

# COPD and Anticoagulation Therapy: Time for a New Approach?

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**Abstract:** Chronic obstructive pulmonary disease (COPD) is one of the most challenging chronic disease nowadays due to increased morbidity and mortality, despite the multiple new therapies included in the therapeutic scheme. A possible cause may be insufficient approach to thromboembolic risk in these patients, scientific data being so far insufficient and relatively controversial. Areas covered: anticoagulant therapy is used mainly during severe exacerbations. There are data that have shown that therapy with low weight heparins injectable anticoagulants causes not only a reduction in thromboembolic risk but also an improvement in respiratory function parameters. Expert opinion: a number of COPD phenotypes are more prone to procoagulant status and thrombus formation. A layered approach to COPD patients in terms of antithrombotic prophylaxis is needed. Although current published clinical data have not provided irrefutable evidence, possibly due to the relatively heterogeneous approach to inclusion criteria, the frequent identification of autopsy holes in patients with COPD suggests that the high risk of mortality is due to specific bronchopulmonary changes and pulmonary embolism.

**Keywords:** coagulation, prophylaxis, heparin, embolism

## Introduction

World Health Organisation estimated that by 2030 the chronic obstructive pulmonary disease (COPD) will become the third leading cause of death worldwide, but this prediction has already been fulfilled, causing a major impact worldwide with 3.23 million deaths in 2019.<sup>1</sup> Chronic exposure to respiratory toxins causes inflammation of the airways with progressive evolution and leads to the destruction of the lung parenchyma and to hypersecretion of mucus. Recent studies have shown that the inflammatory process is not limited to the airways and that systemic inflammation exists in most cases. Although a large part of the morbidity and mortality associated with COPD is attributed to the exacerbations, it seems that in a significant number of COPD cases the unfavorable evolution is due to pulmonary embolism insufficiently recognized in current practice.<sup>2</sup>

However, thromboembolism is another major public health problem, with an annual incidence of 1.5 per 1000 people in Europe<sup>3</sup> and with a mortality of about 10% 3 months after onset.<sup>4</sup> Deep venous thrombosis (DVT) represents over 250,000 hospitalizations annually in the United States,<sup>5</sup> and worldwide morbidity and mortality from venous thromboembolism (VTE) is substantial.<sup>6</sup> VTE is a common and potentially fatal complication in COPD patients. Conversely, COPD moderately increases the risk of VTE (odds ratio between 2 and 9).<sup>7</sup> The association of COPD with embolic risk may be the basis for the poor

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prognosis of patients diagnosed with lung disease, and may contribute to the 50% survival rate four years after the first exacerbation with hospitalization.<sup>8</sup> Autopsy studies show that 28–51% of people who die from COPD had pulmonary embolism (PE), and among patients with cor pulmonale, 88.9% had thrombi in the arterioles and pulmonary arteries.<sup>9</sup> In patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD), there is a significant correlation between blood clotting and anticoagulation processes, and between oxidation and antioxidant mechanisms. Early administration of anticoagulant therapy may improve the prognosis in these patients. Administration of low molecular weight heparin or oral therapy in patients with acute exacerbation of COPD seems to improve lung function of the patients, slows the progression of the disease, and reduces the period and frequency of hospitalizations.

In this article, we will focus on the main mechanisms that explain the increase of thromboembolic risk in patients with COPD, the therapeutic opportunities and the effect of anticoagulant medication in these patients.

## COPD Pathogenesis

Neutrophilic inflammation is classically described in COPD involving, in addition to neutrophils, macrophages, and CD8+ (cytotoxic) T-lymphocytes. However, in recent years, there have been discussions about multiple pathogenic pathways such as different macrophage phenotypes.<sup>10</sup> Inhaled particles activate epithelial cells and alveolar macrophages responsible for triggering the release of cytokines and chemokines. As a result, the secretion of interleukins (IL)  $-1\alpha$ , IL- $1\beta$ , IL-33 and IL-18 is stimulated,<sup>11</sup> IL- $1\beta$  and IL-18 activating neutrophils, macrophages, helper lymphocytes T (Th) 1. These cytokines inhibit plasminogen activators. The procoagulant effect is initiated by the tissue factor, IL-6, and the tumor necrosis factor. The pathway of plasminogen activator inhibitor 1, the inhibition of tissue plasminogen activator, and inhibition as the mechanism capable of contributing to the amplification of procoagulant processes have also been described.

Plasma fibrinogen level is elevated in smokers and during acute exacerbation of COPD.

