Critical Review Form
Therapy

Computed Tomographic Pulmonary Angiography vs Ventilation-Perfusion Lung Scanning in Patients with Suspected Pulmonary Embolism: A Randomized Controlled Trial, *JAMA* 2007; 298:2743-2753

Objective: **"To determine whether CTPA [CT pulmonary angiography] is a reliable safe alternative to V/Q scanning as an initial noninvasive imaging procedure for evaluating the diagnosis of pulmonary embolism." (p. 2744)**

Methods: **A randomized, controlled, physician and investigator-blinded diagnostic management study designed as a non-inferiority study to assess whether the newer CTPA was as safe as the three-decade old V/Q scan at not missing the detection of clinically important pulmonary embolism at 5 academic medical centers (inpatient, ED, and outpatient). From May 2001 until April 2005, consecutive patients with suspected PE were risk-stratified by physicians using the Well's score. PE was suspected based upon symptoms (acute onset of new or worsening dyspnea, chest pain, homoptysis or syncope). Exclusion criteria included DVT or PE previously diagnosed within 3 months, no change in pulmonary symptom severity over 2 weeks, >48 hours of therapeutic anticoagulation, life-expectancy <3 months, contraindication to contrast, pregnancy, age <18 years, refusal to consent, geographic inaccessibility to follow up, or pre-existing need for long-term anticoagulation.**

D-dimer testing was performed according to local practices. Patients considered clinically unlikely to have PE (Well's score <4.5) with a negative D-dimer, did not undergo further testing and were not randomized. Patients with Wells >4.5 or with a positive D-dimer were randomized to undergo either V/Q scanning or CTPA via computer-generated numbers in blocks of 4 to 6 stratified by hospital and setting (inpatient/outpatient).

CTPA used either single-detector (28%) or multi-detector (72%) scans. Single-detector scans used 150 mL contrast at 5 mL/s with 3mm images at 3mm intervals during a single breath hold over 15-25 seconds. Multi-detector scans used 100 mL contrast injected at 4 mL/s with 1.25 mm images at 1.2 mm intervals. PE was diagnosed if an intraluminal filling defect was seen. Scans were inadequate only if main or labor pulmonary arteries were not seen.

V/Q scans were categorized (based upon PIOPED) as high probability if there were 1 or more segmental perfusion defects with normal ventilation or 2 or more large sub segmental perfusion defects (>75% of a segment with normal ventilation).

Patients with a high-probability V/Q scan or positive CTPA were considered to have a PE. Patients with normal V/Q scan were considered to have PE excluded. All other patients had LE ultrasound performed for DVT. Study and attending physicians were blinded to the initial diagnostic allocation group and received generic pulmonary imaging reports: positive for PE, non-diagnostic study, or no evidence of PE. Patients with negative leg US and non-diagnostic V/Q scan were considered to have PE excluded if D-dimer was negative or Well's score <4.5. If the D-dimer was positive, repeat LE US in 1-week were scheduled, but these patients did not receive anti-coagulation. Crossover from CTPA to V/Q scanning or vice versa was not permitted by the protocol.

All patients were reassessed for symptoms of VTE at a clinic visit or by telephone 1-week and 3-months after initial presentation. Causes of death were investigated by review of medical records and by contacting patients' families or physician. The primary outcome was the development of VTE in the 3-month follow-up period. An expert adjudication committee blinded to diagnostic scan allocation reviewed all clinical details for those with possible outcome events and deaths.

RCT was designed as a non-inferiority trial. Based upon a 3-month rate of VTE of 1.4% for V/Q, a minimal clinically important difference for CTPA of 2.5% was derived based upon the assumptions that a) <15% of undetected PE by CTPA would be fatal and b) 0.45% mortality of pulmonary angiogram if all non-diagnostic V/Q scans had angiogram. In other words, 15% of 2.5% is less than 0.45%. Based upon 16% incidence of initial PE diagnosis and 3% inadequate scan rates a sample size of 1380 was projected.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, "Randomization lists were generated by computer in variable blocks ranging from 4-6. Randomization was stratified by center and by patient location (inpatient vs outpatient)." (p. 2745)
2.	Was randomization concealed (blinded)?	Yes, "Randomization assignments were kept locally, concealed in consecutively numbered opaque sealed envelopes distributed to each center. The next consecutively numbered allocation envelope was opened by an experienced research coordinator otherwise not involved in the study." (p. 2745)
3.	Were patients analyzed in the groups to which they were randomized?	Uncertain since there is no intention-to-treat statement.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes, although "cancer (as defined as malignancy or treatment with chemotherapy in the previous 6 months) was present in 9.7% of the CTPA group and in 12.2% of the V/Q group."
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Although there is no clear statement of blinding patients, they probably were unaware of differences between imaging strategies unless they had medical background or other personal experiences.
2.	Were clinicians aware of group allocation?	No. "Physicians (study and attending) were blinded to the initial diagnostic test allocation group." (p. 2745)

