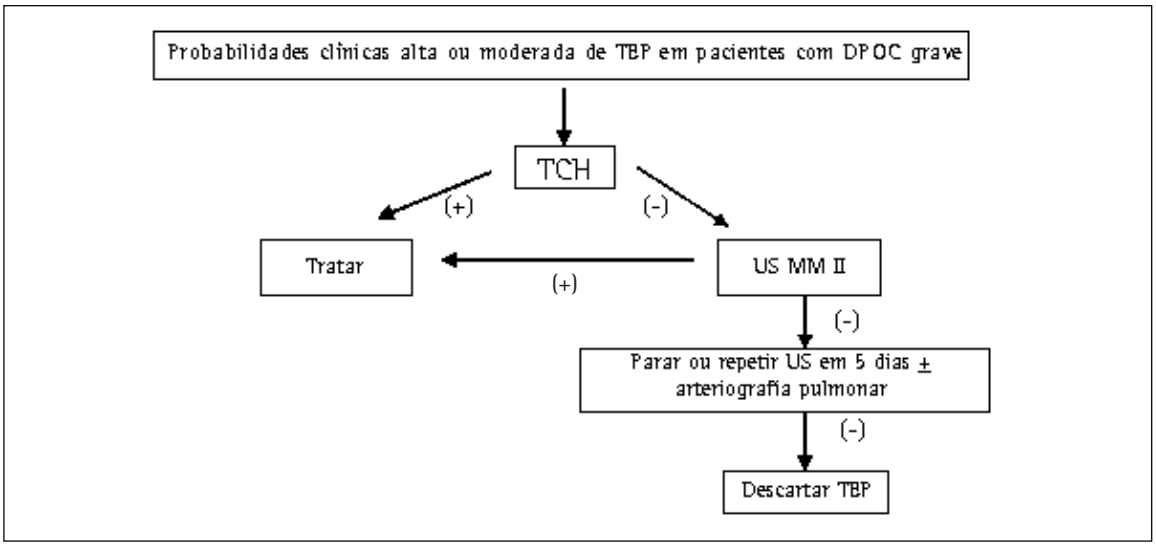

Figure 1 - Diagnostic algorithm of pulmonary thromboembolism in patients with COPD or altered chest X-ray.
(+) finding of deep vein thrombosis or pulmonary thromboembolism; (-) exam without confirmation of deep vein thrombosis or pulmonary thromboembolism. COPD: chronic obstructive pulmonary disease; CTA: (single-detector spiral) computed tomographic angiography (of the chest); US LL: (duplex) ultrasound of the lower limbs.

imaging techniques used for DVT diagnosis.

Finally, it must be borne in mind that multidetector-row spiral computed tomography allows the visualization of subsegmental vessels. Through the use of high quality tests, PTE can be ruled out. The negative predictive value of multidetector-row spiral computed tomography has been estimated at between 98% and 99%.(53-54) Since COPD did not interfere with the diagnostic performance of the single-detector CTA,[44] the expectation that it would have a favorable specific impact on patients with severe COPD is justified.

