Excluding Pulmonary Embolism According to V/Q Scanning versus CT Angiography

The Case:
The patient is a 20 year-old woman with a PMH of WPW (no ablation), vasovagal syncope, endometriosis s/p exploratory laparoscopy, and appendicitis s/p appendectomy who presented with resolved vomiting and persistent RUQ pain that began during a trip to Mexico. Her RUQ pain worsens with inspiratory effort. Physical exam is notable for positive Murphy's sign and fixed split S2. Abdominal ultrasound and abdominal/pelvic CT showed no evidence of cholelithiasis or nephrolithiasis. Laboratory tests show positive troponins (0.05, 0.15, 0.98, 0.78 ng/mL) and positive d-dimer (1.57 ug/ml FEU).

The patient travelled to Mexico via airplane and she takes oral contraceptive pills – risk factors for pulmonary embolism (PE). According to Wells Clinical Prediction Rule, PE is likely (patient's score = 3.0).[1]

Imaging is needed to better determine the diagnosis of PE and thus guide the treatment of this patient. CT angiography (CTA) has high positive (86%) and negative (95%) predictive value,[2] but it is important to consider the potential risks of this test to this patient. Thoracic CT subjects her to 2.0 to 3.5 rad of radiation, and 1 rad to the breasts of a woman younger than 35 increases the risk of breast cancer 13.6%.[3] Ventilation-perfusion (V/Q) scanning, however, subjects her to much less radiation – only 0.5 to 5% of that of CTA.[4] Is V-Q scanning an acceptable imaging procedure relative to CTA for evaluating this patient and then managing her accordingly?

The Search:
I entered terms into Ovid-Medline following the PICO format:

- P – pulmonary embolism
- I – ventilation-perfusion [scanning]
- C – tomography, x-ray computed
- O – morbidity, mortality, treatment outcome, anticoagulation, venous thromboembolism or thromboembolism

I also entered the term "randomized clinical trials" to limit my search to this study design.

Unfortunately, this search yielded one study that did not answer the clinical question. Therefore, I removed the outcome (O) terms. This second search yielded five studies, one of which applied directly to the clinical question and was recently published (2007) in a reputable journal (JAMA).

[1] The patient's heart rate was 69 bpm at presentation, but it is important to note that she takes metoprolol daily.
[2] Stein PD et al, for the PIOPED II investigators. 2006. Multidetector computed tomography for acute pulmonary embolism. NEJM 354:2317-20.
[3] Remy-Jardin M and J Remy. 1999. Spiral CT angiography of the pulmonary circulation. Radiology 212:615-636.
[4] Stein PD et al. 2008. Challenges in the diagnosis acute pulmonary embolism. American J of Medicine 121:565-71.

The Study:
Citation: Anderson DR, et al. 2007. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA 298:2743-53.

Population: The study participants were patients (n = 1417) from outpatient clinics, emergency departments, and inpatient units of 4 Canadian and 1 US tertiary care centers. The study was conducted between May 2001 and April 2005.

Inclusion criteria were: 1) presenting with symptoms or signs suspected by a physician to be caused by acute PE with or without signs of deep vein thrombosis (DVT); and 2) considered likely to have acute PE based on a Wells clinical model score of 4.5 or greater or a positive d-dimer assay result.

Exclusion criteria were: 1) DVT or PE diagnosed within the previous 3 months; 2) no change in the severity of pulmonary symptoms within the previous 2 weeks; 3) use of therapeutic doses of parenteral anticoagulants for greater than 48 hours, 4) comorbid conditions making life expectancy less than 3 months; 5) contraindication to contrast media (including renal insufficiency); 6) a need for long-term use of anticoagulants; 7) pregnancy; 8) age younger than 18 years; 9) refusal to give informed consent; and 10) geographic inaccessibility to follow-up.

Intervention: Patients were randomized to undergo CTA (n = 701) or V/Q scanning (n = 716).

Patients with positive CTA or high-probability V/Q scan were treated for PE with anticoagulation. Patients with a negative CTA or a non-diagnostic V/Q scan underwent leg vein ultrasonography; they were treated for PE if ultrasonography was positive. If ultrasonography was negative but the patient had both a Wells score $\geq$4.5 and a positive d-dimer, ultrasonography was repeated at 1 week.

PE was considered excluded in patients with a normal V/Q scan or negative ultrasonography after negative CTA or a non-diagnostic V/Q scan. They did not receive antithrombotic therapy.

Follow-up: Patients in whom PE was considered excluded were followed up for 3 months.

Outcome: "The primary outcome was the subsequent development of symptomatic PE or proximal DVT in patients in whom pulmonary embolism had initially been excluded." Another outcome was mortality in these patients.

