Value of prothrombin fragments F1+2 in the diagnosis of pulmonary embolism in patients hospitalized due to COPD exacerbation

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Prevalence of Pulmonary Embolism in Acute Exacerbations of COPD*
A Systematic Review and Metaanalysis
Jacques Rizkallah, MD; S. F. Paul Man, MD, FCCP; and Don D. Sin, MD, FCCP
CHEST 2009; 135:786–793

**Methods:** A systematic review of the literature was performed to determine the reported prevalence of PE in acute exacerbations of COPD in patients who did and did not require hospitalization. The literature search was performed using MEDLINE, CINAHL, and EMBASE, and complemented by hand searches of bibliographies. Only cross-sectional or prospective studies that used CT scanning or pulmonary angiography for PE diagnosis were included.

**Results:** Of the 2,407 articles identified, 5 met the inclusion criteria (sample size, 550 patients). Overall, the prevalence of PE was 19.9% (95% confidence interval [CI], 6.7 to 33.0%; p 0.014). In hospitalized patients, the prevalence was higher at 24.7% (95% CI, 17.9 to 31.4%; p 0.001) than those who were evaluated in the emergency department (3.3%). Presenting symptoms and signs were similar between patients who did and did not have PE.

**Conclusions:** One of four COPD patients who require hospitalization for an acute exacerbation may have PE. A diagnosis of PE should be considered in patients with exacerbation severe enough to warrant hospitalization, especially in those with an intermediate-to-high pretest probability of PE.
Prevalence of Pulmonary Embolism in Acute Exacerbations of COPD*

Selection bias?

- Indiscriminate enrollment of patients with moderate-to-severe COPD by Rutschmann et al revealed that the prevalence of PE was only 3.3%.
- Those with a severe exacerbation with an unclear precipitant yielded a prevalence of PE approaching 25%.
- High percentage of malignancy and immobilized patients in the studies included in the meta analysis may independently account for the increased risk for VTE.
One in four patients hospitalized with a COPD exacerbation may actually have a PE?

- The 2-week mortality of patients with untreated PE - 25%
- Repeated clots increase the risk of death 2-3 fold
- When the diagnosis of PE is missed, mortality is 4-6 fold higher

*Missing the diagnosis of PE*  

- IV contrast (nephrotoxicity, allergic reaction)  
- Empiric full-dose anticoagulation  
- Radiation
TABLE 4
Scales of Clinical Probability in Pulmonary Embolism (PE)*

<table>
<thead>
<tr>
<th>Pretest Rule</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells Scale*</td>
<td></td>
</tr>
<tr>
<td>PE most likely diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>Signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery during the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Cancer treated in the prior 6 months or palliative treatment</td>
<td>1</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>1</td>
</tr>
<tr>
<td>Clinical probability</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0-1</td>
</tr>
<tr>
<td>Moderate</td>
<td>2-6</td>
</tr>
<tr>
<td>High</td>
<td>≥7</td>
</tr>
<tr>
<td>Improbable</td>
<td>≤4</td>
</tr>
<tr>
<td>Probable</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

| Geneva rule* | |
| Recent surgery | 3 |
| Previous PE or DVT | 2 |
| PaO₂, mm Hg <48.7 | 4 |
| 48.7-59.9 | 3 |
| 60-71.2 | 2 |
| 71.3-82.4 | 1 |
| PaCO₂, mm Hg | |
| <36 | 2 |
| 36-38.9 | 1 |
| Age, years | |
| ≥80 | 2 |
| 60-79 | 1 |
| Pulse rate >100 beats/minute | 1 |
| Atelastasis | 1 |
| Elevation of hemidiaphragm | 1 |
| Clinical probability | |
| Low | 0-4 |
| Moderate | 5-8 |
| High | ≥9 |

*VDT indicates deep vein thrombosis.

Ar

scan if CT negative and high pretest probability

Clinical Suspicion of Pulmonary Embolism

- Pretest CP (Rules or Empiric)
  - Low
  - Moderate
  - High

- DD, VIDAS, or Turbidimetrics
  - Low
  - Moderate
  - High

On a Case-by-Case Basis

- CT Angiography
  - (+)
  - (-)

- Venous Ultrasound
  - (+)
  - (-)

- Low CP
  - Moderate CP
  - High CP

PE Ruled Out

Arteriography
Why we need more PE predictors:

- Geneva risk scores may not be optimal in risk stratifying COPD patients for PE. A total of 9.2% (CI, 4.7% to 15.9%) of patients with a low-probability Geneva score received a diagnosis of PE.

Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors.
Tillie-Leblond I, Marquette CH. Ann Intern Med. 2006 Mar

- Wells criteria, have not been validated in COPD patients during exacerbations.

- Ddimer was normal in 26% of patients with COPD and suspected PE.

Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure and in older patients with suspected pulmonary embolism.

Coagulation cascade:

Intrinsic pathway

XIIa → XIa
IXa → VIIIa → Xa → Va → Prothrombin

Extrinsic Pathway

TF

Prothrombin → VIIa

Prothrombin fragments (F1+2)

Thrombin

Fibrinogen → Fibrin

Platelets activation
endothelial cells stimulation.
Fibrinogen transformations to fibrin

Soft clot

Fibrin Split Products (FSP)

XIIIa

Hard clot
Prothrombin fragments F1+2:

- Prothrombin fragments 1+2 (F1+2; 2.5 +/- 0.5 nmoL/L vs 1.2 +/- 1.0 nmoL/L) were significantly elevated in the presence of spontaneous echo contrast in patients with atrial flutter.

  Activation of the endogenous coagulation system in patients with atrial flutter: relationship to echocardiographic markers of thromboembolic risk
  Cardiol J. 2010;17(4):390-6

- F1+2 levels are elevated in young patients with cerebrovascular syndromes who have aPL and in whom other causes of hypercoagulability and atherosclerotic vascular disease are absent.

  Value of prothrombin fragment 1.2 (F 1.2) in the diagnosis of stroke in young patients with antiphospholipid antibodies
  Ellis MH, Kesler A, Friedman Z, Drucker I, Radnai Y, Kott E
  Clin Appl Thromb Hemost. 2000 Apr;6(2):61-4
Prothrombin fragments F1+2:

- Elevated DD and F1+2 levels after stopping OAT were significantly associated with recurrence of thromboembolism.

Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism.


- The cumulative probability of developing VTE after 6 months was highest in patients with both elevated D-dimer and elevated F 1+2 (15.2%) compared with patients with non elevated D-dimer and non elevated F 1+2 (5.0%; P < 001).

D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study.

The aim:

To assess:

- the clinical usefulness of F1+2 in the diagnosis of PE in patients with exacerbation of COPD who require hospitalization
- whether F1+2 may have an additional value in the subgroup of patients with an abnormal Ddimer
- whether it may increase the proportion of patients in whom pulmonary embolism can be safely ruled out.
- To determine the sensitivity, specificity, negative predictive value (NPV) of F1+2 at various cut off values, and overall performance of F1+2 test by the calculation of the area under the ROC curve
The Methods:

The patients:
- The patients admitted to internal disease department with the diagnosis: COPD exacerbation

Exclusion criteria:
- Unable to give informed consent
- Unable to perform spirometry
- Impaired renal function
- Iod allergy
- Anticoagulant treatment
- A known hypercoagulable state
The Methods:

1. PFT: FEV1, FVC were measured by spirometry
2. Contrast enhanced CT angiography by the protocol for pulmonary vessels imaging
3. Blood samples for:
   • D-dimer (ELISA)
   • Prothrombin fragments F1+2,
     Plasma F1+2 concentration was measured by an enzyme immunoassay (Enzygnost, Marburg, Germany), according to the manufacturer's instructions
   • CRP
   • Creatinin: basal and 24 h after CT performance
Results:

- 49 patients: 35 M; 14 F
- Mean age: 65.5 (43–92)
- All current or former smokers
- Mean FEV1: 36% (18–65%) of predicted
- In the majority of the patients, CT was performed on the 2nd day of hospitalization (1st–6th)
- Creatinin changed by average 0.034
- PE was confirmed in 9 patients;

Prevalence of PE (18.37%)
The Results:

D-Dimer was normal in 20 patients

One patient with normal D-Dimer had PE

- Sensitivity – 88.9% ; Specificity – 42.5%
- PPV – 0.26; NPV – 0.94

F1+2 values: 50.0 – 1195 pmol/l

Mean = 254.73 pmol/l
(SD 220.8; SE 31.5519)

Median = 182.1 pmol/l

Reference range (137 healthy adults):
69 to 229 pmol/l ; Median = 115 pmol/l
The Results:

PE group:
- Mean = 380.
  95% confidence interval for Mean: 235.5 thru 523.7
  Standard Deviation = 190.
  Hi = 691. Low = 184.
  Median = 288.
  Average Absolute Deviation from Median = 135.
  
