PIOPED II: Is Spiral CT the Best and Only Test for Suspected Pulmonary Embolism?

Disclosures

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Introduction

Pulmonary embolism (PE) and deep venous thrombosis (DVT) share risk factors and treatment.\(^1\) These 2 separate entities form the spectrum of the same disease process known as venous thromboembolism (VTE) because PE is a complication of DVT.\(^2\) VTE is relatively common and remains a diagnostic challenge in clinical medicine reflecting ongoing difficulties with clinical and laboratory diagnosis. The need for an accurate diagnosis is crucial because untreated PE is potentially fatal and the therapy itself for VTE can produce significant complications. Conventional pulmonary angiography is generally considered the "gold standard" in the diagnosis of PE, but this procedure is invasive and is occasionally associated with major complications. A variety of noninvasive imaging modalities are available, but each has its own limitations.

There has been increasing utilization in contrast-enhanced spiral computed tomographic pulmonary angiography (CTPA) in the diagnosis of PE. P. D. Stein\(^3\) pointed out that by 2001, there was a higher proportion of spiral CT studies than ventilation-perfusion (VQ) lung scans performed among hospitalized patients diagnosed with PE in the United States. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study was designed to assess the validity of contrast-enhanced spiral CT in the diagnosis of acute PE. The study was supported by the National Institutes of Health and the National Heart, Lung, and Blood Institute.

Design of PIOPED II

PIOPED II was a multicenter, prospective trial. The clinical centers were the University of Calgary, Calgary, Alberta, Canada; Cornell University, Ithaca, New York; Duke University, Durham, North Carolina; Emory University, Atlanta, Georgia; Henry Ford Hospital, Detroit, Michigan; Massachusetts General Hospital, Boston, Massachusetts; University of Michigan, Ann Arbor, Michigan; and Washington University in St. Louis, St. Louis, Missouri.

Inclusion Criteria

- \(\geq 18\) years of age;
- Suspected acute PE;
- Able to give informed consent; and
- Willing to undergo VQ lung scan, spiral CT, venous compression ultrasound of the lower limbs (U/S), and digital subtraction angiography (DSA).

Exclusion Criteria

- Prisoners;
- Pregnant women;
- Allergy to intravenous contrast;
- Renal failure;
- Chronic pulmonary hypertension;
- Chronic anticoagulant therapy or planned thrombolytic therapy;
- Inferior vena cava filter;
- Major ventricular arrhythmias in the preceding 24 hours;
- Myocardial infarction in the preceding month; and
Critically ill or ventilated patients.

**Clinical Likelihood of PE**

Based on the validated Wells criteria,[4] each patient was assigned a clinical likelihood (pretest probability) of acute PE according to total score from the following clinical parameters:

- 3.0 points for each category if clinical symptoms and signs of DVT and PE is best diagnosis;
- 1.5 points for each category if heart rate > 100 bpm, history of immobilization or surgery in the preceding 4 weeks, and previous PE/DVT; and
- 1.0 point for each category if hemoptysis and malignancy (on treatment, received treatment in the last 6 months, or palliative).

The clinical likelihood of PE was defined as:

- Low if Wells score < 2;
- Intermediate if Wells score > 2 but < 6; and
- High if Wells score > 6.

**Composite Reference Criteria**

In the PIOPED II study, VQ lung scans were considered diagnostic studies if:

- High-probability VQ scans in patients *without* prior PE (positive predictive value [PPV] of 91% for acute PE, according to the original PIOPED trial[5]); and
- Normal VQ scans.

Other VQ probabilities were considered nondiagnostic, ie:

- High-probability VQ scans in patients *with* prior PE (which carries a reduced PPV of only 74% for acute PE, according to the original PIOPED trial[5]); and
- Other "nonnormal" VQ scans: intermediate, low, or very low probabilities.

Unlike in the original PIOPED study, DSA was not the gold-standard reference test. In the PIOPED II trial, DSA was performed only when required. Instead, the diagnosis and exclusion of acute PE were based on the following sets of composite reference criteria.