Validity:
Design: This study is a "randomized, single-blinded, non-inferiority clinical trial."

Comparison of pretest groups: There were no statistical differences between the CTA and V/Q groups with regard to age (mean 53.3 and 53.1 years), sex (37.3% and 38.1% men), outpatient status (90.0 and 89.5%%), and risk factors of prior VTE (9.2% and 9.9%) or recent surgery

(23.2% and 23.8%). The CTA group had significantly fewer patients with cancer (9.7% versus 12.2%).

Blinding: Radiologists were blinded to clinical probability of PE and d-dimer levels. Treating physicians were blinded to imaging test allocation until initial diagnosis was completed.

Non-inferiority: The authors determined that 2.5% was the minimal clinically important difference (MCID) of PE/DVT events during follow-up between the two groups. The rationale was as follows. There is a 0.45% mortality rate for CTA. Given that less than 15% of PE/DVT events would likely be fatal, the mortality rate associated with this MCID (0.38% – 15% of 2.5%) would be less than that among patients with non-diagnostic V/Q scans undergoing CTA.

Cross-over: The study protocol did not permit cross-over. Rather, it provided the option of "classical pulmonary angiography" for patients with non-diagnostic imaging and negative ultrasonography but in whom PE was still considered highly likely.

However, cross-over did occur:

- 51 patients assigned to CTA underwent V/Q scanning (3 despite clear CTA results; 10 with "technically inadequate" CTA results; 8 for technical problems; 3 refused; 8 for whom physicians refused; 16 for whom CTA was contraindicated; 3 for unknown reason)
- 25 patients assigned to V/Q scanning underwent CTA (2 because for technical problems; 23 because V/Q scan was non-diagnostic, ultrasonography was negative, and PE was still considered highly likely.)

Attrition: Eleven patients (0.8%) were lost to follow-up.

Analysis: Intention-to-treat analysis was conducted.

Results:

14.2% of patients in the V/Q scanning group and 19.2% of the patients in the CTA group were diagnosed with PE/DVT (difference 5.0%, p=0.01). The authors note that this difference was driven by the higher rate of PE (versus PE and DVT or DVT alone) diagnosed in patients undergoing CTA scanning versus V/Q – 13.5% and 9.0%, respectively.

Predictive accuracy of imaging tests: Of the patients with normal V/Q scan (35.0%), 0.8% had DVT on ultrasound and none had PE/DVT during follow-up. Of the patients with "technically adequate," negative CTA, 1.3% had DVT on ultrasonography and another 0.4% had PE during follow-up.

Of the patients with non-diagnostic V/Q scan (54.2%), 7.0% had PE/DVT during the initial diagnosis period (via ultrasonography, CTA, pulmonary angiography, or clinical decision) and another 1.0% had PE/DVT during follow-up. Of the patients with "technically inadequate" CTA, 22.9% had PE/DVT during the initial diagnosis period (via ultrasonography or V/Q scanning).

Outcomes: Among the patients in whom PE was considered excluded during the initial diagnosis period, 1.0% of those in the V/Q scanning group and 0.4% in the CTA group were diagnosed with PE/DVT during follow-up (difference -0.6%, p=0.29).

Among the patients in whom PE was considered excluded during the initial diagnosis period, 4.9% in the V/Q scanning group and 3.0% in the CTA group died during follow-up (difference 1.9%, p=0.12); 0.3% in each group died from PE, sudden death, or unknown cardiopulmonary compromise. The majority of deaths in both groups were secondary to complications of cancer.

Study Application:
The study was conducted among a large group of patients (n = 1417) from multiple centers (5 across the U.S. and Canada), making the results fairly generalizable. Furthermore, the patient in the case meets the recruitment criteria for the study. However, it is important to note that the great majority of participants (~90%) were outpatients, which this patient was not.

The study showed that CTA was not inferior to V/Q scanning for ruling out PE with regard to both diagnosed PE/DVT and mortality during 3-month follow-up. Either imaging test may be applied clinically. To avoid large radiation exposure, V/Q scanning may indeed be preferred. However, many of the patients assigned to V/Q scanning had non-diagnostic imaging (54.2%) and required further imaging with other modalities. Therefore, CTA and its associated radiation exposure ultimately may not be avoided in such patients. In conclusion, I would suggest that the case patient initially undergo V/Q scanning and then ultrasonography if the scan is non-diagnostic. I would also explain to her that depending on the results of these imaging tests CTA may still be recommended to help rule out PE.

The study also found that more PEs were diagnosed by CTA compared to V/Q scanning. It is unclear whether these were true or false positives, but given no significant differences in the measured outcomes between CTA and V/Q scanning groups they may be clinically insignificant true positives or false positives. The question then becomes, what are the risks/costs of anticoagulating these patients.

