Diagnostic performance of complete lower limb venous ultrasound in patients with clinically suspected acute pulmonary embolism

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Summary
A limited ultrasound (US) confined to the popliteal and femoral veins is usually performed to detect deep vein thrombosis (DVT) in patients with clinically suspected acute pulmonary embolism (PE). Our objective was to assess the diagnostic accuracy of complete lower limb US examining both the proximal and distal veins in this setting. In this prospective study, 210 consecutive patients were included. Complete US was performed by independent operators and compared blindly with a reference strategy combining clinical probability, ventilation perfusion scan and pulmonary angiography to a three-month clinical follow-up. Simultaneously, VIDAS D-dimer (DD) assay and helical computed tomography (HCT) of the lungs were assessed independently and blindly. PE was present in 74 patients (35%). Complete US detected DVT in 91 patients (43%), proximal in 51 and distal in 40. Sensitivity and specificity with a 0.95 confidence interval were respectively 0.93 [0.85 – 0.97] and 0.84 [0.77 – 0.89]. Limited US detected DVT in only 46 patients (22%). Sensitivity and specificity were respectively 0.55 [0.44 – 0.66] and 0.96 [0.92 – 0.98]. For DD they were 0.92 [0.83 – 0.96] and 0.24 [0.17 – 0.32] and for HCT 0.84 [0.73 – 0.90] and 0.87 [0.80 – 0.92]. Complete lower limb US has higher sensitivity and capacity to exclude PE than limited US, but a slightly lower specificity. Complete US results also compared favourably with those of HCT and DD. The utility of including this method in diagnostic strategies for PE needs to be assessed in cost-effectiveness analysis and in outcome studies.

Keywords
Pulmonary embolism, deep vein thrombosis, ultrasound/diagnosis

Introduction
Various strategies are currently used for the diagnosis of pulmonary embolism (PE). The combination of clinical probability with ventilation perfusion scan (V/Q scan), and pulmonary angiography has been widely recommended as the reference standard (1, 2). However, it is no longer used in clinical practice because diagnostic modalities are not readily available, angiography is required, and more recent and less invasive diagnostic tests like D-dimer (DD) assay, venous ultrasonography (US), and helical computed tomography (HCT) of the lungs, have good potential performance and utility. Inclusion of these tests...
in existing, or new strategies has proved to be effective in diagnostic management studies (3-6), and decreases drastically the need for an angiogram.

One way to obtain non-invasive confirmation in patients with clinically suspected PE is to identify deep vein thrombosis (DVT), a finding that is highly suggestive of the diagnosis (7-12) and provides sufficient grounds for treating patients with anticoagulants. Up to now, US limited to the popliteal and femoral veins has been used to detect residual DVT (3, 13-16). However, the prevalence of DVT detected by this method is low, and there is a wide variation between series, contrasting with the results of venography and autopsy studies. It is not known whether complete US examining both the proximal and distal veins might be more effective in this situation.

The objective of this study was to assess the diagnostic accuracy of complete venous US as compared with a reference diagnostic strategy in patients with clinically suspected PE. Simultaneous assessment of limited US, DD and HCT lung scan in the same patient sample allowed comparison to the respective performances of these different tests.

This descriptive study is the first step in evaluating this diagnostic modality before cost-effectiveness analysis and an outcome study.

**Methods**

**Patients**

Consecutive inpatients and outpatients with clinically suspected acute PE were included, whether or not they presented associated clinical symptoms or signs suggestive of DVT. Non inclusion criteria were unstable haemodynamic status, need for thrombolytic therapy, age less than 18 years, pregnancy, contraindication to contrast media, such as a history of allergic reaction, renal failure, plasma creatinine ≥ 200 µmol/L or use of nephrotoxic medications, difficulty in obtaining informed consent from the patient, refusal of consent by the patient or physician, and pre-established diagnosis of PE. Patients with chronic thromboembolic pulmonary hypertension were not included.

**Study design**

The study was prospectively performed in a single centre with multidisciplinary participation. Patients were assessed using the
reference diagnostic strategy, and underwent contemporary complete lower limb venous US, DD assay and HCT of the lungs. All investigations were performed within 48-72 hours by independent operators, and interpretation of the tests was blinded. The reference diagnostic strategy derived from the PIOPED study (1), and combined clinical probability assessment, V/Q lung scan and pulmonary angiography as shown in Table 1 and Figure 1. This strategy also included a three-month clinical follow-up. Echocardiography was not routinely performed, and the results were not included in the statistical analysis.

