Dear Editors,

In emergency departments, suspected pulmonary embolism (PE) can be safely ruled out by a normal multi-slice CT angiography (CTPA) [1–4] without the need for additional leg compression ultrasonography (CUS). This diagnostic approach for those who develop symptoms of PE during hospitalization has been validated by only a limited number of studies. [2,5]. In this study we aim to estimate prevalence of both proximal and distal deep vein thrombosis (DVT) in hospitalized patients with suspected pulmonary embolism (PE) and estimate the clinical utility of a bilateral whole leg CUS in patients with suspected PE. We conducted a prospective single center cohort study approved by the ethics board at the Hospital Italiano de Buenos Aires; a 500 hundred bed academic hospital. The original plan was to conduct the study at two centers and recruit 210 subjects however, one of the research teams were unable to recruit subjects due to financial constraints. As the study had already enrolled more than 30% of the expected sample size, an analysis was done in order to rule out futility. Patients evaluated for suspected PE were eligible to participate in the study if: 1–They were able to provide consent; 2–Presented with symptoms suggestive of PE (acute onset of new or worsening shortness of breath, chest pain, hemoptysis, presyncope, or syncope); 3–Symptoms developed >48 hours after admission in medically ill patients; or >24hs of admission after a major surgical procedure (defined as an anesthesia time >90 minutes); and were evaluated with CTPA.

All patients were evaluated with a 64- multi-slice CT scanner (Aquilion, Toshiba). Patients were excluded if they had symptoms compatible with PE prior to admission. Within 24 hours of providing written consent, all patients had a bilateral whole leg CUS. Proximal DVT was defined as non-compressible segment above the trifurcation of the popliteal vein. PE was considered diagnosed when the CTPA showed a filling defect in a segmental or larger pulmonary artery and was present in at least two consecutive images (single sub-segmental embolus was considered as a PE only if the CUS was positive for a proximal DVT).

Between November 2011 to December 2013, 95 patients were originally enrolled in the study. Fourteen patients (16.8%) had a CTPA performed (one had a sub-segmental PE) but did not complete any further testing as decided by the treating physician and were therefore, excluded. Six patients were evaluated with V/Q scans and were also excluded. Seventy five hospitalized patients with suspected PE (baseline characteristics are presented in Table 1) satisfied our inclusion criteria, of which 65 (85.5%) were receiving pharmacological thromboprophylaxis with low molecular weight heparin; all others were treated with unfractioned heparin or some form of mechanical thromboprophylaxis. The median amount of days from admission to development of symptoms compatible with PE was 8 days (SD 5 to 10 days). Forty percent of the patients (95% CI 29.3-51.3) developed symptoms post major surgery and 41.3% (95% CI 30.6-52.7%) had active malignancy at the time of the evaluation. Shortness of breath was the presenting symptom in 85.1% (95% CI 75.8-91.2) of the patients, 23% (95% CI 15.1-33.5) had symptoms of DVT. Eighteen patients were classified as low clinical probability (24%; 95% CI 15.3-34.6), 31 were classified as intermediate (41.3%; 95% CI 30.6-52.7) and 18 as high clinical probability (24%; 15.3-34.6). The overall prevalence of PE was 34.6% (95% CI 24.6-45.9). The PE was located in the main pulmonary artery in 17.8% of the participants (95% CI 6.8-35.2%) and only one had sub-segmental PE plus DVT (3.5%; 95% CI 0.5-16.3). The prevalence of PE in those with low clinical probability was 5.5% (95% CI 0.2-24.4), 22.5% (95% CI 10.4-39.6) in those with intermediate probability and 83% (95% CI 61.3-95.3%) in those classified as high probability. The overall prevalence of proximal DVT was 16.5% (95% CI 9.3-25.5) and 8% (95% CI 3.3-15.8%) had distal isolated DVT. In those with confirmed PE 10 out of 27 had proximal DVT (37%; 95% CI 20.5-56.1) vs. 3 out of 48 in those without PE (6.25%; 95% CI 1.6-16.1); whereas the incidence of isolated distal DVT 18.5% (95% CI 7.1-36.3) in those with PE vs. 2% (95% CI 0.1-9.8) in those without PE (p-value 0.04). In those without PE in the CTPA who had DVT symptoms of having a proximal DVT was significantly increased (RR 12.6; 95% CI 1.4-108). The DVTs found in patients without PE were located in the common femoral vein in two cases, one in the popliteal vein, and one in the tibial vein (classified as distal). The diagnostic accuracy of CUS for the diagnosis of PE is reported in Table 1.

