A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients

Grégoire Le Gal¹, Marc Righini², Oliver Sanchez², Pierre-Marie Roy³, Mohamed Baba-Ahmed¹, Arnaud Perrier⁵, Henri Bounameaux⁴

¹EA3878 (GETBO), Department of Internal Medicine and Chest Diseases, Brest University Hospital, Brest, France; ²Service of Pneumology, Georges Pompidou European Hospital, Paris, France; ³Emergency Department, Angers University Hospital, Angers, France; ⁴Division of Angiology and Hemostasis and ⁵Division of General Internal Medicine, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland

Summary

The presence of a clot – even asymptomatic – in the proximal lower limb veins of a patient with clinically suspected pulmonary embolism (PE) provides evidence for venous thromboembolism and indicates anticoagulant therapy in such patients. We aimed at assessing the diagnostic performance of compression ultrasonography as compared to multi-slice computed tomography (MSCT) for the diagnosis of PE. We analyzed data from a large outcome management study that included consecutive outpatients referred to the emergency ward with clinically suspected PE. All high clinical probability patients, and all non-high clinical probability patients with a positive D-dimer test underwent both MSCT and CUS. Of the 756 included patients, 232 had PE ruled out on the basis of a negative D-dimer test, and 524 patients underwent both MSCT and CUS. PE was found in 187 out of the 511 patients with a conclusive MSCT. The sensitivity of CUS for the presence of PE on MSCT was 39% (95% confidence interval: 32 to 46%), and its specificity was 99% (95% CI: 97 to 100%). Positive and negative likelihood ratios were 42.2 (95% CI: 13.5 to 131.9) and 0.6 (95% CI: 0.5 to 0.7), respectively. We conclude from that large study of unselected patients that CUS has high specificity but low sensitivity, for the diagnosis of PE at MSCT in suspected patients. It allows ruling in the diagnosis of PE without further invasive and/or expensive testing in suspected patients.

Keywords

Pulmonary embolism, deep vein thrombosis, diagnosis, compression ultrasonography

Introduction

During the past decade, pulmonary angiography, the gold standard for the diagnosis of pulmonary embolism (PE) has been replaced by diagnostic strategies that combine various non-invasive or less invasive diagnostic tests: plasma D-dimer measurement, clinical probability assessment, ventilation perfusion lung scan, chest computed tomography, or proximal lower limb veins compression ultrasonography (1). The rationale for searching a deep vein thrombosis (DVT) in a patient with clinically suspected PE derives from the natural history of venous thromboembolism: most of the pulmonary clots originate from lower limb veins. Hence, the presence of a clot in a proximal lower limb vein – even asymptomatic – provides evidence for venous thromboembolism and thus indicates anticoagulant therapy in suspected patients. Moreover, although this is still a matter of some debate, DVT and PE are widely thought to be two clinical expressions of the same disease, both requiring anticoagulant therapy, which allows stopping the diagnostic work-up in a patient suspected of PE when a DVT is found.

Compression ultrasonography has a good sensitivity and specificity (both above 95%) for clinically suspected DVT (2). However, the diagnostic accuracy of this test is dramatically reduced in patients without leg symptoms (3, 4), which is often the case in patients suspected of PE. In this particular setting, little is known about the diagnostic performance of CUS, because data on direct comparison with pulmonary angiography as the gold standard are scarce. Moreover, along with a ventilation perfusion...
lung scan or a spiral computed tomography, recent diagnostic strategies for PE include assessment of the lower limb veins byCUS among their sequential testing (5, 6), precluding any evaluation of its diagnostic accuracy.

The development of multi-slice computed tomography is a new step in the diagnostic work-up of patients with suspected PE. The specificity of spiral computed tomography for the diagnosis of PE is high (7), although a precise evaluation is difficult due to the limited number of patients who underwent both pulmonary angiography and MSCT (8). Moreover, although this remains to be tested against previously validated strategies, recent data suggest that MSCT is a highly sensitive test and that a negative MSCT of the chest might allow ruling out the diagnosis of PE (1, 9), even when performed as the single imaging test (10). Hence, MSCT could become the new reference standard for PE in the next years (11).