Systemic inflammation present in patients with COPD can generate, along with other factors, various complications, especially in the cardiovascular system.

Smoking is associated with reduced plasminogen activator inhibitor 1 and increased Factor XIII concentrations,<sup>12</sup>

and the multiple mechanisms caused by hypoxia include increased thrombin-antithrombin complexes, prothrombin fragment 1+2 and interleukin 6 concentrations.<sup>13</sup> In addition, mechanisms generating vasoconstriction may favour thrombogenic mechanisms. Clinical studies also suggest an increase in thrombogenic risk after COPD exacerbations.<sup>14</sup>

Therefore, in patients with COPD, chronic hypoxia and hypercapnia stimulate the hematopoietic function of the bone marrow to induce a compensatory increase in the number of red blood cells leading to an increase in blood viscosity, as well as an abnormal blood rheology. In addition, dehydration, reduced erythrocyte deformability, reduced blood flow, and acid-base imbalance cause the blood to be in a hypercoagulable state.<sup>15</sup>

## Vascular Changes in COPD

Pulmonary hypertension may occur as a result of vasoconstriction induced by chronic hypoxia.<sup>16</sup> Mean pulmonary artery pressure (mPAP) is higher in patients with BB-type polymorphism (BB homozygous genotype of intron 4 VNTR polymorphism) of the endothelial nitric oxide synthase (eNOS) gene compared to those without this mutation.<sup>17</sup> In terms of triggers, these patients were found to have an increased reactivity to hypoxia and exposure to cigarette smoke, possibly by reducing eNOS activity.<sup>18</sup> Hypoxia may reduce the expression of endothelial thrombomodulin or activate the X factor.<sup>19</sup> Another factor associated with the development of pulmonary vascular disease in COPD is the destruction of the lung parenchyma and the appearance of emphysema, which is accompanied by the loss of vascularity of surrounding tissues. Different mechanisms (including inflammation) are involved in the processes of pulmonary capillaries loss, due either to vascular endothelial growth factor<sup>20</sup> or to disruption of the pulmonary parenchymal architecture. Current data support the association of inflammation with a prothrombotic state involving endothelial cell dysfunction and coagulation abnormalities.<sup>21</sup> Increased muscle infiltration with CD8+ T lymphocytes occurs in the pulmonary arteries<sup>22</sup> correlated with the developing hypertension. In this context, inflammation can promote the coagulation process by stimulating the tissue factor gene in endothelial cells.<sup>23</sup> Conversely, coagulation amplifies inflammation and together acts as initiators of atherothrombosis.<sup>23</sup> It was noticed that there is a direct relationship between the increase in serum fibrinogen and cardiovascular events, which suggests that the procoagulant state may promote atherothrombosis in COPD.<sup>24</sup>

Based on these findings, it can be suggested that thrombotic events are present in patients with COPD due to a procoagulant status promoted by atherosclerotic vascular lesions.

The above data are supported by studies like that of Zielinski et al<sup>25</sup> which included 196 COPD patients admitted to a respiratory intensive care unit. In these patients, the DVT rate was 10.7%, but this was probably underestimated by the low sensitivity of ultrasound to asymptomatic DVT. This study excluded patients who previously had cancer, heart failure, or previous thromboembolism, suggesting that COPD itself or the resulting reduced mobility play important roles in DVT sensitivity. Pulmonary embolism accounts for approximately 10% of the deaths in stable COPD patients on chronic oxygen therapy.<sup>26</sup> The frequency of PE during acute exacerbation of COPD has not been evaluated by large, randomized clinical trials, but can be significantly higher.

## Anticoagulant Medication

### Unfractionated Heparin

Heparin is an effective anticoagulant and acts by improving hypercoagulable status and preventing pulmonary artery thrombosis.

The most important effects of heparin are reduced blood cell cohesion and blood viscosity, decreased resistance in the pulmonary circulation, and improved gas exchange. At the level of the respiratory system, heparin blocked the release of mediators such as 5-hydroxytryptamine (HT) and bradykinin, reduced bronchospasm and consequently increased the ventilatory function expressed by improving gas exchange at this level.<sup>15</sup> The frequent administration of systemic corticosteroids, in conjunction with other comorbidities (severe hepatic or renal impairment, neoplasms, etc.) in patients with exacerbations of COPD, significantly increases the risk of bleeding when unfractionated heparin is combined in the treatment regimen.<sup>27</sup>

