

## Pulmonary embolus and acute exacerbations of chronic obstructive pulmonary disease

Hawa Edriss MD, Kenneth Nugent MD

In this issue of *The Southwest Respiratory and Critical Care Chronicles*, Thompkins and coworkers report a series of four patients with presumed chronic lung disease who presented with acute exacerbations of respiratory symptoms which did not respond to conventional therapy.<sup>1</sup> Pulmonary angiography by computed tomography (CTA) eventually demonstrated bilateral pulmonary emboli (PE) in these patients. The authors then discuss the difficulty in making the diagnosis of PE in patients with established chronic lung disease, especially patients who have the diagnosis of COPD. This report raises several important questions, including the frequency of PE in patients with acute exacerbations of COPD, the diagnostic utility of Wells and other criteria in this patient group, the diagnostic utility of D-dimer assays, the best approach to diagnosis in these patients, and the outcomes in these patients.

Tillie-Leblond *et al* investigated the frequency of PE in patients with COPD who were hospitalized with severe exacerbations of unknown origin and did not require invasive mechanical ventilation and investigated the factors associated with PE.<sup>2</sup> One hundred and ninety-seven patients with COPD exacerbation were included; all patients had spiral CTAs and 180 had Doppler ultrasound studies of the lower extremities. Forty-three patients had a positive CTA. Six patients had a positive ultrasound study and a negative CTA; 19 of the 43 patients (44%) with confirmed PE by spiral CTA had positive results on the Doppler ultrasound studies. Overall 49 patients (25%) had PE by their criteria which included either a positive CTA or a positive Doppler study and a negative CTA. The risk factors for PE included a previous thromboembolic event, malignant disease, and a decrease in PaCO<sub>2</sub> >5 mmHg from the base line.<sup>2</sup> Symptoms and signs, such as pleuritic chest pain, hemoptysis, palpitations, hypoxemia with a PaO<sub>2</sub> <60 mmHg, a PaCO<sub>2</sub> <39 mmHg, and HR >100 beats per minute, did not predict

the diagnosis of PE in these patients. The presence of cough was not helpful in supporting the diagnosis of a typical COPD exacerbation.<sup>2</sup> Eleven patients with low probability Geneva scores (9% of 119 with low probability in study cohort), 35 patients with intermediate probability scores (47% of 75 with intermediate probability), and three patients with high probability scores (100% of three with high probability) had confirmed PE.

Bertoletti and his colleagues prospectively evaluated COPD patients who had venous thromboembolic disease (VTE, i.e., DVT and/or PE) and found that COPD patients presented more frequently with PE (59%) than with DVT (41%).<sup>3</sup> Compared to non-COPD patients the three month prognosis in patients with COPD and PE was worse, and they had higher mortality rates and more VTE recurrences.<sup>3</sup> In 2013 Bertoletti *et al* reviewed 4036 patients with COPD enrolled in Registro Informatizado de la Enfermedad TromboEmbolica registry.<sup>4</sup> The patients presented with symptomatic VTE and were followed for three months. COPD patients with PE had a higher cumulative incidence of recurrent VTE as PE, all-cause mortality, and fatal PE than COPD patients presenting with DVT. Patients with PE had a slightly higher risk of major bleeding.<sup>4</sup>

Gunen studied 131 patients with known and unknown causes of COPD exacerbations and followed them for a year.<sup>5</sup> All patients were evaluated with Wells and Geneva criteria and D-dimer assays and underwent CTA to investigate for thrombi in the lower extremities and emboli in the lung and Doppler ultrasound studies of the lower limbs. The frequency of VTE was 16%. PE was found in 18 patients (13.7%), and DVT was detected in 14 (10.6%). DVT was detected in 11 out of 18 (61.1%) patients with PE. The prevalence rate of VTE was three times higher in patients with an unknown cause of their COPD exac-

