The Emperor May Still Have No Clothes: Are We Over-diagnosing PE?

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Why Worry About Overdiagnosing Pulmonary Embolism?

- Risk of bleeding from unnecessary AC
  - Minor bleeding
  - Major bleeding
- Contrast-induced complications
  - Anaphylaxis
  - Acute kidney injury
- Exposure to ionizing radiation
- Cost
Outline for today’s talk

• Over-diagnosis of pulmonary embolism
  • Problems related to x-ray interpretation
  • Problems related to patient selection

• Approach to managing patients with SSPE
  • Patients with active malignancy
  • Patients without cancer

• Best Practice Advice from ACP Clinical Guideline Committee and recommendations on high-value care from the Choosing Wisely campaign
Important clinical questions that need to be addressed

• Which patients with suspected pulmonary emboli should undergo CT-pulmonary angiography (CTPA)?

• Should we anticoagulate all patients with asymptomatic, incidentally-discovered, isolated sub-segmental pulmonary emboli (SSPE)?
The emperor has apparently been naked for a quite a long time

Overdiagnosis and Overtreatment of Pulmonary Embolism: The Emperor May Have No Clothes

EUGENE D. ROBIN, M.D., F.A.C.P.; Stanford, California

Pulmonary embolism is being overdiagnosed and overtreated, especially in previously normal women using oral contraceptives, with undesirable consequences in heparin treatment. This is in part a consequence of high estimates of its occurrence based on postmortem data and in part of technologic developments in diagnostic methods. Blood gas data are not diagnostically very helpful. Perfusion scans should be used, largely to exclude the diagnosis. Ventilation scans are only occasionally helpful and are expensive. Pulmonary angiography is the most accurate diagnostic means currently available. Further studies are needed to elucidate the prevalence and natural life history of pulmonary embolism in the previously healthy person.

Ann Intern Med 1977; 87: 775-781
Recent trends in the incidence of pulmonary embolism

Arch Intern Med 2011; 171: 831 - 837
Has there been a real increase in the incidence of PE?
Multi-detector row CT pulmonary angiography (CTPA)
Is it possible that CTPA is too good of a test for diagnosing PE?
ANALYSIS

TOO MUCH MEDICINE

When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found

Renda Soylemez Wiener assistant professor\textsuperscript{1,2}, Lisa M Schwartz professor\textsuperscript{3,4}, Steven Woloshin professor\textsuperscript{3,4}

\textsuperscript{1}Pulmonary Center, Boston University School of Medicine, Boston, MA, USA; \textsuperscript{2}Center for Health Quality, Outcomes and Economic Research, ENRM VA Hospital, Bedford, MA, USA; \textsuperscript{3}Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth Medical School, Lebanon, NH, USA; \textsuperscript{4}VA Outcomes Group, VA Medical Center, White River Junction, VT, USA
Pulmonary arterial tree with segments and sub-segments
Subsegmental pulmonary emboli

• How often do SSPE occur?

• How often are SSPE mischaracterized by the radiologist?

• Why does patient selection matter?

• Who should undergo CT-pulmonary angiography?
Frequency of SSPE in 3 Canadian Academic Teaching Hospitals

Total CTPA reviewed: 2216

Frequency of PE: 550 (24.8%)

Frequency of SSPE: 82 (3.9%)

15% of PE were subsegmental
Frequency of SSPE in 3 Canadian Academic Teaching Hospitals

- 52% (43/82) of SSPE patients received AC.

- No documented recurrent VTE in any SSPE patient with or without anticoagulation.

- 67% (55/82) of SSPE patients had an alternative CT diagnosis to explain their sx.

- Isolated SSPE with no alternative diagnosis was identified in 27% (22/82) patients.
Over-diagnosis of PE by CTPA

Interpretive Discordance
Evidence for over-diagnosis of pulmonary embolism by CTPA

• Retrospective review of all CTPA exams (n=937) performed over a 12-month period in a tertiary-care university hospital.