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# ▲	Searches	Results	Search Type	Display
1	Pulmonary Embolism/	26268	Advanced	DISPLAY
2	ventilation-perfusion.mp.	7320	Advanced	DISPLAY
3	Tomography, X-Ray Computed/	207532	Advanced	DISPLAY
4	Randomized Controlled Trial/	263468	Advanced	DISPLAY
5	Morbidity/	19327	Advanced	DISPLAY
6	Mortality/	29472	Advanced	DISPLAY
7	Treatment Outcome/	349363	Advanced	DISPLAY
8	Anticoagulants/	38780	Advanced	DISPLAY
9	Venous Thromboembolism/ or Thromboembolism/	18135	Advanced	DISPLAY
10	8 or 6 or 7 or 9 or 5	442755	Advanced	DISPLAY
11	4 and 1 and 3 and 10 and 2	1	Advanced	DISPLAY
12	4 and 1 and 3 and 2	5	Advanced	DISPLAY

Results of your search: from 5 [4 and 1 and 3 and 2] keep 1
Results Available: **1**
Results Displayed: **#1**

Result 1.	Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, Lang E, Stiell I, Kovacs G, Dreyer J, Dennie C, Cartier Y, Barnes D, Burton E, Pleasance S, Skedgel C, O'Rouke K, Wells PS	*Link to...* • Abstract • Complete Reference • EBM Article Review • Columbia e-Link

Unique Identifier	18165667
Status	MEDLINE
Authors	Anderson DR. Kahn SR. Rodger MA. Kovacs MJ. Morris T. Hirsch A. Lang E. Stiell I. Kovacs G. Dreyer J. Dennie C. Cartier Y. Barnes D. Burton E. Pleasance S. Skedgel C. O'Rouke K. Wells PS.

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Title	Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial.[see comment].
Comments	Comment in: JAMA. 2007 Dec 19;298(23):2788-9; PMID: 18165674
Source	JAMA. 298(23):2743-53, 2007 Dec 19.
Abstract	**CONTEXT:** Ventilation-perfusion (V(dot)Q(dot) lung scanning and computed tomographic pulmonary angiography (CTPA) are widely used imaging procedures for the evaluation of patients with suspected pulmonary embolism. Ventilation-perfusion scanning has been largely replaced by CTPA in many centers despite limited comparative formal evaluations and concerns about CTPA's low sensitivity (ie, chance of missing clinically important pulmonary embuli). **OBJECTIVES:** To determine whether CTPA may be relied upon as a safe alternative to V(dot)Q(dot scanning as the initial pulmonary imaging procedure for excluding the diagnosis of pulmonary embolism in acutely symptomatic patients. DESIGN, SETTING, **AND PARTICIPANTS:** Randomized, single-blinded noninferiority clinical trial performed at 4 Canadian and 1 US tertiary care centers between May 2001 and April 2005 and involving 1417 patients considered likely to have acute pulmonary embolism based on a Wells clinical model score of 4.5 or greater or a positive D-dimer assay result. **INTERVENTION:** Patients were randomized to undergo either V(dot)Q(dot scanning or CTPA. Patients in whom pulmonary embolism was considered excluded did not receive antithrombotic therapy and were followed up for a 3-month period. **MAIN OUTCOME MEASURE:** The primary outcome was the subsequent development of symptomatic pulmonary embolism or proximal deep vein thrombosis in patients in whom pulmonary embolism had initially been excluded. **RESULTS:** Seven hundred one patients were randomized to CTPA and 716 to V(dot)Q(dot scanning. Of these, 133 patients (19.2%) in the CTPA group vs 101 (14.2%) in the V(dot)Q(dot scan group were diagnosed as having pulmonary embolism in the initial evaluation period (difference, 5.0%; 95% confidence interval [CI], 1.1% to 8.9%) and were treated with anticoagulant therapy. Of those in whom pulmonary embolism was considered excluded, 2 of 561 patients (0.4%) randomized to CTPA vs 6 of 611 patients (1.0%) undergoing V(dot)Q(dot scanning developed venous thromboembolism in follow-up (difference, -0.6%; 95% CI, -1.6% to 0.3%) including one patient with fatal pulmonary embolism in the V(dot)Q(dot group. **CONCLUSIONS:** In this study, CTPA was not inferior to V(dot)Q(dot scanning in ruling out pulmonary embolism. However, significantly more patients were diagnosed with pulmonary embolism using the CTPA approach. Further research is required to determine whether all pulmonary emboli detected by CTPA should be managed with

anticoagulant therapy. TRIAL **REGISTRATION:** isrctn.org Identifier: ISRCTN65486961.

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