Reference diagnostic strategy
All patients underwent clinical assessment before the diagnostic tests. On the basis of this assessment, clinical probability, derived from the clinical model of Wells (17), was estimated and classified into three categories: high, intermediate and low (Table 1).

The V/Q lung scan protocol was derived from the PIOPED study (1). Images in six views were obtained. V/Q scans were classified according to PIOPED modified criteria (18) as normal or near-normal, high probability (defined as a V/Q mismatch of at least two segmental perfusion defects) or inconclusive. Low-probability scan classification was not used. PE was excluded, when the V/Q scan was normal, or when it was near-normal with low clinical probability. PE was accepted when a high-probability V/Q scan was associated with high clinical probability. In other cases, a pulmonary angiogram was obtained.

Pulmonary angiography was performed by the brachial vein Seldinger technique with a multiple side-hole 5F pigtail catheter. If there was no haemodynamic contraindication, after measurement of pulmonary artery pressures, a non-ionic low osmolar contrast agent (iohexol, Omnipaque®) was selectively injected into each pulmonary artery. A digital subtraction angiography technique (19) was used. Images were acquired during apnea. At least two views were obtained for each artery injection. The angiographic criteria for PE were the presence of an endoluminal filling defect or of an embolus obstructing a vessel with a perfusion defect (1). If artefacts were present or the quality of opacification was insufficient, the angiogram was considered inadequate. If the image was graded as excellent or good, and no thrombus was visualised, angiography was considered to be normal.

Complete venous ultrasound
The method of venous US has been described previously (20, 21). US was performed bilaterally and included not only the popliteal and femoral veins, but also the calf veins, the iliac veins and the inferior vena cava. Study of the calf veins included the posterior tibial and fibular veins, gastrocnemius (internal and external) and soleal veins. All these venous segments were examined over their entire length in transverse and longitudinal views. Venous imaging in real-time B mode and colour doppler, as well as venous haemodynamics, were studied using different probes according to the depth of the vascular structures. Ultramark 9 HDI ESP (High Definition Imaging Extension Signal Processing) and Ultramark HDI 3000 equipment from Philips ATL (Advanced Technology Laboratories) were used. The criterion for venous thrombosis was the direct image of an endoluminal thrombus associated with vein non-compressibility. The lower limit of the popliteal vein was defined as the confluence of the posterior and the fibular veins.

D-dimer assay
For plasma DD measurement, a 4.5 ml blood sample was collected in a vacuum tube containing 0.5 ml of 0.105 M sodium citrate solution (Vactainer Becton Dickinson) using the Vidas DD test (bioMérieux, Marcy l’Etoile, France), a fully automated enzyme-linked immunosorbent assay (ELISA) which provides results in 35 minutes (22). Two cut-off points at 400 ng/ml and 500 ng/ml were assessed. The test was considered positive above each of the cut-off values, and negative when it was equal to or below the cut-off level.

Helical computed tomography
Single-detector HCT scans were obtained with a Somaton Plus Scanner (Siemens Medical Instruments, Erlangen, Germany).

Table 1: Reference diagnostic strategy used to exclude or confirm pulmonary embolism. Diagnosis of pulmonary embolism relied upon clinical probability assessment, ventilation perfusion (V/Q) scan, angiography (angio) and a three-month clinical follow-up.