• All positive studies were retrospectively reviewed by three subspecialty chest radiologists with over 10 years experience.
Evidence for over-diagnosis of pulmonary embolism by CTPA

PE initially diagnosed in 174 cases (18.6%)

Discordance between original interpretation and retrospective review in 45 cases (25.9%). On further review:

- 46.2% of solitary PE considered negative
- 59.4% of SSPE considered negative
- 66.7% of solitary SSPE considered negative
Relative frequency of artifact responsible for misdiagnosis of PE

Breathing: 40
Beam hardening: 20
Cardiac: 10
Mixing: 10
Airspace disease: 5
Valsalva: 5

AJR 2015; 205: 271 - 277
Over-diagnosis of PE by CTPA

Patient selection and false positive results
Magnitude of false positive results depends on disease prevalence

Influence of population prevalence of PE in a cohort of 2500 patients tested with CT pulmonary angiography

<table>
<thead>
<tr>
<th>Scenario</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.4%</td>
<td>485</td>
<td>78</td>
<td>100</td>
<td>1837</td>
<td>86%</td>
<td>94.8%</td>
</tr>
<tr>
<td>10%</td>
<td>207</td>
<td>90</td>
<td>43</td>
<td>2160</td>
<td>70%</td>
<td>98.1%</td>
</tr>
<tr>
<td>5%</td>
<td>105</td>
<td>95</td>
<td>20</td>
<td>2280</td>
<td>52.5%</td>
<td>99.1%</td>
</tr>
</tbody>
</table>
Evaluation pathway for suspected acute pulmonary embolism

Patients with suspected PE

Assess pretest probability*

Low

PERC

Positive

No PE work-up indicated

Intermediate

Negative

No imaging indicated

High

d-Dimer

Positive

Imaging indicated

Negative
Diagnosis of SSPE more likely to be correct (true positive) if:

- CTPA is of high quality with good opacification of distal pulmonary arteries
- Multiple intraluminal defects
- Defects involve more proximal subsegmental arteries (larger vessels)
- Defects are seen on more than one image
- Defects seen on more than one projection
Diagnosis of SSPE more likely to be correct (true positive) if:

• Defects are surrounded by contrast rather than appearing adherent to pulmonary arterial walls

• Patients are symptomatic, as opposed to PE being an incidental finding

• High pretest clinical probability of PE

• Elevated d-dimer level, particularly if increase is marked and/or otherwise unexplained
Like this signage, the clinical significance of SSPE is unclear
Reasons for uncertainty in deciding to treat SSPE

• Because of their small size, a diagnosis of SSPE is more likely to be a false-positive finding.

• True SSPE likely arise from small DVT and risk of progression or recurrent VTE without anticoagulation is expected to be lower than in patients with larger clots.
Approach to incidentally discovered subsegmental PE

Cancer present

Cancer not present
Frequency of incidental pulmonary embolism in cancer patients

- Incidental PE detected in 1-4% of cancer patients on routine staging with chest CT.

- Incidental findings of PE and/or DVT (including splanchnic and visceral vein thrombi) were *frequently reported* during routine staging with CT scans of abdomen and pelvis.
Incidental VTE in Cancer Patients

• One retrospective cohort analysis noted 44% of all thromboembolic events were incidental.

• Another cohort study showed 50% of DVTs and >35% of PEs were discovered incidentally.
Risk factors for incidental PE in cancer patients

- Metastatic disease
- Recent chemotherapy
- Type of cancer
Rationale for treating incidental VTE in cancer patients

Cancer patients with incidental (asymptomatic) VTE have similar rates of recurrent VTE, bleeding and mortality compared to those with symptomatic VTE.

- *Cancer* 2011; 117: 3860-3866
- *J Clin Oncol* 2011; 29: 2405-2409
VTE Prophylaxis and Treatment in Patients with Cancer - ASCO Clinical Practice Guideline

Recommendation 4.7

• Based on consensus, incidental PE and DVT should be treated in the same manner as symptomatic VTE.

• Treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.

