Deep Venous Thrombosis in Patients With Acute Pulmonary Embolism*

Prevalence, Risk Factors, and Clinical Significance

Philippe Girard, MD, FCCP; Olivier Sanchez, MD; Christophe Leroyer, MD; Dominique Musset, MD; Guy Meyer, MD; Jean-Baptiste Stern, MD; and Florence Parent, MD; for the Evaluation du Scanner Spiralé dans l'Embolie Pulmonaire Study Group

Study objectives: **To determine the prevalence of lower-limb deep venous thrombosis (DVT) that can be detected by compression ultrasonography (CUS) in patients with symptomatic pulmonary embolism (PE) diagnosed with spiral CT pulmonary angiography (CTPA); and to explore the risk factors for positive CUS results and the prognostic significance of such findings.**
Design: Post hoc **analysis of data from a prospective multicenter outcome study of 1,041 patients with clinically suspected nonsevere PE. All patients underwent CTPA and CUS within 24 h of enrollment and were followed up for 3 months.**
Patients: **Among the 290 patients with positive CT findings, CUS was diagnostic in 281 patients who constitute the study population.**
Results: **Mean age ± SD was 64.3 ± 17.7 years; 128 patients (44.8%) were men. DVT signs or symptoms were present in 90 patients (32%). CUS detected DVT in 169 patients (60.1%; 95% confidence interval [CI], 54.1 to 65.9%), including 127 patients (45.2%; 95% CI, 39.3 to 51.2%) with proximal DVT. Sensitivity and specificity of DVT symptoms for CUS-detectable DVT were 43% and 85%, respectively. Multivariate analysis showed that an age ≥ 70 years (odds ratio [OR], 1.90; 95% CI, 1.14 to 3.17) and the presence of DVT signs or symptoms (OR, 4.12; 95% CI, 2.24 to 7.55) were independent risk factors for positive CUS results. DVT symptoms (OR, 4.78; 95% CI, 2.75 to 8.33) and a history of venous thromboembolism (OR, 2.59; 95% CI, 1.46 to 4.62) were independent risk factors for proximal DVT. The 3-month risk of recurrent thromboembolic event or death was not significantly different among patients with and without DVT (6.5% vs 2.7%, p = 0.15).**
Conclusion: **These results do not support screening for DVT in patients with CTPA-proven symptomatic PE; however, they suggest that CUS might prove especially efficient and safe as a frontline test in elderly patients with suspected PE. Further studies are needed before these conclusions can be translated into clinical recommendations.**

(CHEST 2005; 128:1593–1600)

Key words: deep venous thrombosis; diagnosis; Doppler; duplex; prognosis; pulmonary embolism; spiral CT; ultrasonography

Abbreviations: CI = confidence interval; CTPA = spiral CT pulmonary angiography; CUS = venous compression ultrasonography; DVT = deep venous thrombosis; ESSEP = Evaluation du Scanner Spiralé dans l'Embolie Pulmonaire; NS = not statistically significant; OR = odds ratio; PE = pulmonary embolism; V̇/Q̇ = ventilation/perfusion; VTE = venous thromboembolism

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are thought to represent two clinical manifestations of the same disease, and it is widely admitted that approximately 90% of symptomatic pulmonary emboli arise from thrombi located in the leg veins.[1–3] However, relatively little is known on the epidemiology of DVT at the time of

*From the Institut Mutualiste Montsouris (Dr. Girard), Paris; Hôpital Européen Georges Pompidou (Drs. Sanchez and Meyer), Paris; Hôpital de la Cavale Blanche (Dr. Leroyer), Brest; Hôpital Antoine Béclère (Dr. Parent), Clamart; and Hôpital Beaujon (Dr. Stern), Clichy, France.
The ESSEP study was supported by grants from Programme Hospitalier de Recherche Clinique, Ministry of Health, Paris, France, and was promoted by la Délégation de la Recherche Clinique (Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, France).

Manuscript received January 25, 2005; revision accepted March 30, 2005.

Correspondence to: Philippe Girard, MD, FCCP, Département thoracique, Institut Mutualiste Montsouris, 42 Boulevard Jourdan, 75014, Paris, France; e-mail philippe.girard@imm.fr

PE diagnosis. In patients with symptomatic PE, systematic assessment of lower-limb deep veins has provided a wide range of DVT prevalence rates, from 10 to 93%, depending on the methodology used to diagnose DVT and on the type and size of the population samples.[4–10] Incidentally, spiral CT pulmonary angiography (CTPA) and venous compression ultrasonography (CUS), currently the frontline morphologic tests for PE and DVT, have not been used in previous descriptive studies of DVT at the time of PE diagnosis. Further, the risk factors for detectable DVT as well as the possible prognostic significance of detectable DVT in patients with symptomatic PE are virtually unexplored.