<table>
<thead>
<tr>
<th>1</th>
<th>Assessment of clinical probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical probability was assessed prior to the diagnostic tests, based on the analysis of clinical symptoms and context, a physical examination, an electrocardiogram, a chest X-ray and a blood gas sample. It was estimated in relation to the presence or absence of symptoms and signs compatible with PE, a risk factor for venous thrombo-embolism and an alternative diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Clinical probability was classified into three categories:</td>
<td></td>
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<tr>
<td>- high: compatible symptoms or signs of PE + at least one risk factor + no alternative diagnosis.</td>
<td></td>
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<tr>
<td>- low: symptoms or signs more and less compatible + no risk factor + an alternative diagnosis.</td>
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<tr>
<td>- intermediate in other cases.</td>
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<tr>
<td>2</td>
<td>Ventilation perfusion (V/Q) scan (+ clinical probability assessment)</td>
</tr>
<tr>
<td>3</td>
<td>Angiography (if V/Q scan and clinical probability were inconclusive)</td>
</tr>
<tr>
<td>4</td>
<td>Follow-up (three months)</td>
</tr>
<tr>
<td>5</td>
<td>Final diagnostic criteria</td>
</tr>
<tr>
<td>PE present:</td>
<td></td>
</tr>
<tr>
<td>- high-probability V/Q scan + high clinical probability</td>
<td></td>
</tr>
<tr>
<td>or positive angiogram</td>
<td></td>
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<tr>
<td>or an incidental venous thromboembolic event confirmed by objective tests</td>
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<tr>
<td>PE absent:</td>
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<tr>
<td>- normal V/Q scan</td>
<td></td>
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<tr>
<td>or near-normal V/Q scan with low clinical probability</td>
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<tr>
<td>or negative angiogram</td>
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<tr>
<td>or absence of venous thromboembolic event without anticoagulant therapy.</td>
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</table>
The study protocol was adapted from Remy-Jardin (23, 24). Patients were examined supine during breath-holding. The main, lobar and segmental arteries were scanned. Contrast agent (iohexol, Omnipaque®) was administered intravenously. Image reconstruction was done at 3 mm intervals. HCT results were categorized as positive if there was a partial or complete endoluminal filling defect with an image of low attenuation material, as negative when all vessels including the segmental arteries were correctly identified without any artefact or image suggesting a thrombus, and finally as inadequate, if there was an artefact, or when all the vessels from the main to the segmental arteries inclusive were not fully and correctly visualized.

Follow-up
For practical reasons, the decision to treat or not to treat was taken by the attending physician from the department participating in the study, who was in charge of the patient, and was aware of both the different test results, and the risks of anticoagulant treatment. Clinical outcome during the three-month follow-up was assessed systematically either by telephone call, or by a visit to the centre, and objective tests were used for the diagnosis of venous thromboembolic events: V/Q lung scan and/or angiography for PE and US for symptomatic DVT. The final diagnostic criteria used to confirm or exclude PE are listed in Table 1.

Data analysis
Data collection and analysis were performed using Epi Info Software (Centers for Disease Control and Prevention, Atlanta, GA, USA). Test results were compared with the reference strategy, and expressed in terms of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for the identified prevalence, with their corresponding 95% confidence interval (CI) using Wilson’s method (25). The likelihood ratio (LR) with the 95% CI was estimated using the log method (25). The LR is defined as the ratio of the probabilities of a particular test result or finding among patients with and without PE. Confidence interval analysis software (CIA software version 2.0.0, University of Southampton, UK) was used. To measure the discriminatory power of an index test (26), the odds ratio (the odds of a positive test result among diseased persons relative to the odds of a positive test result among non-diseased persons) was computed. The diagnostic odds ratio, which corresponds to LR(+) divided by LR(-), is a global measure of accuracy and may be helpful in deciding whether a test generally performs better than another one.

Ethical considerations and financial support
The study protocol was approved by the local Ethics Committee (CCPPRB: Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale). The funding sources had no role in the design or conduct of the study, collection and analysis of the data, or the decision to submit the paper for publication.

Results
From July 1996 to June 1998, 313 patients were referred for clinical suspicion of PE. Ninety-three patients (29.1%) were not included because of unstable haemodynamic status (n=20), need for thrombolytic therapy (n=1), severe infectious disease (n=3), contraindication to contrast media (n=27), pregnancy (n=4), pre-established diagnosis of PE (n=3), difficulty in obtaining informed consent from the patient (n=12), or refusal of consent by the patient or physician (n=23). Of the 220 patients who met the inclusion criteria, 10 were subsequently excluded for various reasons: angiography was impossible (n=1), or incomplete (n=2) due to technical problems or complications, the patient or physician withdrew consent (n=4), or an emergency procedure or operation was necessary (n=3). Finally, 210 patients (67%) were included in the analysis.

The clinical characteristics were mean age 61 ± 17 years, median 65 (range 20 – 91) years, male/female sex ratio 0.91, presence of clinical manifestations suggestive of DVT 42 patients (20%), presence of at least one risk factor for venous thromboembolism 72 patients (34.3%), outpatients 171 (81.4%), time elapsed from clinical onset 4.5 ± 7.0 days for thoracic symptoms and 5.7 ± 5.8 days for venous symptoms.