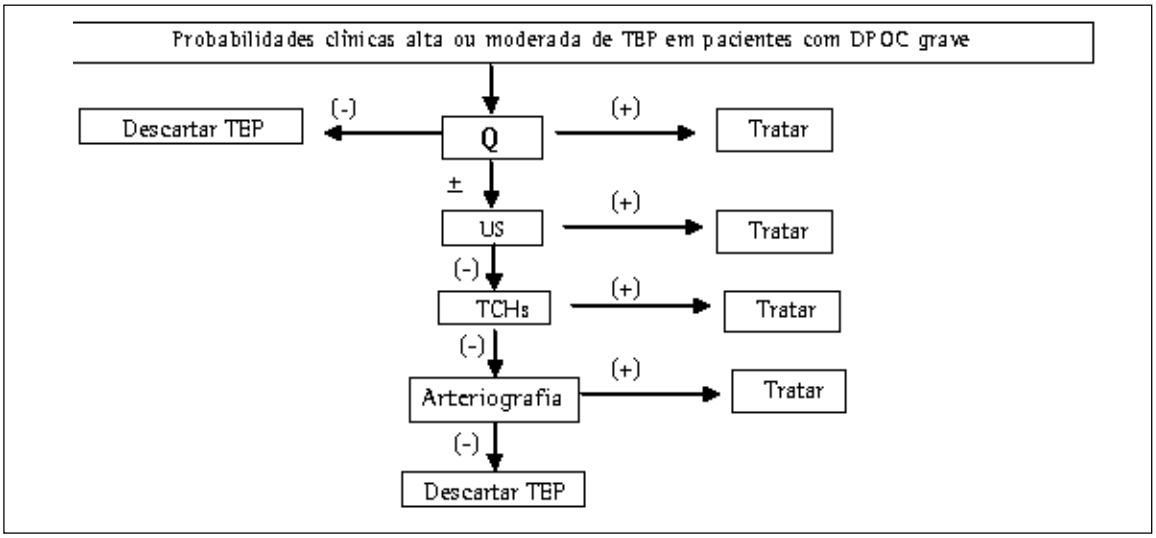

Figure 2 - Diagnostic algorithm of pulmonary thromboembolism in patients with COPD or altered chest X-ray, initially using perfusion mapping.
Q (-): normal exam, ruling out PTE; Q (+): high probability; (+): finding of deep vein thrombosis or pulmonary thromboembolism; (-): exam without confirmation of deep vein thrombosis or pulmonary thromboembolism. COPD: chronic obstructive pulmonary disease; Q: perfusion (mapping); US LL: (duplex) ultrasound of the lower limbs; CTA: (single-detector spiral) computed tomographic angiography (of the chest).

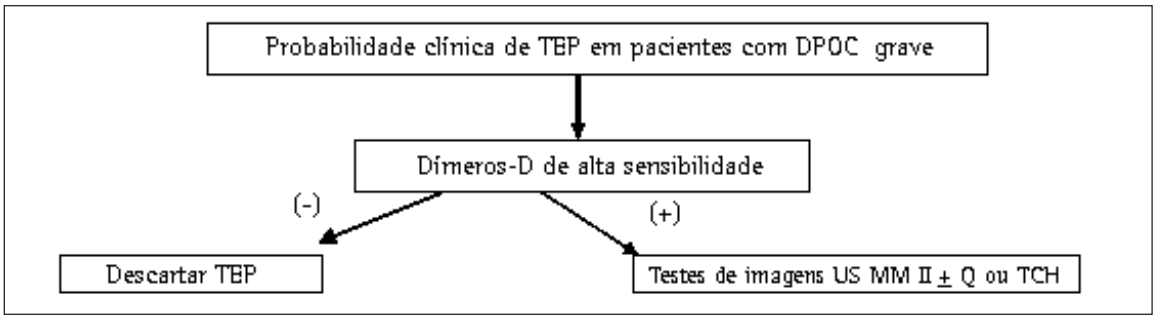

Figure 3 - Diagnostic algorithm of pulmonary thromboembolism in patients with COPD or altered chest X-ray, initially using the determination of high sensitivity D-dimer measurement (ELISA or LIATEST)
(+): levels of D-dimers above the cut-off point; (-): levels of D-dimers below the cut-off point. COPD: chronic obstructive pulmonary disease; Q: perfusion (mapping); US LL: (duplex) ultrasound of the lower limbs; CTA: (single-detector spiral) computed tomographic angiography (of the chest).

The results of a multicenter study for the evaluation of computed tomography of the chest and venous phase images used to diagnose acute thromboembolic disease (NHLBI Collaborative Prospective Investigation of Pulmonary Embolism Diagnosis II - PIOPED II) are soon to be published (results presented at the 2005 American Thoracic Society Conference in San Diego - USA).A new chapter in VTE diagnosis will certainly follow.

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