J Clin Oncol 2015; 33: 654 - 656
J Clin Oncol 2013; 31: 2189 - 2204
Cancer patients with isolated SSPE

- Recommend careful review of images by experienced chest radiologists.
- Suggest performing bilateral CUS of lower limbs to detect concomitant incidental DVT.
ISTH recommendations
Cancer and Thrombosis SCC

Cancer patients with multiple SSPE

• Recommend LMWH for at least 6 months

Cancer pts with isolated SSPE + DVT

• Recommend LMWH for at least 6 months
ISTH recommendations
Cancer and Thrombosis SCC

Cancer patients with isolated SSPE and no DVT or DVT limited to distal lower extremity

- Suggest the decision to provide AC be made on case-by-case basis considering:
  - Risk of bleeding
  - Presence of risk factors for recurrent VTE
  - Performance status of the patient
  - Patient preference

If decision is made not to anticoagulate patients with isolated SSPE and there is either no DVT or a DVT limited to distal leg, suggest

- Clinical monitoring

- Serial bilateral CUS after one week in those with distal DVT to detect thrombus propagation
ISTH recommendations
Cancer and Thrombosis SCC

Incidental VTE reported

Yes

Symptoms compatible with VTE?

Treat as symptomatic VTE

No

Location of incidental VTE?

Proximal DVT, segmental or more proximal PE, multiple SSPE

Isolated SSPE

US of lower limbs

DVT

No DVT

Case-by-case anticoagulation or serial US and clinical monitoring

Anticoagulation
Approach to incidentally discovered subsegmental PE

Cancer not Present
Cochrane Systematic Review: Anticoagulant treatment for SSPE

- Patients with isolated SSPE or incidental PE may have a more benign clinical presentation compared to those with proximal PEs.

- However, the clinical significance and prognosis in these patients has to be studied to evaluate whether anticoagulation therapy is required.
Cochrane Systematic Review: Anticoagulant treatment for SSPE

• No randomized controlled trial evidence for effectiveness & safety of AC therapy versus no intervention in patients with isolated or incidental SSPE and therefore we cannot draw any conclusions.

• Well-conducted research is required before informed practice decisions can be made.
AT 10 panel recommendations

• If no anticoagulant therapy is an option, then patients with SSPE should have bilateral compression ultrasound (CUS) examinations to exclude proximal DVT of legs.

• Clinicians may opt to perform serial testing with CUS to detect (and then treat) evolving proximal DVT.
AT 10 panel recommendations

• In patients with SSPE and no proximal DVT in the legs who have a **low risk of recurrent VTE**, we suggest **clinical surveillance over anticoagulation** (Grade 2C).

• In patients with SSPE and no proximal DVT in the legs who have a **high risk of recurrence**, we suggest **anticoagulation over clinical surveillance** (Grade 2C).
Risk factors for recurrent/ progressive VTE if SSPE patients not anticoagulated

• Patients who are hospitalized or who have reduced mobility

• Patients with active cancer (particularly if they have metastatic disease or being treated with chemotherapy)

• No reversible risk factor such as recent surgery
Risk factors for recurrent/progressive VTE if SSPE patients not anticoagulated

- **Favor anticoagulation** if low cardiopulmonary reserve or marked symptoms that cannot be attributed to another condition

- **Favor no anticoagulation** if there is a high risk of bleeding

- Patient preference should be taken into account
Additional slides not shown during this talk
**Best Practice Advice 1:**

- Use validated clinical prediction rules to estimate pretest probability in patients in whom acute PE is being considered.

*Ann Intern Med 2015; 163: 701 - 711*
Wells Prediction Rule to Determine Pretest Probability of PE

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Simplified Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous PE or DVT</td>
<td>1</td>
</tr>
<tr>
<td>HR &gt; 100 beats/min</td>
<td>1</td>
</tr>
<tr>
<td>Recent surgery or immobilization</td>
<td>1</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
</tbody>
</table>

*Thromb Haemost* 2008; 99: 229 - 234
Revised Geneva Score to Determine Pretest Probability of PE

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Simplified Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1</td>
</tr>
<tr>
<td>Surgery (GA) or LE fracture in past month</td>
<td>1</td>
</tr>
<tr>
<td>Cancer (currently active or cured &lt; 1 year)</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>HR 75-94 beats/min</td>
<td>1</td>
</tr>
<tr>
<td>HR &gt; 95 beats/min</td>
<td>2</td>
</tr>
<tr>
<td>Pain on deep venous palpation of lower limb and unilateral edema</td>
<td>1</td>
</tr>
</tbody>
</table>
Predicting pretest probability of PE using simplified Wells and RGS