We recently validated a diagnostic strategy based on clinical probability assessment, plasma D-dimer measurement, lower limb CUS and chest MSCT. In that study, all patients with either a high clinical probability or a non-high clinical probability and a positive D-dimer test underwent a MSCT of the chest and a lower limb CUS. We assessed the diagnostic accuracy of lower limb CUS for the diagnosis of PE compared to MSCT in that large population of unselected patients.

**Methods**

We analyzed a database of consecutive outpatients suspected of PE included in a prospective management study designed to validate a diagnostic strategy for PE (1). Suspicion of PE was defined as acute onset of new or worsening shortness of breath or chest pain without another obvious etiology. The study was designed as a prospective management trial with a three-month follow-up. Data were collected from August 1, 2002, to November 30, 2003, at three participating medical centers that serve as general and teaching hospitals (Geneva University Hospital, Geneva, Switzerland; Angers University Hospital, Angers, France; and Hôpital Européen Georges-Pompidou, Paris, France). The study was approved by the ethics committees of the three institutions, and all patients provided written informed consent before they were enrolled. During the study period, 1,014 patients were screened. Of them, 185 were excluded because of predefined exclusion criteria: ongoing anticoagulant treatment, known allergy to contrast iodine agents, creatinine clearance below 30 ml/min, pregnancy, and life expectancy less than three months. Moreover, 73 patients were excluded because of protocol violations. This left a sample of 756 patients available for analysis. A standardized data form was filled out for each patient by physicians in charge before any specific tests for suspected PE were performed, recording demographic characteristics, risk factors, clinical signs and symptoms of venous thromboembolism. All patients underwent a sequential diagnostic work-up. First, the clinical probability of PE was assessed by the Geneva score (12). In non-high clinical probability patients, PE was ruled out by a D-dimer level (rapid ELISA assay, VIDAS D-dimer Exclusion®, bioMérieux, Marcy-l’Etoile, France) below the cut-off value of 500 μg/l. All the patients with a D-dimer level above this cut-off, and all high clinical probability patients underwent both a multislice computed tomography (MSCT) of the chest and a lower limb veins compression ultrasonography. Real-time B-mode bi-lateral venous compression ultrasonography was limited to proximal veins (i.e. popliteal and common femoral veins). The criterion for diagnosing deep vein thrombosis was the lack of full compressibility of the vein. In non-high clinical probability patients, PE was ruled out if both tests were negative. Furthermore, in patients with a high clinical probability, and in patients with a non-conclusive MSCT (either for technical reason or for the finding of an isolated unique subsegmental image), a normal ventilation-perfusion lung scan or a normal pulmonary angiogram were required to definitely rule out the diagnosis of PE. PE was established by i) a positive MSCT; ii) a high-probability ventilation-perfusion lung scan or a positive pulmonary angiogram when required; iii) in that study that aimed at assessing the diagnostic performance of MSCT for the diagnosis of PE, patients with a proximal deep vein thrombosis on lower limb ultrasonography and a normal MSCT were also considered as having PE, and were prescribed an anticoagulant therapy. All patients underwent a three-month follow-up.

**Statistical analysis**

The sensitivity, specificity, positive and negative likelihood ratios of CUS finding for the diagnosis of PE at MSCT were computed along with their 95% confidence intervals (CI). Positive results of CUS despite of a negative MSCT were analyzed according to the most proximal level of thrombosis at CUS. Correlation between the presence of a DVT at CUS and the most proximal PE level at MSCT was assessed.

