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Review article

Prevalence and prevention of venous thromboembolism in patients with acute exacerbations of COPD

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Abstract

Background: Little information exists on the prevalence and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients admitted for acute exacerbations of chronic obstructive pulmonary disease (COPD). *Objective*: To review available literature, we performed a Medline search on papers published on this topic between 1966 and 2003. *Data synthesis*: Pulmonary emboli have been frequently found (up to 30% of cases) in autoptic series that included patients who died from acute exacerbation of COPD, while the real incidence of PE during exacerbation has never been prospectively evaluated by large-scale clinical studies. Diagnosis of concomitant PE in these patients is often missed because symptoms of acute exacerbation of COPD may mimic PE, and non-invasive evaluation by pulmonary scintigraphy or CT scan is less specific. Even if not fatal, undetected and untreated PE may lead to long-term morbidity from pulmonary hypertension and predispose to recurrent venous thromboembolism (VTE). DVT of the lower extremities affects about 10% of patients with acute exacerbation of COPD at admission, but the rate is likely to be underestimated. The results of clinical trials conducted on general medical patients, including COPD patients, indicate that unfractionated heparin (UH) and low molecular weight heparin (LMWH) significantly reduce VTE rates. However, subgroup data on COPD patients are generally not available. In a single randomised, controlled trial specifically conducted on COPD patients, nadroparin reduced the rate of DVT from 28% to 15% without affecting mortality. *Conclusions*: Despite a substantial lack of consistent data, VTE appears as a major threat to patients admitted for acute exacerbation of COPD, and pharmacologic prophylaxis should be considered in all high risk situations. However, methodologically rigorous studies in this setting are still needed.

Keywords: Deep vein thrombosis, pulmonary embolism; COPD, prevalence, prevention

1. Introduction

Venous thromboembolism (VTE) is a common disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). PE most commonly results from DVT of the lower limbs and represents a major cause of morbidity and mortality. Clinical risk factors for VTE include increasing age, prolonged immobility, previous VTE, cancer, surgery, trauma, estrogen use, and congenital and acquired thrombophilic disorders. The prevalence of VTE and the efficacy of thromboprophylaxis have been less extensively evaluated in medical patients than in surgical patients: it was calculated that nearly 100,000 patients have been enrolled in trials evaluating VTE in surgery whereas approximately only 15,000 patients were included in trials evaluating medical patients [1].

Among medical conditions, patients with myocardial infarction and ischaemic stroke are those with the highest risk of VTE. The overall incidence of DVT is approximately 24% among patients with myocardial infarction, and increases to more than 50% after ischemic stroke [2].

Patients who are admitted for acute exacerbations of chronic obstructive pulmonary disease (COPD) are generally considered to be at moderate risk for the development of VTE because of the presence of concomitant risk factors such as immobilization, bronchial superinfection, right ven-

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tricular failure, and venous stasis. As recently confirmed [3], death occurs in approximately 8% of patients admitted for an acute exacerbation of COPD, and the rate of mortality increases following hospital discharge to up to 23% after 1 year. However, little attention has been given to VTE as a cause of morbidity and mortality in this patient setting. To evaluate all available information on the prevalence and prevention of VTE in patients hospitalized for acute exacerbations of COPD, and to possibly generate evidence based recommendations, a systematic search of the literature was carried out.

2. Literature search and data sources

We performed a series of MEDLINE database searches for English language literature published from 1966 to November 2003 using the following Medical Subject Headings' terms: *deep vein thrombosis*, *pulmonary embolism*, *venous thromboembolism*, *chronic obstructive pulmonary disease*, *chronic bronchitis*, and *heparin*. We also supplemented references by cross checking bibliographies of retrieved articles to identify additional studies.

The prevalence of VTE in patients with COPD was evaluated by reviewing autoptic studies and prospective observational studies, while the efficacy of prophylaxis was estimated by evaluating randomised controlled trials. Criteria for the inclusion of trials on prophylaxis in medical patients were those defined by the Sixth Consensus Conference on Antithrombotic Therapy of the American College of Chest Physicians (randomized design, sample size not <10 patients per group, contrast venography or fibrinogen leg scanning as diagnostic tool and adoption of currently approved drugs) [2]. This strategy produced a total of 20 articles, 8 on the prevalence of VTE [4,5,10–12,14–16] and 12 on VTE prophylaxis [9,17–27]. Because a formal combined statistical analysis of these studies was not appropriate due to the heterogeneity of methodology, a simple qualitative overview of available data was carried out.