Results of the reference diagnostic strategy
(Fig. 1)
V/Q lung scan and clinical probability indicated PE in 42 patients (20%). One patient underwent angiography, that did not demonstrate PE, a result confirmed by the clinical outcome.

V/Q lung scan and clinical probability indicated PE in 42 patients (20%). Angiography was considered necessary in four patients, and in only one patient failed to demonstrate PE. This result was supported by the three-month clinical follow-up.

V/Q lung scan was non-diagnostic in 122 patients (58%) and so angiography was deemed necessary. However in 12 patients, angiography was not performed because of a rectified diagnosis (n=7), the occurrence of fatal PE before the investigation could be performed (n=1) and refusal (n=4). None of these last four patients had a venous thromboembolic event during follow-up. Of the 110 patients who underwent angiography, 74 had a negative angiogram, of whom one presented PE during follow-up, 31 patients had PE, and 5 patients had an inadequate result, none of whom experienced a venous thromboembolic event during follow-up. Finally in this category of non-diagnostic V/Q lung scans, PE was considered to be present in 33 patients (27%).

Altogether, angiography was performed in 115 patients (55%) after clinical assessment and a V/Q lung scan. On the basis of this diagnostic strategy, 74 patients had PE, a prevalence of 35% which is similar to that reported in other studies (1).
Results of complete and limited venous ultrasound

Complete US data were available for all patients and showed venous thrombosis in 91 (43.3%). The thrombi were located distal to the popliteal level in 40 patients (44%) and were equally distributed in the muscle veins and in the main venous segments. They were located in the proximal veins in the other 51 patients (56%). Forty-six of the proximal venous thrombi involved at least the popliteal and/or femoral veins and 5 were isolated either in the internal and common iliac veins (n=3) or in the inferior vena cava (n=2). The distribution of DVT on US in patients with or without PE according to the reference strategy, and the corresponding management and clinical events during follow-up, are shown in Table 2. The sensitivity, specificity, NPV and PPV of complete venous US as compared with the reference strategy (Table 3) were 0.93 [0.85 – 0.97], 0.84 [0.77 – 0.89], 0.96 [0.90 – 0.98] and 0.76 [0.66 – 0.83] respectively. The LRs for a positive test and a negative test were 5.76 [3.91 – 8.49] and 0.08 [0.03 - 0.19] respectively. This results in a low LR for a negative test and a high capacity to exclude PE.

In contrast, US limited to the popliteal and the femoral veins alone would have detected thrombosis in only 46 patients (22%) with lower sensitivity and NPV of 0.55 [0.44 – 0.66] and 0.80 [0.73 – 0.85] respectively, but higher specificity and PPV of 0.96 [0.92 – 0.98] and 0.89 [0.77 – 0.95] respectively, as compared with complete US. This results in a higher LR for a positive test of 15.07 [6.22 – 36.49] and a high capacity to confirm PE. The LR for a negative test was 0.46 [0.36 – 0.60]. Extension of investigation from the popliteal and femoral veins alone to all the proximal veins, including the iliac veins and inferior vena cava, did not significantly modify the performance of the US diagnostic strategy.

Results of D-dimer and helical computed tomography

DD assays were not available in 6 patients for technical reasons and DD results were analysed in 204 patients. Sensitivity and NPV decreased at the cut-off level of 500 ng/ml as compared with the 400 ng/ml level. With a 500 ng/mL DD cut-off value, sensitivity and specificity were respectively 0.92 [0.83-0.96] and 0.24 [0.17 – 0.32]. LRs showed that DD was not informative as an individual test (Table 4).

HCT was performed in 199 patients. In 11 patients, this test was not available for various reasons: HCT was technically impossible (n=1), an alternative diagnosis was established (n=4), HCT was refused by patients who had PE excluded with the reference strategy (n=5), and one patient died from PE before the investigation could be performed (n=1). HCT results
were positive in 62 patients (31%), inadequate in 22 (11%) and negative in 115 (58%). Among the patients with inadequate results, 15 (68%) did not present PE and HCT was equivocal at the level of the segmental arteries (n=11) or the lobar and the segmental arteries (n=4); US was negative in 13 patients or showed DVT distal to the popliteal vein in 2. On the other hand, 7 patients had PE detected by angiography where HCT was inadequate either at the segmental arteries (n=6) or the lobar and lobar arteries (n=1).