### Low Weight Heparins

Because low molecular weight heparins have a high bioavailability in subcutaneous administration and antithrombotic effect, this causes less thrombocytopenia and bleeding. Low molecular weight heparins have a half-life of 24 hours, they can be administered slightly subcutaneously, and the patients' pain levels remain low. They are also cheap, and strict monitoring of blood clotting indicators is not necessary.<sup>15</sup> These features allow a safe use, without side effects. Fractionated heparins should be

administered as soon as possible in the acute phase to patients with hemodynamic instability. In a large, prospective, randomized, placebo-controlled study, administration of low molecular weight heparins resulted in a 45% reduction of the incidence of DVT in patients with acute conditions, the efficacy being confirmed in patients with COPD.<sup>28</sup> A review characterized the clinical problem of VTE in patients experiencing an acute exacerbation of COPD.<sup>29</sup> This review was performed based on a Medline search on papers published on this topic between 1966 and 2003. The conclusion of the study was that the risk of VTE during acute exacerbations of COPD appears to be significant and the high-risk situation need a pharmacologic prophylaxis.

### Direct Oral Anticoagulant

Currently, direct oral anticoagulant (DOAC) is recommended for first-line use in the treatment of PE.<sup>30</sup> Warfarin is the most common DOAC but newer medications (apixaban, dabigatran, fondaparinux, edoxaban, betrixaban, and rivaroxaban) were shown to be effective in preventing thrombotic events in patients with cardiovascular disease. The combination of drugs that alter the metabolism of vitamin K antagonists (macrolides, tetracyclines and fluoroquinolones) may cause prolongation of the Quick time, increasing the risk of bleeding complications.<sup>31</sup> New anticoagulant medications have the advantage of a superior safety profile, and they do not require dose adjustment or periodic evaluation of coagulation time. Comparative studies with vitamin K antagonists have revealed at least one non-inferior effect with the advantages described above.<sup>32</sup>

## Anticoagulant Therapy: Clinical Data in COPD

A study that included 70 patients hospitalized for exacerbations of COPD, of whom 38 received anticoagulant treatment, and 32 constituted the control group, revealed a superior improvement in lung function and arterial gasometry parameters in the treatment group.<sup>15</sup> Also, a significant reduction in the level of D-Dimers and blood coagulation parameters was obtained in the group that received anticoagulant therapy. These data demonstrate that patients hospitalized for exacerbations of COPD and treated with low molecular weight heparins show a significant improvement in lung function, as demonstrated by increased FEV1, PaO<sub>2</sub> and decreased PaCO<sub>2</sub>, and therefore the reduction of D-Dimers and blood clotting parameters. Furthermore, the authors

suggest that SaO<sub>2</sub> and PaO<sub>2</sub> are inversely proportional to the serum levels of D-Dimers and fibrinogen. Administering anticoagulant therapy was devoid of significant adverse events, which supports the idea that such therapies in patients with exacerbations of COPD are safe. The conclusion of the study was that the administration of low molecular weight heparins is followed by improved blood rheology indicators, improved circulation and lung function, as well as a reduction in blood viscosity.

Other studies have established a direct relationship between the existence of COPD and elevated levels of prothrombin, factor VIII, V, VII and IX, respectively reducing the plasma level of tissue pathway inhibitor. These interrelationships were present regardless of the severity of COPD, being therefore present in all patients suffering from this pathology.<sup>33</sup>

Although the triggers of COPD exacerbation have been extensively studied, the role of pulmonary embolism is less well known. A study that included 211 hospitalized patients for severe exacerbations found that 25% of subjects met the diagnostic criteria for pulmonary embolism.<sup>14</sup>

The study concluded that the use of the Geneva score or modified Geneva score should be included in the prospective assessment of COPD patients. From this perspective, we must consider that at least some of the symptoms encountered in patients with pulmonary embolism are similar to those encountered in COPD exacerbations, which may lead to clinical confusion.<sup>34</sup> A systematic search of the MELINE and EMBASE platforms shows that from 1974 to 2015 shows that the percentage of patients with exacerbations of COPD was 16.1%, out of which 68% suffered from emboli of the main pulmonary arteries, lobar arteries, or interlobar arteries.<sup>2</sup> This approach emphasizes that clinicians must consider other long-term therapeutic principles, in addition to the classic ones represented by anti-inflammatory, bronchodilator or sometimes antibiotics, given the observation that 2/3 of the emboli, depending on the location, have therapeutic indication.

