Influence of specific alternative diagnoses on the probability of pulmonary embolism

Testuz, Ariane Marie; Le Gal, Grégoire; Righini, Marc Philip; Bounameaux, Henri; Perrier, Arnaud

Influence of specific alternative diagnoses on the probability of pulmonary embolism

Ariane Testuz[1,2], Grégoire Le Gal[1,2], Marc Righini[1], Henri Bounameaux[1], Arnaud Perrier[2]

[1]Division of Angiology and Hemostasis and [2]Service of General Internal Medicine, Department of Internal Medicine, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland

Summary

The presence and likelihood of an alternative diagnosis to pulmonary embolism is an important variable of the Wells' prediction rule for establishing clinical probability. We assessed whether evoking specific alternative diagnoses would reduce the probability of pulmonary embolism enough to forego further testing. We retrospectively studied a cohort of 965 consecutive patients admitted for suspicion of pulmonary embolism at three medical centers in Europe in whom the presence of an alternative diagnosis at least as likely as pulmonary embolism was recorded before diagnostic testing. We divided the patients into 15 categories of alternative diagnoses evoked. We then assessed the prevalence of pulmonary embolism in each diagnostic category and compared it to the prevalence of pulmonary embolism in a reference group (patients with no alternative diagnosis or a diagnosis less likely than pulmonary embolism). The prevalence of pulmonary embolism in the reference group was 48%. The presence of an alternative diagnosis as or more likely strongly reduced the probability of pulmonary embolism (OR 0.15, 95% CI: 0.1–0.2, p<0.01). In almost every diagnostic category, the prevalence of pulmonary embolism was much lower than in the reference group whith an odds ratio below or near 0.2. Bronchopneumonia (OR 0.4, 95% CI 0.2 to 0.7) and cancer (OR 0.6, 95% CI 0.3 to 1.5) reduced the likelihood of pulmonary embolism to a lower extent. Evoking an alternative diagnosis at least as likely as pulmonary embolism reduces the probability of the disease, but this effect is never large enough to allow ruling it out without further testing, especially when bronchopneumonia or cancer are the alternative diagnoses considered.

Keywords

Pulmonary embolism, alternative diagnosis, probability assessment

Thromb Haemost 2006; 95: 958–62

Introduction

Several studies have demonstrated the importance of pre-test or clinical probability assessment in suspected pulmonary embolism (1–3), and it is now incorporated in recent diagnostic algorithms (4–6). Implicit assessment has been well validated (2, 7, 8) but might be less accurate when applied by physicians of lesser experience (9, 10). Therefore, clinical prediction rules or scores have been developed to provide a more standardized pretest probability assessment. The Wells' score (11) and the Geneva score (12) are the most extensively validated (13–15).

While the Geneva score uses objective clinical variables (12), the Wells' score (11) is composed of six objective clinical variables and one subjective variable, the presence of an alternative diagnosis less likely than pulmonary embolism. Although considered by some authors as a weakness of the Wells' score because of its subjectivity (3, 12) and inter-rater variability (10, 16), that item has a considerable weight: its presence is enough to put the patient into the intermediate probability group of pulmonary embolism. Conversely, evoking an alternative diagnosis at least as likely as pulmonary embolism should lower the probability of the disease. However, to our knowledge, this effect and its impact on the probability of pulmonary embolism have not been reported.

In a previous prospective outcome study (15) on a diagnostic algorithm for pulmonary embolism, we recorded the likelihood and nature of alternative diagnoses for each patient prior to diagnostic testing. We herein present a retrospective analysis of that cohort to determine: i) the influence of specific alternative diagnoses on the probability of pulmonary embolism; ii)

Correspondence to:
Prof. Arnaud Perrier
Service of General Internal Medicine
Geneva University Hospital
24 rue Micheli-du Crest, CH-1211 Geneva 14, Switzerland
Tel.: +41 22 372 90 52, Fax: +41 22 372 91 16
E-mail: arnaud.perrier@medecine.unige.ch

Financial support:
The present study was supported by a grant from the Hirsch Fund of the University of Geneva.

Received February 24, 2006
Accepted after revision April 18, 2006

Prepublished online May 11, 2006 doi:10.1160/TH06–02–0114

whether evoking specific alternative diagnoses would reduce the probability of pulmonary embolism enough to forego further testing.