exacerbations than in patients with an apparent cause of their COPD exacerbations. D-dimer levels were elevated in all patients except one. Moreover, it was significantly elevated in the VTE group ( $5.2 \pm 4.5$  vs  $1.2 \pm 1.8$   $\mu\text{g/ml}$ ;  $p < 0.0001$ ; with D-dimer level of  $< 0.5 \mu\text{g/ml}$  considered normal). The negative predictive value of the D-dimer level was 98%. No patient with either a low risk Wells criteria score or Geneva score had a PE. All patients with PE had either moderate or high risk scores using the Wells and Geneva criteria. The sensitivity and positive predictive value for the Wells criteria for moderate and high risk cases were higher than the Geneva criteria.

In conclusion, based on these studies, we strongly recommend that physicians consider pulmonary embolus in the differential diagnosis in patients with COPD exacerbations. The clinical symptoms and signs of COPD exacerbation and PE can be identical, and the clinical differentiation between the two is challenging.<sup>1</sup> Since patients with COPD have reduced gas exchange and pulmonary vascular reserve, PE may have a worse outcome in these patients, and they have an increased one year mortality rate.<sup>4,5</sup> Some studies suggested that COPD may increase biological thrombotic activities.<sup>6</sup> In addition, during COPD exacerbations patients often have limited mobilization due to dyspnea, and most patients with COPD are either former or current smokers which increases the VTE risk. D-dimer is still the most useful test to exclude VTE with a negative predictive value of 98%. VTE evaluation with normal D-dimer levels should be done in only exceptionally high risk patients. An elevated D-dimer level gives a more precise risk assessment for VTE when combined with either Wells or Geneva criteria scores. Moderate and high risk Wells and Geneva scores should identify almost all cases of PE.<sup>2,5</sup> Doppler ultrasound studies might be considered before spiral CTA in some high risk COPD patients, but some of these patients only have a PE and do not have DVT. Islam and Test have written a detailed review of diagnostic tests in patients with venous thromboembolic disease in this issue.<sup>7</sup> Berdine has written a commentary on this diagnosis in this issue based on his 30 years of clinical practice.<sup>8</sup>

**Author Affiliation:** Hawa Edriss is a resident in internal medicine at Texas Tech University Health Science Center in Lubbock, TX. Kenneth Nugent is a faculty member in the pulmonary and critical care division at TTUHSC in Lubbock, TX.

**Corresponding Author:** Hawa Edriss MD

**Author Contact Information:** hawa.edriss@ttuhsc.edu

**doi:** 10.12746/swrccc2014.0208.096

## REFERENCES

1. Robert B Tompkins RB, Harris V, Brown C, Griffith DE. Diagnosing Pulmonary Embolism in Patients with Suspected or Established Chronic Lung Disease. *The Southwest Respiratory and Critical Care Chronicles*. 2014; 2(8):5-16.
2. Tillie-Leblond I, Marquette CH, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006; 144: 390-396.
3. Bertoletti, Quenet S, Mismetti P, et al. Clinical presentation and outcome of venous thromboembolism in COPD. *Eur Respir J* 2012; 39:862-868
4. Bertoletti L, Quenet S, Laporte S, et al. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: data from the RIETE registry. *Respir Res* 2013, 14:75.
5. Gunen H, Gulbas E, Yetkin O, et al. Venous thromboemboli and exacerbations of COPD. *Eur Resp J* 2010; 35: 1243-1248.
6. Sabit R, Thomas P, Shale DJ, et al. The effect of hypoxia on marker of coagulation and systemic inflammation in patient with COPD. *Chest* 2010; 138:47-51.
7. Islam E, Test V. The Diagnosis of Acute Pulmonary Embolism. *The Southwest Respiratory and Critical Care Chronicles*. 2014; 2(8):21-30
8. Berdine G. Pulmonary Embolism in Patients with Chronic Lung Disease. *The Southwest Respiratory and Critical Care Chronicles*. 2014; 2(8):68-69.