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>Test + / PE +</th>
<th>Test - / PE -</th>
<th>Sensitivity [0.95 CI]</th>
<th>Specificity [0.95 CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (proximal and distal veins)</td>
<td>69 / 74</td>
<td>114 / 136</td>
<td>0.93 [0.85 - 0.97]</td>
<td>0.84 [0.77 - 0.89]</td>
</tr>
<tr>
<td>US (proximal veins)</td>
<td>45 / 74</td>
<td>130 / 136</td>
<td>0.61 [0.49 - 0.71]</td>
<td>0.96 [0.91 - 0.98]</td>
</tr>
<tr>
<td>US (popliteal and femoral veins)</td>
<td>41 / 74</td>
<td>131 / 136</td>
<td>0.55 [0.44 - 0.66]</td>
<td>0.96 [0.92 - 0.98]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>PE- / Test -</th>
<th>PE+ / Test +</th>
<th>NPV [0.95 CI]</th>
<th>PPV [0.95 CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (proximal and distal veins)</td>
<td>114 / 119</td>
<td>69 / 91</td>
<td>0.96 [0.90 - 0.98]</td>
<td>0.76 [0.66 - 0.83]</td>
</tr>
<tr>
<td>US (proximal veins)</td>
<td>130 / 159</td>
<td>45 / 51</td>
<td>0.82 [0.75 - 0.87]</td>
<td>0.88 [0.77 - 0.94]</td>
</tr>
<tr>
<td>US (popliteal and femoral veins)</td>
<td>131 / 164</td>
<td>41 / 46</td>
<td>0.80 [0.73 - 0.85]</td>
<td>0.89 [0.77 - 0.95]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>LR (Result Positive) [0.95 CI]</th>
<th>LR (Result Negative) [0.95 CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (proximal and distal veins)</td>
<td>5.76 [3.91 - 8.49]</td>
<td>0.08 [0.03 - 0.19]</td>
</tr>
<tr>
<td>US (proximal veins)</td>
<td>13.78 [6.17 - 30.78]</td>
<td>0.41 [0.31 - 0.55]</td>
</tr>
<tr>
<td>US (popliteal and femoral veins)</td>
<td>15.07 [6.22 - 36.49]</td>
<td>0.46 [0.36 - 0.60]</td>
</tr>
</tbody>
</table>

US : ultrasound, Test + / PE + : test result positive given the presence of pulmonary embolism, Test - / PE - : test result negative given the absence of pulmonary embolism, PE + / Test + : presence of pulmonary embolism given the test result positive, PE - / Test - : absence of pulmonary embolism given the test result negative, NPV : negative predictive value, PPV : positive predictive value, LR : likelihood ratio, 0.95 CI : 95% confidence interval.

<table>
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<tr>
<th>Diagnostic tests</th>
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<th>Test - / PE -</th>
<th>Sensitivity [0.95 CI]</th>
<th>Specificity [0.95 CI]</th>
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</thead>
<tbody>
<tr>
<td>DD (500 ng / ml)</td>
<td>67 / 73</td>
<td>31 / 131</td>
<td>0.92 [0.83 - 0.96]</td>
<td>0.24 [0.17 - 0.32]</td>
</tr>
<tr>
<td>HCT (positive)</td>
<td>61 / 73</td>
<td>125 / 126</td>
<td>0.84 [0.73 - 0.90]</td>
<td>0.99 [0.96 - 1.00]</td>
</tr>
<tr>
<td>HCT (positive + inadequate)</td>
<td>68 / 73</td>
<td>110 / 126</td>
<td>0.93 [0.85 - 0.97]</td>
<td>0.87 [0.80 - 0.92]</td>
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<tr>
<th>Diagnostic tests</th>
<th>PE- / Test -</th>
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<th>PPV [0.95 CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD (500 ng / ml)</td>
<td>31 / 37</td>
<td>67 / 167</td>
<td>0.84 [0.69 - 0.92]</td>
<td>0.40 [0.33 - 0.48]</td>
</tr>
<tr>
<td>HCT (positive)</td>
<td>125 / 137</td>
<td>61 / 62</td>
<td>0.91 [0.85 - 0.95]</td>
<td>0.98 [0.91 - 1.00]</td>
</tr>
<tr>
<td>HCT (positive + inadequate)</td>
<td>110 / 115</td>
<td>68 / 84</td>
<td>0.96 [0.90 - 0.98]</td>
<td>0.81 [0.71 - 0.88]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>LR (Result Positive) [0.95 CI]</th>
<th>LR (Result Negative) [0.95 CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD (500 ng / ml)</td>
<td>1.20 [1.07 - 1.35]</td>
<td>0.35 [0.15 - 0.79]</td>
</tr>
<tr>
<td>HCT (positive)</td>
<td>105.29 [14.91 - 743.64]</td>
<td>0.17 [0.10 - 0.28]</td>
</tr>
<tr>
<td>HCT (positive + inadequate)</td>
<td>7.34 [4.62 - 11.64]</td>
<td>0.08 [0.03 - 0.18]</td>
</tr>
</tbody>
</table>