A retrospective analysis in China<sup>35</sup> that analysed the factors associated with increasing the length of hospitalization of COPD patients included 565 patients hospitalized between 2016 and 2017. VTE resulted in an increase of the hospital stay to 16 days versus 10 days ((rate ratio) RR 1.38, 95% CI 1.07 to 1.76). Consequently, the study supports anticoagulation or mechanical prophylaxis as therapeutic methods to prevent thrombotic events in patients hospitalized with COPD.

Fraisse et al,<sup>28</sup> in a study investigating the efficacy and safety of prophylactic administration of nadroparin in mechanically ventilated patients due to COPD decompensation, revealed that therapeutic intervention is followed by a 45% reduction in the incidence of DVT compared to placebo.

A meta-analysis based on the observation that approximately 30% of all patients with COPD exacerbations did not identify a clear etiology investigated 550 patients and found that pulmonary embolism was present in 19.9% of cases, and respectively in about a quarter of hospitalized patients.<sup>36</sup>

In a study that included 5991 Danish patients diagnosed with COPD and right heart failure that treatment with oral anticoagulants results in a reduction in mortality. After a follow-up period of  $2.2 \pm 2.8$  years (0–19.6 years), 5% of patients died, compared to the group of patients who did not receive anticoagulant treatment. These therapies were associated with adjusted hazards ratio 0.87 (0.79–0.95). The authors concluded that although randomized clinical trials are needed to confirm these data, there are favourable prospects for oral anticoagulant therapy in patients with COPD and right heart failure.<sup>37</sup>

A prospective study analyzing the risk of recurrent VTE in COPD patients after discontinuation of anticoagulant therapy given after an episode of VTE was conducted over a period of up to 5 years and included 136 patients with COPD.<sup>38</sup> The study group that also included patients with COPD consisted of 1468 subjects, of which, 306 had recurrences of VTE (with an annual incidence of 7.2%), during the follow-up period. Of the 136 COPD patients, 34 suffered a recurrence of VTE (annual incidence of 9.1%). The authors conclude that patients with a history of COPD and VTE do not have a significant additional risk for embolic recurrence.

However, the analysis of deaths found an increased risk in patients with known COPD, even if this difference was not maintained when adjustment for baseline characteristics were made.

These data suggest that the comparative analysis of the risk of embolism in patients with COPD is subject to multiple factors that may disrupt the results. However, even in the absence of statistical significance, it can be seen that patients with COPD maintain both a risk of death and a risk of recurrence of VTE compared with those with any condition other than COPD.

A similar study by Piazza et al analyzed post-VTE complications over a 30-day follow-up period.<sup>39</sup> Higher

mortality, in line with the results provided by the RIETE registry,<sup>34</sup> emphasizes that the association between COPD and VTE is a major health problem and is potentiated by factors such as immobility, anticoagulant treatment, COPD phenotype.

A recent study published by Jiménez et al assessed whether active research of pulmonary embolism by D-Dimer dosing and computed pulmonary angiogram in hospitalized patients for COPD exacerbations is followed by a reduction in the composite risk of nonfatal symptomatic venous thromboembolism (VTE), readmission for COPD, or death within 90 days.<sup>40</sup> In the analysis were included 370 actively investigated cases, compared to 367 cases that received the usual care. Standard therapy included administration of oxygen, bronchodilators, antibiotics and prophylactic thromboprophylaxis. For patients with confirmed pulmonary embolism, a regimen was instituted that included parenteral anticoagulation, vitamin K antagonists, dabigatran or edoxaban, or monotherapy with apixaban or rivaroxaban. This multicenter study concludes that active strategies aimed at identifying hospitalized patients for exacerbations of COPD, which are associated with pulmonary embolism, have not been followed by an improvement in the composite risk pursued.

## Expert Opinion

COPD is a heterogeneous disease, associated with many comorbidities, which leads to an increased risk of exacerbations and high mortality. For these reasons, the treatment of COPD patients has become an important therapeutic issue. The increased thrombogenic risk caused by the multiple pathophysiological mechanisms underlying hypoxia, oxidative stress, endothelial dysfunction, and inflammation requires attention to the association of anticoagulant medication. Administering anticoagulants can be considered both during periods of exacerbation and during periods of illness, especially in patients with associated cardiovascular comorbidities (such as atrial fibrillation, right heart failure and pulmonary hypertension). Although a number of studies have evaluated the prevalence of VTE in COPD patients, due to the different inclusion criteria, the reported results vary. However, based on existing data, up to 29.1% of patients hospitalized with COPD associate thrombotic events. Studies such as Rizkallah's systematic review demonstrate the significant impact of pulmonary embolism in patients with exacerbations of COPD.<sup>36</sup>

Current guidelines, as well as the recommendations of the Global Initiative for Chronic Obstructive Lung Disease, support the use of antithrombotic treatment in patients with severe exacerbations of COPD.<sup>41</sup> Regarding the anticoagulant prophylactic therapy, there has been no consensus so far.