Methods

Patients

We analyzed a database of 965 consecutive patients admitted for suspected pulmonary embolism at three university hospital emergency departments (Geneva, Switzerland; Lausanne, Switzerland; and Angers, France) from October 1, 2000 to June 30, 2002 (15). This was a prospective outcome study designed to evaluate a diagnostic strategy for pulmonary embolism combining clinical probability assessment, plasma D-Dimer measurement, lower limb venous ultrasonography (US) and helical computed tomography (hCT), pulmonary angiography being performed only in case of a non conclusive diagnostic work-up. All patients above 18 years presenting to the emergency department with suspicion of pulmonary embolism, defined as acute onset of new or worsening shortness of breath or chest pain without any other obvious etiology, were eligible. Exclusion criteria were: ongoing anticoagulant treatment for reasons other than thromboembolism, contraindication to CT scan [allergy to iodine contrast agents or creatinine clearance below 30 ml/min calculated by the Cockroft formula (17)], informed consent impossible or patient refusal, suspected massive pulmonary embolism with shock, pregnancy, survival estimated below three months, and follow-up impossible.

Clinical assessment

Physicians filled out a standardized data collection form for each patient recording demographic characteristics, risk factors for pulmonary embolism, co-morbidities, clinical signs and symptoms of venous thromboembolism, results of the arterial blood gas analysis, and description of electrocardiogram and chest X-ray. We also asked if an alternative diagnosis to pulmonary embolism was evoked, and if so, its nature and likelihood compared with pulmonary embolism. The alternative diagnosis could either be chosen from a list or written down in free text on the data form (Table 1). We requested that only the most likely should be mentioned. The clinical probability of pulmonary embolism was then assessed by the Geneva score (12), which could be overridden by the physicians' clinical judgment in case of disagreement (13, 15).

Diagnostic criteria

For patients with a low or intermediate probability, pulmonary embolism was ruled out if the D-dimer level was below 500 ng/ml (highly sensitive ELISA assay, Vidas DD; BioMérieux, Marcy l'Etoile, France), or if both US and hCT were negative. In patients with a high clinical probability and a negative US and hCT, a ventilation-perfusion pulmonary scintigraphy or a pulmonary angiography was performed. Pulmonary embolism was considered established in patients with a proximal deep venous thrombosis shown by US, a positive helical CT or pulmonary angiogram, or a high-probability ventilation-perfusion scan (2). Each patient had a follow-up of three months.

Table 1: Diagnostic categories used in the analysis.

Diagnostic categories	At least as likely as PE (n)	Total (n)	Diagnoses mentioned on the data form	Diagnoses written down by the physician
Chest wall pain	149	172	chest wall pain, costovertebral joint dysfunction, osteoarticular affection, Tietzes syndrome	postherpetic neuralgia, radicular pain, intercostal neuralgia
Bronchopneumonia	67	104	bronchopneumonia	bronchopneumonia with pleural effusion
Left ventricular failure	52	78	left ventricular failure	
Coronary heart disease	44	63	angina pectoris, myocardial infarction	
Psychiatric affection	55	63	anxiety disorder, psychiatric affection	
Acute exacerbation of COPD	29	36	acute exacerbation of COPD	
Acute bronchitis	21	31	acute bronchitis	
Pericarditis	23	30	pericarditis	
Neoplastic disease	22	30	complication due to neoplasia, complication of a bronchogenic carcinoma, neoplastic affection, carcinomatous pleural effusion	
Non cardiac non pulmonary specific diagnosis	39	53	reflux esophagitis, cholecystitis, gastroduodenal ulceration, digestive affection, other digestive affection	orthostatic hypotension, renal colic, vasovagal attack, flu syndrome, multiple lymph nodes, renal affection, epistaxis, pharyngeal hematoma, pyelonephritis, thyrotoxicosis, gastritis
Other cardiovascular diagnosis	34	44	supraventricular tachycardia, cardiovascular affection, other cardiovascular affection	atrial fibrillation, rhythmic disorder, mitral papillary muscle rupture
Unexplained symptoms	48	99	chest pain of UO, dyspnea of UO, malaise/syncope of UO, other symptoms of UO, unexplained symptoms	hypoxemia of UO, hemoptysis of UO
Other specified pulmonary diagnosis	18	27	asthma, pulmonary contusion, pulmonary affection	pleuritis, pleurisy, bronchiectases, pneumothorax, pulmonary fibrosis, tuberculous pleurisy
Other unspecified pulmonary diagnosis	12	21	other unspecified pulmonary affection	
Other	1	1		other
Total	*614*	*852*		

PE: pulmonary embolism, COPD: chronic obstructive pulmonary disease, UO: unknown origin.