Our results suggest that in hospitalized patients with suspected PE ruled out by a negative multi-slice CTPA the prevalence of DVT is high and that a bilateral CUS could be required to safely exclude PE (especially in those with symptoms of DVT or high clinical probability) as suggested by the Prospetive Investigation of Pulmonary Embolism Diagnosis II (PIOPED II)[6]. Although previous studies have reported a low prevalence of DVT among patients for whom PE was ruled out by CT scan (around 1%) [7], the high prevalence of DVT in our study could be explained by the higher number of subjects with cancer or recent surgery, which was double the prevalence of prior studies conducted in outpatient settings[2–4,6,7]. The diagnostic utility of both proximal and distal CUS did not vary significantly from prior studies, suggesting that CUS has high specificity for the diagnosis of PE but lacks sensitivity [5,8,9]. Finally, does the presence of a DVT in patients without PE influence the rate of recurrent VTE at 90 days? The study by Rigini et al comparing CUS plus CTPA vs. CTPA alone, supported by data of Christopher [2], suggested that identification of DVTs is not needed as it does not affect the 90 day rate of recurrent VTE, although the number of patients with DVT without PE was low (0.57%) [5]. The clinical outcome of the DVTs appears to differ the one in patients who present with PE [12,13]. Yet if these patients had been first evaluated by US or VQ, they would have received a diagnosis of PE, and despite the differences between in the

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Letter to the Editors-in-Chief

especially in those classiﬁcations. Third, it could be argued that the prevalence of PE is high, but the prevalence of PE in our institution these tests are performed by radiologists who specialize in CUS. Alternatively, an outpatient-based cohort similar to the Christopher study could be conducted.

between CTPA only group and a CTPA plus CUS. Alternatively, an outpatient-based cohort similar to the Christopher study could be conducted.

Our preliminary findings suggest that CUS could identify a proximal DVT in 6% of the patients with negative CTPA and that CTPA might not be enough to rule out PE in this population. A larger sample size is required to corroborate our ﬁndings.

Conﬂict of Interest

The authors have no conﬂict of interest to report.

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Presented as oral presentation at The International Thrombosis Congress/Mediterranean League Against Thrombosis Meeting in Valencia Spain May 16th 2014.

Table 1

Baseline characteristics and results.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>No PE = 48</th>
<th>PE = 27</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66 (18)</td>
<td>67 (11)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Female</td>
<td>30 (62)</td>
<td>16 (59)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Cancer</td>
<td>16 (33)</td>
<td>15 (55)</td>
<td>0.1</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>42 (89)</td>
<td>23 (85)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Surgery</td>
<td>22 (45)</td>
<td>8 (29)</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior VTE</td>
<td>7 (14)</td>
<td>5 (7)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>DVT symptoms</td>
<td>8 (17)</td>
<td>10 (35)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Symptoms and clinical probability

Alternative diagnosis found on CT

<table>
<thead>
<tr>
<th></th>
<th>No PE</th>
<th>PE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>98</td>
<td>97</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Hb</td>
<td>128</td>
<td>126</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>SOB</td>
<td>42</td>
<td>89</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>RR</td>
<td>20</td>
<td>4</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>3</td>
<td>4 (14)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Diagnostic accuracy of proximal CUS for the diagnosis of PE

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LLR</th>
</tr>
</thead>
</table>
| Proximal CUS     | 0.37 (0.2-0.56) | 0.93 (0.81-0.9) | 5.9 (1.7-19.6)
| Proximal and Tibio/peroneal trunk | 0.44 (0.2-0.4) | 0.91 (0.71-1) | 5.3 (1.9-14) |

DVT: Deep vein thrombosis; VTE: venous thromboembolism; HR: Heart rate; SBP: systolic blood pressure; SOB: shortness of breath;

outcomes of DVT and PE both would receive the same antithrombotic treatment [14].

Our ﬁndings have limitations. First, we cannot rule out that our ﬁndings are biased given the small sample size and wide conﬁdence intervals around our estimates. In order to demonstrate that lower bounds of the conﬁdence interval is higher than the accepted <2.7% margin in order to consider PE safely ruled out by CTPA with a two sided alpha of 0.05 and a power of 0.80, a study would require 246 participants. If our ﬁndings are conﬁrmed, the next step would be to conduct a randomized controlled study comparing the 90 day rate of recurrent VTE between CTPA only group and a CTPA plus CUS. Alternatively, an outcome cohort similar to the Christopher study could be conducted. Second, is the lack of rigorous blinding for interpreting the CUS. However in our institution these tests are performed by radiologists who specialize in CUS. Third, it could be argued that the prevalence of PE is high, especially in those classiﬁed as high probability, but the prevalence of PE was not signiﬁcantly different from prior studies conducted in the emergency department.

In conclusion, to our knowledge this is the ﬁrst study speciﬁcally evaluating the role of bilateral leg CUS in hospitalized patients managed with multi-slice CTPA. Our preliminary ﬁndings suggest that CUS could identify a proximal DVT in 6% of the patients with negative CTPA and that CTPA might not be enough to rule out PE in this population. A larger sample is required to corroborate our ﬁndings.

Conﬂict of Interest

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Acknowledgements

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References


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