



The paradoxical association between pulmonary embolism and COPD

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COPD is associated with an increased risk of PE, but not of VTE recurrence after anticoagulant therapy cessation <http://ow.ly/3uio30cAtyd>

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Chronic obstructive pulmonary disease (COPD) is recognised as a moderate risk factor (odds ratio between 2 and 9) for venous thromboembolism (VTE) [1], in the same group as cancer or oral contraceptive therapy. However, as opposed to cancer or the pill, this statistical association may represent a clinical dilemma [2], as COPD and the thoracic clinical presentation of VTE (pulmonary embolism, PE) have similar symptoms. The comprehension of the paradoxical association of COPD and VTE, particularly PE, has improved significantly in recent years [3–8].

What do we know?

First, the majority of VTE in COPD patients are provoked [3]. The most frequent trigger is immobilisation for acute medical disease in the past 2 months, such as acute exacerbation of COPD [3]. Secondly, COPD is also a (poor) prognostic factor in VTE patients, with increased risks of both fatal PE [9] and all-cause 30-day mortality [1]. Even if the two previous observations are not surprising, the modified clinical presentation of VTE in COPD patients remains paradoxical and debated. Although deep venous thrombosis (DVT) is usually twice as frequent as PE in the community [10], PE is the most frequent clinical presentation of VTE in patients with COPD [3, 6, 8]. One explanation could be a diagnostic bias, as presence of respiratory symptoms (due to COPD) may increase the demand for computed tomography and subsequently the number of PE diagnosed. This hypothesis may explain why this modified clinical presentation was also noted in other diseases with respiratory symptoms such as asthma [11], lung fibrosis [12] or chronic heart disease [13]. On the other hand, this potential explanation is totally contradicted by autopsy studies which found that COPD was associated with a high risk of dying from unsuspected PE [14], particularly in patients admitted for acute COPD exacerbation [15]. Hence, specific issues do remain in COPD patients, particularly during COPD exacerbation, such as the frequency of PE (3 or 25%) [16] or how to deal with the PE suspicion (Wells or Geneva score?) [17].

Now, just imagine yourself in front of a patient with mild-to-moderate COPD, who was diagnosed 3 months before with PE while he was admitted for increased dyspnoea.

The PE was a first VTE event and unprovoked (no acute medical disease, no surgery, no cancer). This situation is associated with a high risk of recurrence after stopping anticoagulant treatment (20% at 3 years in the PADIS-PE trial [18]). Regarding the American College of Chest Physicians guidelines [19], the

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decision between short or extended therapy (no scheduled stop date) is discussed after at least 3 months, but we have no clear evidence helping us to decide. So, how do we deal with the anticoagulant treatment? Should we consider ourselves (including the patient) lucky that the PE was diagnosed and the patient protected from undiagnosed fatal PE by the anticoagulant therapy? Or should we treat this patient exactly the same as other PE patients, *i.e.* occulting COPD?

In this issue of the *European Respiratory Journal*, LE MAO *et al.* [20] provide solid data on the risk of VTE recurrence in COPD patients in whom anticoagulant therapy is stopped. In this prospective monocentric study evaluating the risk of VTE recurrence after stopping anticoagulant therapy, the authors did not find any difference in terms of global VTE recurrence in patients with COPD *versus* those without. However, they did demonstrate that PE was the most frequent presentation in case of recurrence, confirming the paradoxical association between COPD and PE. These results were obtained on the whole COPD group, and remain similar in the sensitivity analysis of those with unprovoked VTE. This study has several strengths: to my knowledge, it is the biggest clinical prospective study of patients followed after anticoagulant cessation; the diagnosis of COPD was confirmed by spirometry in most of the cases; the follow-up was extensive (mean of 36.5 months); and all the events were adjudicated by a blinded committee. With regard to its limits, it is a monocentric study involving a team deeply involved both in COPD and VTE care and clinical research. Before being sure of its extrapolability, it should be pointed out that to be included, patients must have stopped their anticoagulant therapy. Hence, we only have the data from patients for whom clinicians felt confident to stop anticoagulant treatment. This potential selection bias was duly recognised in the discussion section [20]. Moreover, the annual incidence of recurrence was elevated: 9.1% (95%CI 6.5–12.8%) for the 136 patients with COPD. We do agree that this rate did not differ significantly from the one found in the 1332 patients without COPD (annual incidence of 7.0% (95%CI 6.2–7.9%)). However, we have to keep in mind that most of these VTE recurrences were PE, and that the case fatality rates differ as widely from VTE recurrence as DVT to VTE recurrence as PE [21].

Hence, although LE MAO *et al.* [20] confirm that PE is the most frequent clinical presentation of VTE (and then the most frequent form of VTE recurrence), they did not find an increased risk of VTE recurrence (all forms) for which they stopped the anticoagulant therapy, when compared to non-COPD patients.

We now have to answer two crucial questions. First, the annual incidence of recurrence was significantly high, between 7 and 9% in patients in whom anticoagulant was stopped. The PADIS-PE trial [18] demonstrates that extended vitamin K antagonists may protect patients from recurrent PE, but increase the risk of major bleeding. Direct oral anticoagulants are as efficient as vitamin K antagonists in randomised controlled-trials, but with a lower bleeding risk [22]. The recent EINSTEIN-Choice trial [23] opened perspectives for direct oral anticoagulants at reduced-dosage in the extended treatment of VTE. We now have to directly compare full-dosage direct oral anticoagulants to reduced-dosage in the extended treatment of PE, and this trial must include COPD patients. Secondly, the difficulties of PE suspicion in patients admitted for acute COPD exacerbation remain. We hope that the current trials (NCT02035293, NCT02238639) will help clinicians to determine when and how we should manage the PE hypothesis in these patients with acute exacerbation of COPD.

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