DD: D-dimer, ng: nanogram, HCT: helical computed tomography, HCT (positive): positive criteria including only positive tests while inadequate tests were considered as negative, HCT (positive + inadequate): positive criteria including positive and inadequate tests, Test + / PE + : test result positive given the presence of pulmonary embolism, Test - / PE - : test result negative given the absence of pulmonary embolism, PE + / Test + : presence of pulmonary embolism given the test result positive, PE - / Test - : absence of pulmonary embolism given the test result negative, NPV : negative predictive value, PPV : positive predictive value, LR : likelihood ratio, 0.95 CI : 95% confidence interval.
thrombosis after the embolic event. The prevalence of venous
We used complete US to attempt to detect residual venous
– Detecting calf vein thrombosis may be helpful in deciding
the management of PE for several reasons:
ability. However, we believe that their detection may be useful in
have been reported to be highly sensitive in the diagnosis of PE,
“workup” bias and “diagnostic review” bias (27, 28).
severity. Only patients with severe hypotension and shock were
consecutive unselected patients with all degrees of clinical
ed and validated reference standard (1) in a broad spectrum of
patients with clinically suspected acute PE. This prospective
study was an independent, blinded comparison with an accept-
ed and validated reference standard (1) in a broad spectrum of
consecutive unselected patients with all degrees of clinical
severity. Only patients with severe hypotension and shock were
not included. We specifically aimed to avoid “verification” or
“workup” bias and “diagnostic review” bias (27, 28).
As several non-invasive strategies incorporating limited US
have been reported to be highly sensitive in the diagnosis of PE,
the need for diagnosing isolated calf thrombi may seem debat-
able. However, we believe that their detection may be useful in
the management of PE for several reasons:
– Patients with PE frequently have not only proximal but also
distal DVT. Autopsy (7, 9, 10), venography (12, 29) and
magnetic resonance direct thrombus imaging studies (30)
show that PE is associated in up to 93% of cases with lower
limb and pelvic DVT and in up to 60% with isolated calf
thrombi (29). PE and fatal PE may originate directly (31,
32) from the calf veins which may be enlarged by the throm-
bus to as much as the diameter of the inferior vena cava
(personal observations), but they may also originate from a
more proximal thrombus which has migrated, leaving a
residual thrombus in the calf as a marker of PE.
– The prognosis of PE depends largely on its cause-related
potential for recurrence, and not only on the size of the
residual thrombus (33).
– Detecting calf vein thrombosis may be helpful in deciding
whether to treat patients when clinical probability is high
and the other diagnostic methods such as HCT, V/Q scan
and angiogram are inconclusive or even negative.

Discussion
To the best of our knowledge, this is the first study analysing the
diagnostic performance of complete venous US investigation in
patients with clinically suspected acute PE. This prospective
study was an independent, blinded comparison with an accept-
ed and validated reference standard (1) in a broad spectrum of
consecutive unselected patients with all degrees of clinical
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not included. We specifically aimed to avoid “verification” or
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whether to treat patients when clinical probability is high
and the other diagnostic methods such as HCT, V/Q scan
and angiogram are inconclusive or even negative.