Table 2: Characteristics of the cohort (n=913).

Characteristics	N (%) or mean (± SD)
General	
Pulmonary embolism	218 (24)
Age	60 (20)
Female gender	534 (59)
Risk factors	
Family history of DVT or PE	98 (11)
Personal history of DVT or PE	158 (17)
Known congestive heart failure	90 (10)
Previous stroke	27 (3)
COPD	90 (10)
Cancer	84 (9)
Surgery, immobilisation, trauma or fracture within one month	222 (24)
Oral contraceptives	66 (7)
Hormone replacement therapy	52 (6)
Symptoms of pulmonary embolism	
Chest pain	639 (70)
Hemoptysis	42 (5)
Syncope	63 (7)
Malaise	67 (7)
Dyspnea	603 (66)
Symptoms of DVT	191 (21)
Clinical examination	
Respiratory rate	20 (7)
Heart rate	86 (20)
Systolic blood pressure (mmHg)	140 (23)
Temperature (°C)	36.9 (0.8)
Varicose veins	214 (23)
Signs of DVT	170 (19)
Signs of chronic venous insufficiency	185 (20)
Chest X-ray	
Pleural effusion	129 (14)
Band atelectasis	85 (9)
Elevated hemidiaphragm	111 (12)
ECG	
Right ventricular overload	209 (23)
Arrhythmia	94 (10)
Blood gases	
PaO2 (kPa)	10.0 (2.6)
PaCO2 (kPa)	4.8 (0.8)
Clinical probability of PE (according to the Geneva score +/- override)	
Low	484 (53)
Intermediate	357 (39)
High	72 (8)

DVT: deep venous thrombosis, PE: pulmonary embolism, COPD: chronic obstructive pulmonary disease.

Measurements

First, we regrouped the alternative diagnoses evoked by the emergency physicians into 15 categories by consensus among three experts blinded to the prevalence of pulmonary embolism in any category. Care was taken to obtain nosological groups that might be helpful and clinically meaningful for the physician in the emergency department (Table 1). For each diagnostic category, we determined the number of patients for whom the alternative diagnosis was judged at least as likely as pulmonary embolism. We calculated the prevalence of pulmonary embolism, which we compared to the prevalence of pulmonary embolism among patients for whom no diagnosis or a diagnosis less likely than pulmonary embolism was evoked.

Statistics

Odds ratios for pulmonary embolism and determination of 95% confidence intervals were calculated by standard methods.

Results

Study sample

We excluded 51 (5%) of the 965 patients of the initial cohort, because the clinician in charge evoked more than one alternative diagnosis, and one patient because of a coding discordance. Hence, 913 patients (94%) were included in this analysis. The patients were predominantly women [534/913 (59%)], were around 60 years old (60 ± 20), and the overall prevalence of pulmonary embolism was 24% (218/913). The main clinical presentations were chest pain (70%) and/or dyspnea (66%). The characteristics of the cohort are listed in Table 2. Sixty-one patients (7%) had no alternative diagnosis to pulmonary embolism and 238 (26%) had an alternative diagnosis judged less likely than pulmonary embolism. The alternative diagnosis was judged at least as likely as pulmonary embolism in 614 of the 913 patients (67%).

Overall, among patients for whom any diagnosis was evoked and judged at least as likely as pulmonary embolism, the prevalence of the disease was 12% (75/614). On the other hand, the prevalence of pulmonary embolism among patients with no alternative diagnosis or a diagnosis judged less likely than pulmonary embolism was 48% (143/299). These patients constitute the reference group with which the prevalence of pulmonary embolism in each diagnostic category is compared for the calculation of the odds ratios.

The odds ratio for pulmonary embolism of any alternative diagnosis at least as likely as pulmonary embolism, was 0.15 (95% CI: 0.1–0.2, $p<0.01$).

