

# Acute exacerbation of chronic obstructive pulmonary disease: The clot matters a lot!

An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as an acute worsening of respiratory symptoms that results in additional therapy.<sup>[1]</sup> Acute exacerbation (AE) is an important event in the natural history of chronic obstructive pulmonary disease (COPD) as it leads to deterioration of lung function and disease progression with worsening of prognosis. The strongest predictor of a patient's future exacerbation frequency is the number of exacerbations they have had in the prior year.<sup>[2]</sup>

Previous studies have shown that 50%–70% of all COPD exacerbations are precipitated by an infectious process, whereas 10% are due to environmental pollution. The cause remains unknown in up to 30% of exacerbations.<sup>[3]</sup> Since thromboembolic events can lead to cough and dyspnea, pulmonary embolism (PE) remains a common, but often overlooked cause of COPD exacerbation. Sidney *et al.* suggest that the patients with COPD have approximately twice the risk of PE and other venous thromboembolic events than those without COPD.<sup>[4]</sup>

COPD, even in the stable phase, is considered to be an independent risk factor for PE. Systemic inflammation is the main atherothrombotic abnormality in COPD, but hypoxia-related platelet activation, procoagulant status, and oxidative stress may also play a role.<sup>[5-7]</sup> An increase of C-reactive protein, fibrinogen, interleukin (IL)-6, IL-8, and tumor necrosis factor  $\alpha$ , hypoxemia, oxidative stress, and endothelial dysfunction may alter the coagulation profile by increasing plasminogen activator inhibitor-1 and decreasing prostacyclin release.<sup>[8]</sup> It has been reported that obstructive spirometric patterns were associated with an increased risk for venous thromboembolism (VTE), after adjustment for VTE risk factors.<sup>[6]</sup>

Emerging evidence suggests that chronic inflammation may be a cause as well as a consequence of VTE. Underlying mechanisms associated with chronic inflammation-associated coagulopathy have been postulated but not yet defined clearly. Pulmonary thrombosis may not always result from embolization of a peripheral clot to the pulmonary arteries. Immunothrombosis normally facilitates the entrapment and disposal of pathogens and cellular debris. However, once getting beyond control, it contributes to the formation of thrombus *in situ*. There is evidence that the patients with inflammatory diseases of the lungs are at great risk of thrombosis directly in the pulmonary vasculature. In these cases, there is an

activation of endothelial cells, platelets, and leukocytes with subsequent formation of microparticles that can trigger the coagulation system through the induction of tissue factors.<sup>[9]</sup>

VTE risk appears to be elevated in patients with AE of COPD. In a systematic review and meta-analysis done by Aleva *et al.*, the prevalence of PE in unexplained AECOPD was 16.1% (95% confidence interval [CI]: 8.3%–25.8%), whereas deep vein thrombosis (DVT) prevalence was 10.5%.<sup>[10]</sup> Rizkallah *et al.* conducted a systematic review and meta-analysis and found that the overall prevalence of PE was 19.9% (95% CI: 6.7–33.0%;  $P = 0.014$ ). In hospitalized patients, the prevalence was higher at 24.7% (95% CI: 17.9–31.4%;  $P = 0.001$ ) than those who were evaluated in the emergency department (3.3%).<sup>[11]</sup> More recent results by Dentali *et al.* revealed a PE prevalence of 12.7% (95% CI 10.7–14.8) among 1043 patients hospitalized with AECOPD and suspected PE, a DVT prevalence of 6.4% (95% CI: 5.0–8.1).<sup>[12]</sup> Although DVT is usually twice as frequent as PE in the general population, PE seems to be the most frequent clinical presentation of VTE in patients with AECOPD. A study conducted by Couturaud *et al.* found that the prevalence of VTE was 11.7% (95% CI, 8.6%–15.9%) among patients in whom PE was suspected and was 4.3% (95% CI, 2.8%–6.6%) among those in whom PE was not suspected. All these findings emphasize the fact that all hospitalized COPD patients should mandatorily receive thromboprophylaxis for the prevention of VTE.

The clinical presentation of AECOPD and PE are similar. Studies comparing symptoms on the presentation in AECOPD with and without PE found that the patients with PE were more likely to complain of chest pain, syncope, and less likely to report cough and purulent sputum.<sup>[13]</sup> The chest pain was pleuritic in 50% of cases. A decrease in PaCO<sub>2</sub> was found in patients with PE. A disproportionate level of hypoxemia should also alert one about the possibility of underlying PE.

In an elegant study published in this issue of the journal by Chaudhary *et al.*, the prevalence of PE in AECOPD has been estimated to be 14%.<sup>[14]</sup> This finding is higher than the results from two earlier studies from India, which had estimated the prevalence of VTE in AECOPD to be 9% and 10.3%, respectively.<sup>[15,16]</sup> An important take home message from this article is that all AECOPD patients who present with chest pain, hemoptysis, tachypnea, tachycardia, and respiratory alkalosis should particularly be screened for PE.

There are challenges in diagnosing PE in AECOPD patients. Dentali *et al.* noted that the accuracy of clinical probability scores such as Wells and Geneva score needs to be validated in COPD patients. D-dimer testing is a tool used to exclude PE, but D-dimers may also increase due to the inflammation during AEs. Among patients with low-to-moderate pretest clinical probability, the age-adjusted D-dimer threshold values may be helpful. With more and more utilization of computed tomography pulmonary angiography, the diagnosis of PE has also increased.

COPD patients with PE have a worse prognosis, with increased mortality and length of hospitalization which reiterates the need for thromboprophylaxis during exacerbations. The occurrence of occult PE necessitates the need for the systematic screening of VTE in all COPD patients presenting with AECOPD.

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#### Conflicts of interest

There are no conflicts of interest.

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