**Results**

The 756 patients had a mean (± standard deviation) age of 60 ± 19 years (range 18–96 years), and 60% were female. The overall prevalence of pulmonary embolism was 26% (194 of 756 patients). PE was ruled out on the basis of a negative D-dimer test in 232 out of the 674 non-high clinical probability patients. Thus, 524 patients – 442 non-high clinical probability patients with a positive D-dimer test, and 82 high clinical probability patients – underwent both MSCT and lower limb compression ultrasonography tests. MSCT was inconclusive in 13 patients: 11 for technical reasons and two because it showed an isolated subsegmental PE, for which the study protocol required further testing. MSCT showed evidence of PE in 187 patients, of whom 73 had DVT on CUS. This represents 14% of the 511 patients with either a non-high clinical probability and positive D-dimer test, or a high clinical probability, and 39% of patients with confirmed PE on MSCT. Only three out of the 324 patients without PE on

| Table 1: Diagnostic accuracy of CUS for the diagnosis of PE. |
|-------------|-------------|-------------|-------------|
|            | Sensitivity % (95% CI) | Specificity % (95% CI) | Positive likelihood ratio (95% CI) |
| All patients | 39 (32 to 46) | 99 (97 to 100) | 42 (13 to 132) |
| Patients without clinical symptoms of DVT | 38 (21 to 36) | 99 (97 to 100) | 39 (12–130) |
| Patients with clinical symptoms of DVT | 72 (58 to 83) | 100 (83 to 100) | *∞* |
MSCT had DVT on CUS. Thus, the sensitivity of CUS for a positive MSCT was 39% (95% CI: 32 to 46%), and its specificity was 99% (95% CI: 97 to 100%). Positive and negative likelihood ratios were 42.2 (95% CI: 13.5 to 131.9) and 0.6 (95% CI: 0.5 to 0.7), respectively (Table 1).

Diagnostic accuracy differs in patients with and without symptoms of DVT. Among the 66 patients with symptoms of DVT, 47 (71%) had PE on MSCT, and CUS was positive in 34. None of the 19 patients with no PE on MSCT had DVT. Hence, in patients with symptoms of DVT, sensitivity of CUS for the diagnosis of PE at MSCT was 72% (95% CI: 58 to 83%) and specificity 100% (95% CI: 83 to 100%). There were no symptoms of DVT in 444 patients. Among them, 139 (31%) had PE on MSCT. CUS was positive in 39 out of the 139 patients with PE, and in three out of the 305 patients with no evidence for this diagnosis on MSCT. Hence, in patients without symptoms of DVT, sensitivity of CUS for the diagnosis of PE at MSCT was 38% (95% CI: 21 to 36), and specificity 99% (95% CI: 97 to 100) (Table 1).

Among the 76 patients with DVT, the most proximal level was iliac in five, femoral in 40 and popliteal in 31. The proportion of positive CUS results despite of a negative MSCT were 0% (0/5) at iliac level, 2.5% (1/40) at femoral level, and finally 6.5% (2/31) at the popliteal level.

There was a strong association between the presence of a DVT on CUS and the most proximal embolic level at MSCT (Table 2).

### Table 2: Proportion of positive CUS according to the level of PE at MSCT.

<table>
<thead>
<tr>
<th>Most proximal level of PE at MSCT</th>
<th>Proportion of patients with positive CUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple subsegmental</td>
<td>7.1% (1/14)</td>
</tr>
<tr>
<td>Segmental</td>
<td>4.6% (7/148)</td>
</tr>
<tr>
<td>Lobar</td>
<td>47.7% (31/65)</td>
</tr>
<tr>
<td>Main pulmonary arteries</td>
<td>56.7% (34/60)</td>
</tr>
</tbody>
</table>

Discussion

In this large prospective study of unselected patients suspected of pulmonary embolism, the finding of a proximal deep vein thrombosis had a 39% (32 to 46%) sensitivity and a 99% (97 to 100%) specificity for the presence of PE on multi-slice computed tomography. Sensitivity was 100% in patients with symptoms of DVT associated with their suspicion of PE. There was a correlation between the presence of a DVT and more proximal PE on CT.