**Acute PE was considered present if:**

- High-probability VQ scan in patient without prior PE;
- Odds ratio positive DSA; and
- Odds ratio positive U/S for DVT (in area[s] without known prior DVT in patients with nondiagnostic VQ lung scans).

**Acute PE was considered absent if:**

- Normal VQ lung scans;
- Odds ratio negative DSA;
- Odds ratio if DSA not performed: low clinical likelihood of PE (Wells score < 2), low or very low
probability VQ lung scan, and U/S negative for DVT.

**Imaging Tests**

Each participating patient underwent VQ lung scan, contrast-enhanced spiral CTPA, venous phase contrast-enhanced CT of the veins of the pelvis and thighs (CTV), and U/S of the lower extremities. All of the tests were required to be completed within a 36-hour period. In addition, chest x-ray was to be performed within 12 hours of the VQ scan, and at least 4 hours elapsed between the administration of intravenous contrast for CTPA and DSA.

All spiral CT studies were performed with multidetector CT equipment, mostly 4-detector systems (90%) with 8- and 16-detector systems used in the remainder of cases. Multidetector CT permits rapid scanning and thin collimation, optimizing visualization of segmental and subsegmental pulmonary arteries.[6] Briefly, CTPA in patients < 250 lb was performed with an injection-to-scan delay of 20 seconds (with low-osmolar nonionic intravenous contrast 4 mL/second, total 135 mL) starting 2 cm below the lowest diaphragm up to the top of the lung apex, with thin collimation (1.25 mm), thin reconstruction (1.25 mm), and fast speed (pitch 6:1, 0.8 second/rotation). The parameters for CTV (no extra intravenous contrast required) included an injection-to-scan delay of 3 minutes, starting from the iliac crest to the level of the knees, 7.5 mm collimation, 6:1 pitch, and 1 second/rotation. Obese patients (> 250 lb) required a modified CTPA protocol, including thicker collimation (3.75 mm), thicker reconstruction (2.5 mm), and lower pitch (3:1) to obtain an interpretable image quality.

**Results**

In a special symposium reviewing the results of the PIOPED II study that was held at the Radiological Society of North America (RSNA) 90th Annual Scientific Assembly and Annual Meeting in Chicago, Illinois, Charles A. Hales, MD (Pulmonary and Critical Care Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts), offered a clinician's viewpoint on the findings of the study.

**Demographic Data**

Seven hundred seventy-three patients were analyzed (out of > 1000 patients recruited). The majority (75%) were outpatients (average age, 52), with the majority being women (62%) and white patients (64%). The prevalence of acute PE in this population was 23% (181 of 773). This was lower than in the original PIOPED trial (33% prevalence).[5,6]

**Overall Sensitivity, Specificity, PPV, and Negative Predictive Value of Spiral CT Angiography**

Dr. Hales remarked that the data from consensus CT reading (CTPA and CTV) could appear difficult to understand, because a number of relevant combinations of patient subgroups exist (with differing patient populations). Not all patients with consensus CTPA interpretation necessarily had a consensus CTV reading and vice versa.

**Patients with consensus CTPA interpretation irrespective of CTV interpretation (997 patients).** In this group, the specificity and negative predictive value (NPV) are high (96% and 95%, respectively) with reasonably high sensitivity and PPV (83% and 86%, respectively).

**Patients with consensus CTPA or consensus CTV interpretation (744 patients).** Dr. Hales considered this to be the clinically most relevant group, because the test results from this population would influence management (treatment would be required whether clots could be demonstrated in pulmonary arterial tree or in proximal deep venous system). When CTV is considered with CTPA, there is an increase in sensitivity to 90% with no loss of specificity (95%). NPV remains very high (97%). PPV remains high (85%), but there is still a significant false-positive predictive value rate of 15%.

**Patients with both consensus CTPA and CTV interpretation (697 patients).** When consensus CTV is considered with consensus CTPA in the same patients, similar trends are observed. Again, sensitivity of spiral CT increases to 87% (from 80% for CTPA alone) without the loss of high specificity (95% from 96%).
NPV remains very high (97% from 95%). PPV remains high at 83% (from 84% for CTPA alone). This still indicates a considerable false-positive predictive rate of 17%.