3. Prevalence of VTE in COPD

PE is a relatively frequent cause of death in patients with COPD. In a multicenter European study conducted on 215 stable COPD patients treated with long-term oxygen therapy (LTOT) [4], PE accounted for 10% of all deaths. The frequency of fatal PE during acute exacerbation of COPD appears to be even higher when evaluated by autoptic studies. Neuhaus et al. [5] found pulmonary emboli in 27% of 66 autopsies performed in patients who had respiratory failure (not only as a decompensation of COPD) and died after admission to a Respiratory Intensive Care Unit. It is remarkable to observe that in this patient population PE was clinically suspected only in half of the cases and that no specific symptoms were described, thus supporting the concept that clinical suspicion of PE in stable [6,7] and acute exacerbation of COPD is particularly difficult, for clinical symptoms of COPD may mimic PE symptoms. Moreover, the intrinsic limitations of the ventilation/perfusion scintigraphy may also contribute to the underestimation of the prevalence of VTE in COPD patients [8].

The frequency of PE during acute exacerbation of COPD has never been evaluated by methodologically rigorous prospective large-scale studies. The prevalence of this condition ranged from 0% [9] to 29% [10] in small series that were limited either by the absence of scintigraphic confirmation or by selection bias.

Several clinical studies have evaluated the prevalence of DVT in patients admitted for an episode of exacerbation of COPD [11,12,14–16]. However, the value of their results is weakened by the sample size and by the diagnostic techniques that were adopted.

Prescott et al. [11] performed contrast venography and ^{125}I-Fibrinogen scans within 7 days after admission in a group of 45 bedridden patients, and showed a 9% overall incidence of DVT in the absence of pharmacologic and mechanical prophylaxis. In a study by Winter et al. [12], a group of 29 patients underwent autologous platelet labelling with indium-111 4 to 13 days after hospital admission. A DVT rate of 45% was observed.

When ultrasonography was used as a diagnostic tool, the prevalence of DVT was reported between 0% [14] in a small study on 33 males and 10% in two larger studies [15,16]. Ultrasonography (US) is safe, noninvasive, and relatively inexpensive, but it is limited by operator dependency and it is inadequately sensitive and specific both in asymptomatic patients and in the detection of calf vein DVT [13].

The largest study was conducted by Schonhofer and Kohler [15] on a population of 196 patients admitted to a respiratory intensive care unit. The authors found a DVT rate of 10.7% as assessed by US. The majority (86%) of cases were asymptomatic and, interestingly, almost all major clinical variables (such as age, weight, severity of dyspnea, lung function, situation of blood gases) failed to predict patients who were more likely to develop DVT. The importance of these results is highlighted by two considerations. First, this observational study excluded COPD patients also suffering from cancer, cardiac failure, or with a history of previous VTE, thus showing the relatively high frequency of DVT in patients without concomitant major risk factors. Second, the reported DVT rate was likely to be underestimated because of the limitations of US and because calf veins were not explored.

4. Prevention of VTE in COPD

To our knowledge, there is only one randomised controlled trial specifically conducted in patients with COPD. The Association of Non-University Affiliated Intensive

Care Specialist Physicians of France [9] compared the low molecular weight heparin (LMWH) nadroparin with placebo in patients with acute decompensated COPD who required mechanical ventilation in 34 intensive care units. In the group of 85 patients randomized to placebo, the observed rate of venographically detected DVT was 28%, with a rate of proximal and isolated calf DVT of 8% and 20%, respectively. In the group of 84 patients randomized to receive nadroparin until they could be weaned from mechanical ventilation, the occurrence of DVT was significantly reduced to 15.6% (proximal and distal DVT 3.6% and 12%, respectively). Since PE was not systematically investigated by objective tests, it is difficult to extrapolate data on the efficacy of LMHW prophylaxis in preventing PE in

Table 1
Summary of major published studies of VTE in COPD patients according to adopted thromboprophylaxis