Our data indicate that the finding of a DVT is highly specific of the presence of PE at MSCT in suspected patients. Thus, CUS not only provides evidence for venous thromboembolism requiring anticoagulant therapy but, if positive, also allows to “rule in” the diagnosis of PE in clinically suspected patients. This supports, when the test is available, the inclusion of CUS in diagnostic strategies for PE as a “rule-in” test for confirming the diagnosis of PE without further more expensive and/or invasive testing. This is particularly interesting in patients with contraindications to CT, such as renal failure, allergy to iodine contrast agents, or pregnancy. In the context of pregnancy, CUS has only been assessed for DVT diagnosis in a retrospective study (13). Its accuracy for diagnosing PE should probably be verified by a specifically designed study in pregnant women. Also, in elderly people, the proportion of PE associated DVT is higher, and CUS might avoid a number of unnecessary CT scans (14). Note-worthy, depending on clinical practices, CUS is sometimes performed only in patients with a negative chest CT (15). This is useful when a single-slice CT is used, but probably no more in patients with a negative multi-slice CT, due to the very low prevalence of PE in those patients (10). Finally, even if CUS is diagnostic for PE, further testing might be discussed. In particular, some clinicians may wish to perform a baseline ventilation perfusion lung scan or CT to better manage further recurrence suspicion.

Our results are in line with previous studies using pulmonary angiography as the gold standard. Specificity of CUS was 100% (95% CI: 96 to 100%) in a subsample of 150 patients suspected of PE who underwent both CUS and pulmonary angiography in a diagnostic study (31% of all included patients underwent both tests: those with either a non-normal or a non-high probability lung scan) (16). It was 98% (95% CI: 92 to 99) in another study subsample where both tests were applied to the same category of patients (17).

The limited sensitivity of CUS in patients with clinically suspected PE is a concern. Indeed, in our study, CUS was positive in only 14% of patients with either a non-high clinical probability and a positive D-dimer test, or a high clinical probability. It allowed ruling in the diagnosis in two out of five patients with PE. Very similar results have been reported in the ESSEP study, with a 45% prevalence of proximal DVT in patients with evidence of PE on helical CT (18). Although its completely non-invasive character alone probably justifies its use in diagnostic strategies, cost-effectiveness analyses are clearly required. In order to improve the sensitivity of CUS, some authors proposed to take into account distal vein thromboses. In a prospective cohort of 210 patients suspected of PE, a complete CUS – exploring not only proximal veins but also calf deep veins – was performed blindly and compared with a diagnostic strategy based on ventilation perfusion lung scan and angiography in case of non-conclusive lung scan. Considering patients with distal vein thromboses as having a positive CUS, the sensitivity of this test rose from 61 to 93%, along, however, with a dramatic decrease in specificity, from 96 to 84% (19). If confirmed, this result would preclude any use of distal thrombosis to make the diagnosis of PE, as 16% of patients without PE would be considered as having this diagnosis. However, this is an interesting way to explore, and stratification on the localization or size of distal thromboses (distal deep vein / muscular or superficial veins) might improve these results.

The correlation between positive CUS results and more proximal pulmonary emboli on MSCT is also of interest. Such correlation between the severity of PE and the presence of a detectable lower limb clot has previously been reported, using pulmonary vascular obstruction index at pulmonary angiography and phlebographic results (20). The presence of clots in proximal veins seems to be associated with more important PE. Thus, patients with PE-associated DVT might be at particularly high risk,
if the presence of an important “residual” deep vein thrombosis is associated with both more important pulmonary emboli and higher recurrent embolic potential. This hypothesis is further supported by the fact that presence of a proximal DVT on CUS has been described as a marker of poorer prognosis in patients with PE (21).

The main limitation of our study for this analysis lies in the lack of rigorous blinding for interpreting CUS and MSCT results. However, those tests are performed by different specialists in our institution (MSCT by radiologists and CUS by specialists in vascular medicine) and they were done in random order according to their availability. Therefore, it is safe to assume that most of those examinations were interpreted without any knowledge of the other tests result.

In summary, we conclude from that large study of unselected patients with clinical suspicion of PE that the specificity of compression ultrasonography of proximal lower limb veins for the diagnosis of PE at MSCT is high, whatever the presence or not of symptoms of DVT. A positive CUS allows ruling in the diagnosis of PE without further testing in suspected patients. This non-invasive test might thus still be of great interest in diagnostic strategies for PE.

References