**Post-test Probability of PE According to Clinical Likelihood of PE**

**CTPA considered alone.** For the diagnostic value of CTPA:

- In patient groups with high or intermediate Wells scores, positive CTPA studies indicate high post-test probabilities of 99% and 89%, respectively, for acute PE; and
- In patients with intermediate or low Wells scores, negative CTPA studies indicate quite low or very low post-test probabilities of 7% and .5%, respectively for acute PE.

For the limited diagnostic value of CTPA in discordant situations:

- In patients with low Wells scores, positive CTPA studies indicate a PPV of only 38% for acute PE. This discordant scenario occurred in a sizeable proportion of patients (23% of evaluable cases).
- Conversely, in patients with high Wells scores, negative CTPA studies are still associated with a post-test probability of 39% for acute PE. This discordant scenario occurred only in a small proportion of patients (approximately 3% of evaluable cases).

**CTV considered with CTPA.** For the diagnostic value of spiral CT angiography:

- Similar trends are observed. In patient groups with high or intermediate Wells scores, positive CTPA or CTV studies indicate high post-test probabilities of 98% and 87%, respectively, for acute PE.
- In patients with intermediate or low Wells scores, combined CT findings (negative CTPA and negative CTV) indicate lower post-test probabilities of 4% and .3%, respectively, for acute PE.

For the limited diagnostic value of spiral CT angiography in discordant situations:

- In patients with low Wells scores, positive CTPA or CTV studies indicate a PPV of only 33% for acute PE. This discordant scenario occurred in a sizeable proportion of patients (23% of evaluable cases).
- In patients with high Wells scores, combined negative CTPA and CTV studies are still associated with a post-test probability of 28% for acute PE. This discordant scenario occurred only in a small proportion of patients (approximately 2% of evaluable cases).

**Post-test Probability of PE According to Index of Clinical Suspicion and the Size of the Largest Pulmonary Arteries Positive for Thromboemboli on CTPA**

The diagnostic value of positive CTPA in large pulmonary arteries indicated that positive CTPA studies have high PPV (89% to 99%) for acute PE when large (main or lobar) pulmonary arteries are involved irrespective of clinical suspicion. The overall PPV is 97% for acute PE in this group.

For the diagnostic value of positive CTPA at the segmental level:

- In patients with high Wells scores, positive CTPA at the level of segmental vessels or smaller may also have high PPV (100%) for acute PE, although the number of patients was small (3 patients);
- In patients with intermediate Wells scores, PPV of positive CTPA appears reasonably high (79%) at the segmental level;
- In contrast, in patients with low Wells scores, PPV of positive CTPA appears low (33%) at the segmental level; and
The overall PPV of this group for acute PE is 64%.

In patients with intermediate or low Wells scores, PPV of positive CTPA at the subsegmental level appeared low (33% and 20%, respectively), giving an overall PPV of 25% for acute PE. Meaningful conclusion is difficult, however, because the largest pulmonary arteries involved were at the subsegmental level based on CTPA, and the total number of cases was small (8 patients). There were no cases recorded with high Wells scores and positive CTPA at the subsegmental level only.

**Location of DVT Detected on CTV**

The vast majority (97%) of DVT detected by CTV was in the thighs (85% in the thighs alone and 12% in the thighs and pelvis). Only 3% of patients had DVT in the pelvis or inferior vena cava alone, based on CTV, and all these patients had positive CTPA. This agrees with the literature that isolated pelvic DVT is rare.[7]

**Interobserver Agreement**

Overall, there was good interobserver agreement for CTPA and CTV at 90%, with similar interobserver agreement of 87% for DSA. Overall interobserver was worse (74%) for the VQ scans, particularly for the intermediate / low-probability categories (interobserver agreement at 60%). The kappa values for interobserver agreement were best for CTPA and CTV (.73), followed by DSA (.6) and then VQ scans (.54). These figures are comparable to those reported in the literature, according to Dr. Goodman.