The SLICE trial<sup>40</sup> revealed that anticoagulant treatment in hospitalized patients for exacerbation of COPD, actively investigated for pulmonary embolism, does not bring additional benefits to prophylactic therapy. This finding substantially supports the arguments regarding the administration of prophylactic treatment to patients with COPD, as recommended by the Global Initiative for Chronic Obstructive Lung Disease in patients with severe COPD. Moreover, we note that the study mentioned above does not stratify the results obtained according to the severity of the underlying disease.

However, there are different approaches depending on the risks, comorbidities and severity of the pre-existing embolism. Thus, in the case of thrombi located at the level of the distal arteries, clinical monitoring is preferred, so that in the proximal emboli the anticoagulant therapy is instituted. Mechanical prophylaxis is preferred when there is an increased risk of bleeding.

By using new generation anticoagulant drugs, no significant risks of side effects were identified, including bleeding. In hospitalized patients, the preferred therapy is injection (unfractionated heparin or low molecular weight) and, among the oral medications, warfarin has been the most commonly used. So far, there has been no clear scientific evidence on the effectiveness of long-term therapy. Based on risk analyses, the American College of Chest Physicians (ACCP) recommends a minimum duration of 3–6 months of anticoagulant therapy.<sup>42</sup> More accurate stratification of patients with COPD and thrombogenic risk is likely to lead to new evidence for anticoagulant therapy. From this perspective, associating anticoagulants in patients with COPD, during exacerbations and post-exacerbation, is a therapeutic premise able to interfere with the progression of the disease and the occurrence of cardiovascular complications. We can also assume that improved survival rates result from reducing the risk of pulmonary embolism in patients who already associate vascular and parenchymal changes due to the underlying disease. These hypotheses need to be further investigated through long-term clinical trials. Therefore, there is multiple evidence today that, over time, patients with COPD, associate clotting dysfunction that leads to increased

thromboembolic risk through the mechanisms shown above: inflammation, hypoxia, endothelial dysfunction, oxidative stress.

Another component to be clarified is the choice of therapy for various circumstances or phenotypes. For example, should certain biomarkers be considered as detectors of thrombogenic risk? At what stage of the disease should prophylactic anticoagulant therapy be initiated? Are new oral anticoagulants at least as effective as low molecular weight heparin in hospitalized patients for COPD exacerbations?

Based on the existing data, we appreciate that early initiation of injectable anticoagulant therapy is the path to follow in patients hospitalized for exacerbations of COPD. The post-hospitalization period of anticoagulant treatment depends on the exacerbatory phenotype and the associated pathology. For patients with an exacerbating phenotype and those associated with cardiovascular risk factors, anticoagulant therapy may be given on a long-term basis. In patients without exacerbating phenotype, the continuation of anticoagulant therapy is recommended for up to 3 months after initiation, depending on the resumption of physical activity. Epidemiological studies need to be made on the risk factors with a large number of patients associated with COPD and pulmonary embolism. Along with the exacerbator phenotype, the eosinophilic phenotype is associated with hypercoagulability, as it was shown that hyper eosinophilia is associated with an increased risk of thrombosis. Consistent with the data shown above, clinicians should consider both the assessment of the risk of pulmonary embolism in patients with COPD and the phenotype of frequent or eosinophilic exacerbator for the inclusion of post-exacerbation anticoagulant therapy. Prevention of pulmonary embolism becomes as important as prevention of respiratory infections and air pollution.

## Conclusion

Despite efforts to identify new COPD therapies and phenotypes in late years, we find that COPD morbidity and mortality are constantly growing. A cause of this unfortunate situation may be the association of insufficiently recognized and treated thromboembolism, though identified in a significant proportion at autopsy. Early diagnosis and continued long-term treatment with anticoagulants in COPD patients could lead to increased survival and prognosis. Extensive stratification-based studies of COPD patients are needed to adapt the anticoagulant therapy in these patients.

## Author Contributions

All authors have read and agreed to the published version of the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest.

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