Group without PE:
- Mean = 227.
  95% confidence interval for Mean: 158.3 thru 295.0
  Standard Deviation = 220.
  Hi = 1.195E+03 Low = 50.0
  Median = 165.
  Average Absolute Deviation from Median = 119.

P = 0.06
**F1+F2 in patients with high DDimer**

**Group without PE:**
- **Mean = 204**
- 95% confidence interval for Mean: 140.2 thru 268.6
- Standard Deviation = 120.
- Hi = 601. Low = 50.0
- Median = 173.
- Average Absolute Deviation from Median = 75.8

**PE group**
- **Mean = 380**
- 95% confidence interval for Mean: 281.6 thru 477.7
- Standard Deviation = 190.
- Hi = 691. Low = 184.
- **Median = 288.**
- Average Absolute Deviation from Median = 135.
Sensitivity, specificity, NPV for F1+2 for different cut-off

### Regardless of DDimer

<table>
<thead>
<tr>
<th>F1+2 cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>1.0</td>
<td>0.6</td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>69</td>
<td>1.0</td>
<td>0.15</td>
<td>1</td>
<td>0.21</td>
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<tr>
<td>115</td>
<td>1.0</td>
<td>0.27</td>
<td>1</td>
<td>0.23</td>
</tr>
<tr>
<td>229</td>
<td>0.78</td>
<td>0.72</td>
<td>0.93</td>
<td>0.39</td>
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<tr>
<td>300</td>
<td>0.44</td>
<td>0.8</td>
<td>0.86</td>
<td>0.33</td>
</tr>
</tbody>
</table>

### Abnormal DDimer

<table>
<thead>
<tr>
<th>F1+2 cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>1.0</td>
<td>0.47</td>
<td>1</td>
<td>0.43</td>
</tr>
<tr>
<td>69</td>
<td>1.0</td>
<td>0.08</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>115</td>
<td>1.0</td>
<td>0.13</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>229</td>
<td>0.77</td>
<td>0.65</td>
<td>0.88</td>
<td>0.46</td>
</tr>
<tr>
<td>300</td>
<td>0.44</td>
<td>0.78</td>
<td>0.78</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Area under the curve ROC

- DDimer: Sensitivity - 0.89 ; Specificity - 0.42
- PPV - 0.26; NPV - 0.94

0.3412

0.4512
Conclusions:

1. Plasma levels of prothrombin fragment F1+2 were higher in patients with COPD exacerbation than in a reference group.
   - Prethrombotic state in patients with chronic obstructive pulmonary disease and treatment with heparin
     Xie M, Wang Z
   - Enhanced thromboxane biosynthesis in patients with chronic obstructive pulmonary disease. The Chronic Obstructive Bronchitis and Haemostasis Study Group
   - Hypercoagulability state in patients with chronic obstructive pulmonary disease. Chronic Obstructive Bronchitis and Haemostasis Group
Conclusions:

2. Patients with confirmed PE had higher values of F1 + 2 (p = 0.06)

3. In the subgroup of patients with abnormal DDimer and proved PE values of F1+2 were significantly higher (p < 0.0042) than in patients in whom PE was not confirmed.
Conclusions:

4. To obtain sensitivities approaching 100%, cutoff levels for F1+2 had to be set at 180 pmol/L or lower. However, the associated specificity then becomes very low. F1+2 may even be more specific than DDimer.

5. Taking a normal F1+2 level (cut-off 180) into account in the subgroup of patients with an abnormal Ddimer added significant clinical significance (11/29 could be withheld from additional imaging testing).

6. Overall performance of the F1+2 test (the area under the ROC curve) was low, but it was higher in the subgroup of patients with high D-Dimer.

7. CT angiography was safe.
Limitations:

- Small sample size
- Absence of standardization and normal value definition for F1+2
- Additional cost for F1+2 tests

Prognostic value of F1+2 and other markers of coagulation activation remains to be fully defined in future studies.
תודה רבה על הקשבה
קרוסון חמאה גבלי = 400 קלוריות
= הלכה 7 ק"מ
רכיבת על אופניים נייחות всемאך كل
(100 אוט) למשר שעתיים בורה.
רכיבת על אופניים נייחות всемאך מתח
ווט לשני כ 150 דקוט.
משתיכ גולף עם רכב מומע (לצליבים)
שעתיים של משחיק.
משתיכ טניס (אחד על אחד) - 50 דקוט.
שחית בריכת סנטונ חופה, מאמצ קלי
עד מתונות כשעה של שחייה.