We used complete US to attempt to detect residual venous
thrombosis after the embolic event. The prevalence of venous
thrombosis detected in patients with confirmed PE varies from
72 to 90% in autopsy series (8, 9) and from 71 to 93% with
venography (2, 11, 12). With US, results vary widely from 13 to
80%. However, in five prospective studies comparing limited
US with a validated standard strategy (3, 13-16), the prevalence
of US-detected proximal vein thrombosis (sensitivity of US)
had a smaller range of between 23 and 70%. We found sensitiv-
ity in detecting proximal vein thrombosis and specificity to be
close to those of these series (3, 13, 14). None of these studies
attempted to investigate the calf veins. Extending US examina-
tion yielded results, comparable to those obtained with veno-
graphy or with autopsy series, by detecting more thrombi located
either proximally in the iliac veins or inferior vena cava or
mainly distally in the calf veins, and significantly increasing the
sensitivity of US from 55% to 93%. Unfortunately, with com-
plete US specificity decreased somewhat, but this could hardly
be explained by false-positive results. Indeed, we were con-
cerned to keep the test specific by using high-definition imag-
ing equipment, carefully distinguishing endoluminal material
from an extravascular image or an artefact, and requiring two
DVT diagnosis criteria: direct thrombus image and vein non-
compressibility. The so-called false-positive results with US
could in fact be due to false-negative results with angiography
which in an experimental study (34), proved to be less sensitive
than expected, at only 87%. Another possible explanation of
decreased specificity is that in patients who did not have PE, the
clinical symptoms and signs might have been related to other
cardiac and respiratory conditions likely to promote the devel-
lopment of venous thrombosis which would then be the conse-
quence and not the origin of the clinical patterns. Despite this
lower specificity, the discriminatory power of complete US
measured by the diagnostic odds ratio was still much higher
(odds ratio: 72) than that of limited US (odds ratio: 33). Distal
venous US thus significantly enhances the diagnostic accuracy
for PE.

These results are consistent with those obtained in patients
with clinically suspected DVT in both diagnostic accuracy (21)
and in outcome (35) studies. Complete US detected 92% to 96%
of isolated calf vein thrombosis as compared with venography
(21). The risk of venous thromboembolic events without anti-
coagulants during a three-month follow-up after a single nega-
tive complete US (35) was only 0.5% (95% CI: 0.1-1.8%).
Complete assessment also proved to be reliable (36) in both
symptomatic and in asymptomatic legs. Nevertheless, the test
needs to be performed by trained operators using a standardized
protocol. In this study, these were specialists in vascular medi-
cine who had at least two months experience of daily practice of
venous US. Another drawback of complete US is that it takes
two to three times longer to perform than limited US.
The role of complete US in the diagnosis of PE has never
been assessed in outcome studies. Only limited US was
included in various strategies (1, 3-6, 13, 37) and was repeated
if negative or if V/Q scan or HCT were non-diagnostic. However serial US is costly, and also does not detect more than 2% additional venous thrombi (6, 38, 39). Complete or highly sensitive US has proved to be cost effective (40, 41). Its utility depends on both the test characteristics and on the prevalence of PE. In clinical practice, including complete US in diagnostic management could be very useful in view of its favourable low LR (-). However, treatment is much more debatable if there is an isolated calf vein thrombus, because of the lower LR (+) and lower specificity of complete US. Overall, the decision to initiate anticoagulation therapy depends on the likely harm/benefit ratio; more precisely, it depends on the net loss in utility due to a false-positive result and the net loss due to a false-negative result (42).

The other diagnostic methods such as DD assay and HCT currently used for the diagnosis of PE were also assessed in our patients. Complete US compared favourably with Vidas D-dimer and HCT. We found the DD assay to be less sensitive than in other series (22, 43). HCT had a sensitivity of 84%, close to that found in an experimental animal model (34) where anatomical study showed that HCT and angiography yielded comparable results. In many series, reliability in interpretation of HCT seems to be high, but there are controversial data concerning its performance (44-46) or its utility in clinical management (5, 6, 47). Perrier et al. (46) found a sensitivity of 70% in patients who had a positive DD, similar to that observed by Hartmann et al. (48) in selected patients who did not have a negative V/Q lung scan. This contrasts with the higher sensitivity of 90% found by Qanadli et al. (49). Overall, we found that HCT is moderately sensitive and highly specific, but with the drawback of 11% of inconclusive results. However, this compared favourably with V/Q scan (about 52% of inconclusive results).

In this setting, complete US was useful. Inconclusive HCT mainly concerned segmental and subsegmental arteries, where very small thrombi may be missed (46). Multi-detector instead of single-detector HCT, with reconstructed scans of 1.25 mm sections, can now accurately analyse peripheral pulmonary arteries down to the fifth order (50).

In conclusion, complete venous US is more sensitive, better able to exclude PE but slightly less specific than limited US. Its utility in diagnostic strategies for PE needs to be evaluated in large outcome studies.

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Trial registry information
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Institutional review board approval
The study was approved by the CCPPRB (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) : 2-96-17.

References