The Evaluation du Scanner Spiralé dans l'Embolie Pulmonaire (ESSEP) study, a prospective multicenter outcome study of 1,041 patients with clinically suspected nonsevere PE, tested a diagnostic strategy in which all patients underwent both CTPA and bilateral lower-limb CUS within 24 h of enrollment into the study, and all patients were then followed up for 3 months.[11] Therefore, the data from the ESSEP study offer a unique opportunity to reliably estimate the prevalence of CUS-detectable DVT in patients with CTPA-proven PE. Also, this large prospective database would allow investigating the risk factors for positive CUS results as well as the prognostic significance of such findings in patients with symptomatic, nonsevere PE.

Materials and Methods

Selection of the Study Population

The ESSEP study is a prospective multicenter outcome study that included 1,041 patients with suspected acute nonsevere PE between September 1999 and December 2000 at 14 centers in France.[11] The main objective of the study was to assess the safety of withholding anticoagulant therapy in patients with low or intermediate clinical probability of PE and negative findings on CTPA and leg CUS. To achieve that goal, a diagnostic strategy was applied. Inclusion criteria were clinical suspicion of PE and age $\geq$ 18 years. The main exclusion criteria included pregnancy, PE with hemodynamic instability (defining severe PE) or unequivocal need for thrombolytic therapy, life expectancy of $<$ 3 months, impossibility of follow-up, and anticoagulant treatment for $>$ 48 h before inclusion.[11] The protocol was approved by the Ethics Committee of Paris XI University, and written informed consent was obtained from all participants before entry into the study.

All patients had an evaluation of the clinical probability of PE rated empirically as low, intermediate, or high and then underwent CTPA pulmonary angiography and bilateral lower-limb CUS within 24 h of enrollment. All patients, whether treated or untreated, were followed up for 3 months.

Regarding signs and symptoms of DVT, the investigators were only asked to record whether any signs or symptoms were present. No clinical details, *ie*, what specific signs and symptoms were present or absent, were collected. The presence or absence of signs and/or symptoms of DVT was recorded before any morphologic test was performed. Active malignancy was defined as any malignancy that deserved specific treatment within the previous 6 months.

CTPA was performed in 1,039 patients, with normal results in 650 patients and nondiagnostic findings in 99 patients. CTPA showed PE in 290 patients, who constitute the eligible population for the present study.

CTPA Technique and Interpretation

Guidelines for CTPA were implemented at each center to standardize methods. Over the study period, single-row detector spiral CTs were used at all participating centers. A total volume of 100 to 140 mL contrast medium with a minimum concentration of 200 g/L iodine was injected at a rate of 4 to 5 mL/s through a large peripheral IV line. Scans were done with a 2- to 3-mm collimation with 120 kilovolts, 150 mA, and a pitch of 1.5 to 2.0. The images were reconstructed with intervals of $\leq$ 2 mm and read by the local radiologist on a workstation on films with mediastinal and lung window settings, or both. PE was diagnosed if a central filling defect outlined by contrast material or complete occlusion was seen in a segmental or more proximal pulmonary artery. CTPA was judged negative for the diagnosis of PE when pulmonary arteries, including all segmental branches, were visualized and free of thrombus. CTPA was judged nondiagnostic when poor opacification or major motion artifacts were observed, precluding the visualization of at least one segmental arterial branch. It must be noticed that isolated subsegmental thrombi were considered nondiagnostic in the ESSEP study. Such thrombi accounted for 12 of the 99 patients with nondiagnostic CTPA results, and all 12 patients had negative CUS findings.[11] Interestingly, according to the ESSEP protocol, these 12 patients underwent pulmonary angiography and/or ventilation/perfusion ($\dot{V}/\dot{Q}$) lung scanning, which confirmed PE in only 3 of them.[11]

Ultrasonography of the Lower Limbs

Bilateral venous CUS of the legs was done in all patients from the common femoral vein to the trifurcation of the calf veins, inclusively. Lack of vein compressibility was taken as diagnostic of DVT. In the calf, only thrombi located in the peroneal or tibial veins were taken into account. When the femoral or popliteal veins could not be examined, ultrasonography was classified as nondiagnostic.

Follow-up

All patients, with or without PE or DVT, and whether treated or untreated, were followed up for 3 months. According to the ESSEP protocol, follow-up consisted of telephone interviews 1 month and 2 months after inclusion, and patients were seen in an outpatient clinic at 3 months. For patients who could not be traced, death registries were systematically consulted after checking with the family physician. Critical events recorded by the investigator during follow-up were death, bleeding complications that prompted medical attention, and symptomatic venous thromboembolism (VTE). All critical events were assessed by a central adjudication committee, the members of which were independent of the study centers. In addition, the adjudication committee classified the deaths during follow-up on the basis of all available information as certainly related to PE, possibly related to PE (if the cause of death could not be clearly established), or definitely not related to PE.

Statistical Analysis

The χ^2 test was used to compare observed percentages. To identify independent risk factors for positive CUS findings, a