**Selected Relevant Issues Discussed at the Session**

Lawrence R. Goodman, MD (Department of Radiology, Medical College of Wisconsin, Milwaukee), suggested the following practical strategies to optimize image acquisition.

To minimize breathing artifacts:

- Encourage several respiratory cycles (with/without oxygen supplement) before breath holding;
- Allow adequate pause of respiration at breath holding before scanning; and
- Scan faster during quiet breathing if patients are unable to perform breath holding.

To improve contrast enhancement of pulmonary vessels:

- Consider increasing contrast concentration;
- Tighter bolus with faster injection or "saline chaser";
- Keep arms relaxed; and
- Judicious use of repeat bolus of intravenous contrast.

To improve contrast enhancement of deep veins in lower extremities:

- Consider increasing contrast load;
- Adequate delay (3-3.5 minutes after intravenous contrast administration); and
- Elastic stockings to compress superficial veins.[8]

**Should CTV Always Be Performed With CTPA?**

Alexander Gottschalk, MD (Department of Radiology, Michigan State University, East Lansing, Michigan), acknowledged the ongoing concern regarding possible radiation risks from diagnostic CT in the literature.[9,10]

Pamela K. Woodard, MD (Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, Missouri), listed the estimates of effective radiation exposure to patients from CTPA (3.8 mSv), pelvic CT (6.0 mSv), and thigh CTV (3.2 mSv). (For rough comparisons, the average annual exposure from natural background activity is about 2.5 mSv, and from a VQ lung scan, it is in the 2-3 mSv range.[11]). Dr.
Woodard suggested that, in light of the relatively low yield of pelvic CTV, which accounts for nearly half of all radiation exposure from CTPA and CTV, reasonable strategies to reduce radiation exposure include:

- Eliminating pelvic CTV and performing thigh CTV from the acetabular level down;
- Modifying protocols of pelvic CTV, such as scanning 5 mm every 2 cm or adjusting the kilovolt peak and milliamperes; and
- Replacing CTV with U/S when possible, particularly in patients who are women of child-bearing age.

**What Is the Validity of Composite Reference Tests?**

Dr. Hales commented that the use of the composite exclusion criteria appeared valid because during subsequent 6-month follow-up, only 1% of patients (6 out of 590 untreated patients) developed venous thromboembolic events (4 with PE by subsequent CTPA, 1 with DVT, and 1 death by fatal PE on death certificate).

It was recognized that the composite reference criteria to diagnose acute PE in the PIOPED II trial were not perfect. Pulmonary angiography has been questioned as a true standard. Dr. Stein pointed out that positive U/S studies and high-probability VQ lung scans (in the absence of prior PE) may be false positives in up to 10% of cases. Dr. Gottschalk commented that the sensitivity, specificity, and likelihood ratios of positive and negative results in the PIOPED II study may need adjusting for the false-positive and false-negative rates of the composite reference tests.

**Would CTPA and CTV Replace Other Noninvasive Imaging Modalities in the Evaluation of VTE?**

The clinicians' armamentarium has certainly been enhanced with the availability of CTPA and CTV with multidetector CT technology in the evaluation of VTE. With improving technology and increasing experience, the application of multidetector CT to noninvasively and rapidly visualize intraluminal thromboemboli is likely to expand. The additional benefit of providing alternative diagnoses or detecting unsuspected pathology by CTPA is well recognized. CTPA and CT angiography are, however, unlikely to completely replace other imaging modalities in the evaluation of VTE. Specific medical contraindications to intravenous contrast use (such as contrast allergy or impaired renal function), the lack of local expertise or appropriate equipment in the use of CTPA, personal preferences of the clinicians (such as the wish to reduce radiation exposure to patients), or local experience with other imaging modalities are some of the factors influencing the choice between spiral CT angiography (CTPA and CTV) and other noninvasive imaging modalities, such as VQ lung scans or U/S. Further, when CT findings contradict clinical suspicion of acute PE spiral CT angiography appears to have low diagnostic value. (This situation accounted for about 25% of all cases in the PIOPED II trial.) Other imaging modalities are likely to play a complementary role in these cases.

**References**