Diagnostic categories

Table 1 shows the number of patients for whom the alternative diagnosis was at least as likely as pulmonary embolism for each of the 15 final diagnostic categories. The prevalence of pulmonary embolism in the reference group (patients with no alternative diagnosis or alternative diagnosis less likely than pulmonary embolism) was 48%. We determined the prevalence of pulmonary embolism within each category and the corresponding odds ratios for pulmonary embolism (Table 3). In nearly every diagnostic category the prevalence of pulmonary embolism was much lower than in the reference group: psychiatric affection (2%), chest wall pain (7%), pericarditis (4%), acute exacerbation of COPD (7%), left ventricular failure (14%), coronary heart disease (14%), or acute bronchitis (14%). All those diagnostic

categories had odds ratios for pulmonary embolism below or near 0.2 (Table 3). Bronchopneumonia considered at least as likely as pulmonary embolism reduced the likelihood of the disease to a lower extent (odds ratio 0.4, 95% CI 0.2 to 0.7). In patients for whom cancer was thought to be more likely than pulmonary embolism, however, there was a non-significant trend towards a lower likelihood of pulmonary embolism (odds ratio 0.6, 95% CI 0.3 to 1.5) (Table 3).

Table 3: Prevalence of pulmonary embolism in diagnostic categories considered at least as likely as pulmonary embolism and corresponding odds ratios for pulmonary embolism.

Alternative diagnostic category	Prevalence of PE*	OR (95% CI)
Psychiatric affection	2 (1/55)	0.02 (0.0–0.1)
Pericarditis	4 (1/23)	0.05 (0.0–0.4)
Chest wall pain	7 (11/149)	0.08 (0.0–0.2)
Acute exacerbation of COPD	7 (2/29)	0.08 (0.0–0.3)
Non cardiac non pulmonary specific diagnosis	10 (4/39)	0.1 (0.0–0.4)
Other specified pulmonary diagnosis	11 (2/18)	0.1 (0.0–0.6)
Unexplained symptoms	8 (4/48)	0.1 (0.0–0.3)
Other cardiovascular diagnosis	9 (3/34)	0.1 (0.0–0.4)
Any alternative diagnosis evoked	12 (75/614)	0.15 (0.1–0.2)
Left ventricular failure	13 (7/52)	0.2 (0.1–0.4)
Coronary heart disease	14 (6/44)	0.2 (0.1–0.42)
Acute bronchitis	14 (3/21)	0.2 (0.1–0.6)
Bronchopneumonia	27 (18/67)	0.4 (0.2–0.7)
Other unspecified pulmonary diagnosis	33 (4/12)	0.5 (0.2–1.9)
Neoplastic disease	36 (8/22)	0.6 (0.3–1.5)

*% of pulmonary embolism (n), PE: pulmonary embolism, OR : odds ratio, COPD : chronic obstructive pulmonary disease, CI: confidence interval.

Discussion

This analysis shows that evoking an alternative diagnosis *at least as* likely as pulmonary embolism reduces the probability of pulmonary embolism approximately six-fold (odds ratio 0.15; 95% CI 0.1 to 0.2). Actually, the corresponding item in the Wells' score was whether an alternative diagnosis was *less* likely than pulmonary embolism, which raised the probability of pulmonary embolism. The odds ratio for pulmonary embolism of an alternative diagnosis less likely than pulmonary embolism was 6.2 in the univariate and 4.6 in the multiple regression analysis in the original derivation set of the Wells' score (11). As these odds ratios assess the same association and are each other's reciprocal, our results are very close (odds ratio for pulmonary embolism of an alternative diagnosis less likely than pulmonary embolism in our cohort: 1/0.15 = 6.7).

Moreover, our data show that the influence of evoking specific alternative diagnoses on the probability of pulmonary embolism is variable. Most alternative diagnostic categories (psychiatric affection, pericarditis, chest wall pain, acute exacerbation of COPD, left ventricular failure, coronary heart disease or acute bronchitis) significantly reduce the probability of pulmonary embolism. The group labeled psychiatric affection, consisting mainly of anxiety disorders accompanied by hyperventilation, is particularly striking. When such a hypothesis is considered the most likely diagnosis by the clinician, the prevalence of pulmonary embolism falls below 2% and would theoretically allow ruling out venous thromboembolism without performing further tests. In fact, the number of patients is too small to allow a precise measurement of the likelihood ratio and the "black box" effect – we do not know what particularities of the clinical presentation prompted the physician to evoke that hypothesis – would not justify that attitude.