3.	Were outcome assessors aware of group allocation?	No. "All CTPA studies were interpreted by experienced chest radiologists unaware of patient clinical probability or D-dimer results." (p. 2745) "All (V/Q) scans were interpreted by experienced nuclear medicine physicians unaware of the clinical probability or D-dimer results." (p. 2745) "D-dimer testing was performed in coagulation laboratories by individuals who were unaware of the clinical probability assessment of the participating patients." (p. 2744)
4.	Was follow-up complete?	Yes, reasonably so. "Eleven patients (0.8%) were lost to follow-up (7 in the CTPA group and 4 in the V/Q scan group) with none of these patients experiencing venous thromboembolism prior to being lost to follow-up." (p. 2747)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• From 3886 patients approached, 1417 were randomized (701 CTPA, 716 to V/Q scan) with mean age 53 years and 38% male. 90% of patients were from the out-patient setting and 9% had prior VTE. • More CTPA patients were initially diagnosed with VTE: 19.2% CTPA vs 14.2% V/Q (mean difference 5.0%, 95% CI 1.1%-8.9%). • In the CTPA 2/561 (0.4%) developed symptomatic VTE compared with 6/611 (1%) of the V/Q group (mean

		difference – 0.6%, 95% CI – 1.6% - 0.3%) and most events occurred within 50 days. One of the V/Q "misses" was a fatal PE at day 49. • Among patients with PE originally excluded, 17/561 (3%) of the CTPA group and 30/611 (4.9%) of the V/Q group died, within 3 months including 1 fatal PE in each group. • Cross-over occurred in 51 patients randomized to the CTPA and 25 patients in the V/Q group. 38 of the CTPA cross-overs were because CTPA could not be performed another 10 had inadequate CT's. • 54.2% of V/Q scans were non-diagnostic and 35% were normal. Ultimately, 7% of nondiagnostic V/Q scans had VTE diagnosed. 97.3% of high probability V/Q scans received anticoagulation (vs all 115 patients with positive CTPA). • PE was detected 14.9% of single slice CTPA vs 19.9% of multi-detector CT's. Amongst CTPA patients, 30.6% of PE's were segmental arteries and 7.3% were sub segmental.
2.	How precise was the estimate of the treatment effect?	
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, mostly ED and outpatients with symptom-based suspicion of PE and non-low risk Well's score and/or D-

		dimer findings.

2.	Were all clinically important outcomes considered?	Yes. Although PE has other sequelae besides mortality (pulmonary hypertension, for example), these outcomes are chronic and would not be captured during a 3-month follow-up period. The current research provides essential, minimally biased evidence that clinicians will not increase 3 month mortality by using CTPA rather than V/Q to diagnose PE.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. "Many of the incremental thrombi detected by CTPA were clinically unimportant." But which ones? Who feels safe not treating segmental or sub segmental PE? "Having CTPA diagnosing about 30% more patients with pulmonary embolism than V/Q scanning may have substantive undesired consequences. First, it would result in increased numbers of patients being exposed to anticoagulation therapy…In addition, the resource consequences of hospitalization, anticoagulation therapy, and potential major bleeding complications would almost certainly make management with CTPA more costly.

Limitations

1) **Limited external validity to inpatients or non-academic medical centers or patients with the numerous exclusion criteria.**

2) **No discussion of CTPA or V/Q complication rates or radiation risks.**

3) **No conjecture about roles of CTPA or V/Q on test-treatment thresholds.**

4) **No data or discussion about the availability or ED resource constraints for V/Q vs. CTPA (bed constraints related to crowding, lack of 24/7 access to either V/Q or CTPA, etc).**

Bottom Line

V/Q scanning should still play a role in the diagnostic evaluation of PE. Although based upon 3-month rates of death or new VTE suggests no differences between a normal V/Q or nondiagnostic V/Q + negative LE ultrasound with Wells score <4.5, clinicians are less accepting of V/Q than CTPA. In addition to the radiation-risk and contrast-dye adverse side effects, clinicians should be aware that a portion of PE's diagnosed by CTPA may be clinically inconsequential.