First author, year (ref no.)	Study population		Patients with DVT by ^{125}I fibrinogen scanning	Patients with DVT by US		Documented DVT and clinically apparent	Patients with venographically confirmed DVT		Patients with PE	Patients with fatal PE	Prophylaxis regimen
	All COPD	Medical patients, COPD included		All DVT	Proximal DVT		All DVT	Proximal DVT			
Dahan, 1986 [18]		131	12 (9.1%)	?	?	?	?	?	?	3 (2.3%)	EA
Dahan, 1986 [18]		132	4 (3%)	?	?	?	?	?	?	1 (0.8%)	EA, LMWH (Pharmuka 10169 60 mg daily)
Bergmann, 1996 [19]		1230[a]								10 (0.8%)	LMWH (Nadroparin 0.3 ml once daily)
Bergmann, 1996 [19]		1244[a]								17 (1.4%)	Placebo
Samama, 1999 [17]		288	?	?	?	2 (0.7%)	41 (14.2%)*	14 (4.9%)*	3 (1%)	0 (0%)	ES
Samama, 1999 [17]		287	?	?	?	3 (1%)	43 (14.9%)*	13 (4.5%)*	1 (0.3%)	0 (0%)	ES, LMWH (Enoxaparin 20 mg)
Samama, 1999 [17]		291	?	?	?	1 (0.3%)	16 (5.5%)*	5 (1.7%)*	0 (0%)	0 (0%)	ES, LMWH (Enoxaparin 40 mg)
Gardlund, 1996 [21]		5776	?	?	?	?	?	?	?	15 (8%)[b]	UFH (5000 IU bid)
Gardlund, 1996 [20]		5917	?	?	?	?	?	?	?	16 (8%)[b]	None
Lechler, 1996 [21]		477					1 (0.2%)		0	0	LMWH (Enoxaparin 40 mg)
Lechler, 1996 [21]		482					4 (0.9%)		2 (0.5%)		UFH (Calciparine 5000 IU tid)
Harenberg, 1996 [22]		810			3 (0.4%)[c]				3 (0.4%)		LMWH (Nadroparin 36 mg)
Harenberg, 1996 [23]		780			1 (0.1%)[c]				3 (0.4%)		UFH (Calciparine 5000 IU tid)
Fraisse, 2000 [9]	109**						13/84 (15.5%)	3/84 (3.6%)	0	0[d]	LMWH (Nadroparin based on patients' body weight)[e]
Fraisse, 2000 [9]	114**						24/85 (28.2%)	7/85 (8.2%)	0	0	Placebo

COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; US = ultrasound; PE = pulmonary embolism; ASA = aspirin; GCS = graded compression stocking; LMWH = low molecular weight heparin; UFH = unfractionated heparin; EA = early ambulation.
*Detection of DVT by venography and ultrasonography in 83% and 17% of all patients, respectively.
**All patients with acute decompensated COPD requiring mechanical ventilation.
[a] Acute pulmonary disease accounted for 22% of the total patients populations (treated plus placebo groups, $n = 2474$).
[b] Necropsy-verified PE.
[c] Distal veins not examined; phlebography only performed in patients with negative or uncertain US results and clinical suspicion of DVT.
[d] One death in the nadroparine group suspected for PE (neither angiography nor autopsy performed).
[e] 0.4 ml daily for 45 to 70 kg; 0.6 ml for 71 to 110.

Table 2
Safety of heparin prophylaxis in patients with COPD

First author, year (ref no.)	Study population		Adverse events in the study period						Prophylaxis regimen
	All COPD	Medical patients, COPD included	Minor bleeding	Major bleeding	Fatal bleeding	Local hematoma	Thrombocytopenia	Severe thrombocytopenia	
Samama, 1999 [17]		362	27 (7.5%)	4 (1.1%)	0	0	13 (3.6%)	3 (0.8%)[a]	ES[b]
Samama, 1999 [17]		351	40 (11.4%)	1 (0.3%)	0	4 (1.1%)[c]	10 (2.8%)	0	ES, LMWH (Enoxaparin 20 mg)[b]
Samama, 1999 [17]		360	39 (10.8%)	6 (1.7%)	1 (0.3%)	5 (1.4%)[c]	8 (2.2%)	0	ES, LMWH (Enoxaparin 40 mg)[b]
Lechler, 1996 [21]		477	13 (2.7%)	2 (0.4%)	0	22 (4.6%)[c]	0		LMWH (Enoxaparin 40 mg)
Lechler, 1996 [21]		482	6 (1.2%)	9 (1.9%)	2 (0.4%)	52 (10.8%)[c]	0		UFH (Calciparine 5000 IU tid)
Harenberg, 1996 [22]		810	3 (0.4%)	5 (0.6%)	0		0		LMWH (Nadroparin 36 mg)
Harenberg, 1996 [23]		780	7 (0.9%)	4 (0.5%)	0		4[d] (0.5%)		UFH Calciparine 5000 IU tid)
Fraisse, 2000 [9]	108		19 (17.6%)	6 (5.6%)	0		10[e] (9.3%)	3 (2.8%)	LMWH (Nadroparin based on patients' body weight)
Fraisse, 2000 [9]	113		15 (13.3%)	3 (2.7%)	0		7[e] (6.2%)	2 (1.8%)	Placebo