Surprisingly, bronchopneumonia, the second largest category (n=67), does not lower the prevalence of pulmonary embolism to the same extent as the other diagnoses mentioned above, and the prevalence of the disease was still 27% in patients in whom this diagnosis was contemplated. Although this is still significantly less than the prevalence of pulmonary embolism in patients without an alternative diagnosis, it suggests that there is considerable mimicry between the clinical presentation of pneumonia and pulmonary embolism. Noteworthy, plain chest X-ray findings were included in the clinical assessment and helped the physicians in the determination of an alternative diagnosis. On the other hand, clear cases of bronchopneumonia presenting with high fever, purulent sputum and radiological infiltrate were probably not included in our study. Indeed, our inclusion criterion was a suspicion of pulmonary embolism defined as acute onset or new worsening shortness of breath or chest pain *without any other obvious etiology*. Although that last criterion is necessarily subjective, it merely reflects sensible clinical practice, since investigating all patients admitted with dyspnea and/or chest pain for pulmonary embolism would hugely increase the number of patients submitted to unnecessary and costly tests. Therefore, patients included in this study who had a final diagnosis of bronchopneumonia had a less clear-cut clinical presentation that explains why pulmonary embolism was evoked as a diagnostic possibility. Furthermore, it also explains why evoking bronchopneumonia *in a patient suspected of pulmonary embolism* did not reduce the likelihood of venous thromboembolism.

Finally, in patients with cancer presenting with suspected pulmonary embolism in whom clinicians estimated that cancer itself rather than pulmonary embolism was the explanation of a patient's symptoms, the likelihood of pulmonary embolism was lower than in the comparison group, but the difference was non-significant. Therefore, although active cancer may certainly produce respiratory symptoms due to local extension in case of bronchogenic carcinoma, or metastases, thereby decreasing the probability of pulmonary embolism, our results suggest that clinical judgment does not allow distinguishing between that explanation and pulmonary embolism. This may be due to the fact that cancer itself is an important risk factor for pulmonary embolism. Hence, all patients with cancer suspected of pulmonary embolism should have a complete diagnostic workup.

What is the clinical significance of our data? Evoking any alternative diagnosis at least as likely as pulmonary embolism reduces the likelihood of pulmonary embolism, which is consistent with the Wells' score. This effect varies according to which alternative diagnosis is evoked, but it is never large enough to allow ruling out pulmonary embolism without further testing, particularly when bronchopneumonia and cancer are the alternative diagnoses under consideration.

References

1. Perrier A. Pulmonary embolism: from clinical presentation to clinical probability assessment. Semin Vasc Med 2001; 1: 147–54.
2. The PIOPED Investigators. Value of the ventilation-perfusion scan in acute pulmonary embolism. JAMA 1990; 263: 2753–9.
3. Chunilal SD, Eikelboom JW, Attia J, et al. Does this patient have pulmonary embolism? JAMA 2003; 290: 2849–58.
4. British Thoracic Society Standards of Care Committee. Suspected acute pulmonary embolism: a practical approach. Thorax 1997; 52: S2-S21.
5. Kruip MJ, Leclercq MG, van der Heul C, et al. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 2003; 138: 941–51.
6. Goldhaber SZ. Pulmonary embolism. Lancet 2004; 364: 244.
7. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999; 353: 190–5.
8. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 2002; 360: 1914–20.
9. Rosen MP, Sands DZ, Kuntz KM. Physicians' attitudes toward misdiagnosis of pulmonary embolism: a utility analysis. Acad Radiol 2000; 7: 14–20.
10. Iles S, Hodges AM, Darley JR, et al. Clinical experience and pre-test probability scores in the diagnosis of pulmonary embolism. QJM 2003; 96: 211–5.
11. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 2000; 83: 416–20.
12. Wicki J, Perneger TV, Junod A, et al. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Arch Intern Med 2001; 161: 92–7.
13. Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment for suspected pulmonary embolism. Am J Med 2002; 113: 269–75.
14. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001; 135: 98–107.
15. Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med 2004; 116: 291–9.
16. de Monye W, Huisman MV, Pattynama PM. Observer dependency of the SimpliRed D-dimer assay in 81 consecutive patients with suspected pulmonary embolism. Thromb Res 1999; 96: 293–8.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.