[a] Platelet count of less than 50,000 per cubic millimeter.
[b] Treatment period 14 days.
[c] >5 cm in diameter.
[d] Platelet count ranged 40,000 to 80,000 per cubic millimeter.
[e] Platelet count of less than 100,000 per cubic millimeter.

these patients. LMWH prophylaxis failed to reduce mortality, although most deaths were due to cardiovascular complications or nosocomial infections, reflecting the serious conditions of these patients. The incidence of major bleeding and thrombocytopenia related to active treatment were not significantly different between the two groups, with an incidence of 5% and 1%, respectively, in the LMWH group and of 2.6% and 1%, respectively, in the placebo group.

COPD patients were also included in a number of clinical trials designed to assess the efficacy and safety of pharmacological prophylaxis in general medical patients (Tables 1 and 2). Unfortunately, these trials did not perform a critical evaluation of patients with COPD. The largest and most rigorous study performed in the medical setting was the Medenox trial [17]. Two dosages of the LMWH enoxaparin, 20 and 40 mg, were compared to placebo in 1102 bedridden medical patients and were administered for 6 to 14 days. Patients with acute respiratory failure, with the exclusion of those requiring ventilatory support, were more than 50% of all study patients and resulted the largest group included. The occurrence of deep vein thrombosis was systematically evaluated with venography at the end of the treatment. After 14 days, there was a statistically significant reduction in terms of venous thromboembolic events in the group treated with enoxaparin 40 mg as compared to placebo, but not in the group treated with enoxaparin 20 mg. Major bleeding rates and mortality rates were comparable among the three groups. Unfortunately, no efficacy and safety data can be extrapolated for the subgroup of patients admitted because of respiratory failure. The results of a meta-analysis evaluating for the first time all clinical trials conducted in medical patients [1] have shown that the risk of deep vein thrombosis in internal medicine is similar to the risk of DVT in general surgery. The meta-analysis also demonstrated that the use of pharmacologic prophylaxis, either unfractionated heparin (UFH) or LMWH, reduces the risk of deep vein thrombosis by 56% and the risk of clinical and fatal pulmonary embolism by 52%. When compared, UFH and LMWH showed a similar efficacy, but this latter offered a 52% reduction in the risk of major bleeding events.

5. Final comment

VTE is a frequent and serious complication in patients hospitalized for acute exacerbations of COPD. As in other medical conditions, there is increasing evidence to support that pharmacological thromboprophylaxis has an important role in the in-hospital management of these patients. However, at the moment specific evidence only exists for patients admitted to intensive care units for acute decompensated COPD requiring mechanical ventilation. Although this evidence is only based on the results of a single study, it is likely that these patients should be considered at moderate to high risk and to conclude that they should receive daily prophylactic LMWH. Indeed, further data are needed to better define the thrombotic risk and to evaluate the efficacy of pharmacological prophylaxis in reducing the risk of PE in

this patient setting. No direct data are yet available for patients with acute exacerbation of COPD who do not require mechanical ventilation, although extrapolation from trials conducted on general medical patients strongly support the need for LMWH or UFH. The GOLD guidelines [28] suggest to adopt LMWH in immobilized, polycythemic, or dehydrated patients with or without a history of thromboembolic disease. In our opinion, since there is no strong evidence to support this approach based on the selection of patients at greatest risk for VTE, the implementation of prophylaxis for every patient admitted with acute exacerbation of COPD is likely to be more efficacious. Thus, since many hospitals are currently developing a formal strategy that addresses the prevention of VTE in high-risk groups, it should be warranted that also patients with acute exacerbation of COPD are included in such a policy.

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