Wells prediction rule

Pretest probability
≤ 1: PE unlikely (low)
> 1: PE likely (high)

Revised Geneva score

Pretest probability
≤ 2: PE unlikely (low)
> 2: PE likely (high)
Best Practice Advice 2:

- Do not obtain D-dimer measurements or imaging studies in patients with a low pretest probability of PE and who met all Pulmonary Embolism Rule-Out Criteria (PERC).
Pulmonary Embolism Rule-Out Criteria for Predicting Probability of PE in Patients with Low Pretest Probability

**Clinical Characteristic**

- Age < 50 years
- Initial HR < 100 beats/minute
- Initial O2 sat > 94% on RA
- No unilateral leg swelling
- No hemoptysis
- No surgery or trauma within 4 weeks
- No history of VTE
- No estrogen use
Pulmonary Embolism Rule-Out Criteria for Predicting Probability of PE in Patients with Low Pretest Probability

If a patient with low pretest probability of PE meets all 8 PERC criteria......

the likelihood of PE is 0.3% and no further testing is required
ACP Clinical Guidelines Committee

**Best Practice Advice 3:**

- Obtain a high-sensitivity D-dimer measurement as the initial diagnostic test in patients who have an \textit{intermediate} pretest probability of PE or in patients with \textit{low} pretest probability of PE who do not meet all PERC.

- Do not use imaging studies as the initial test in patients who have a \textit{low or intermediate} pretest probability of PE.

\textit{Ann Intern Med} 2015; 163: 701 - 711
D-dimer

• Degradation product of cross-linked fibrin
• Typically elevated with acute DVT
• Sensitive but not specific marker for VTE
  - *Negative result can help exclude diagnosis*
  - *Positive result not useful in confirming diagnosis*
Common disorders that may increase D-dimer levels

- Malignancy
- Infection
- Inflammation
- Surgery
- Trauma
- Pregnancy
- DIC
- Atrial fibrillation
- Stroke
- Increasing age
Likelihood of VTE using estimate of clinical probability and D-dimer result

<table>
<thead>
<tr>
<th>Clinical Probability Estimate</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
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</thead>
<tbody>
<tr>
<td>+ D-Dimer</td>
<td>63</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>- D-Dimer</td>
<td>8.6</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Best Practice Advice 4:

• Use an age-adjusted D-dimer threshold (age x 10 ng/ml rather than a generic 500 ng/ml) in patients older than 50 years to determine whether imaging is warranted.
Best Practice Advice 5:

- Do not obtain any imaging studies in patients with a D-dimer level below the age-adjusted cutoff.
Best Practice Advice 6:

• Obtain CTPA in patients with a high pretest probability of PE.

• Reserve ventilation-perfusion (V/Q) lung scans for patients with contraindication to CTPA or if CTPA is not available.

• **Don’t obtain** a D-dimer measurement in patients with a high pretest probability of PE.
Evaluation pathway for suspected acute pulmonary embolism
High Value Care
Choosing Wisely

• In patients with low pretest probability of VTE, obtain a high-sensitive D-dimer measurement as the initial diagnostic test; don’t obtain imaging studies as the initial diagnostic test (American College of Physicians 04/12)

• Do not image for suspected pulmonary embolism (PE) without a moderate or high pre-test probability of PE (American College of Radiology 04/12)
Choosing Wisely

• Don’t perform CTA to evaluate for possible PE in patients with low clinical probability and negative results of a highly sensitive D-dimer assay (American College of Chest Physicians and American Thoracic Society 10/13)

• Avoid CTPA in emergency department patients with low pretest probability of PE and either a negative Pulmonary Embolism Rule-out Criteria (PERC) or a negative d-dimer (American College of Emergency Physicians 10/14)
American College of Physicians
View all recommendations from this society

Released April 4, 2012

In patients with low pretest probability of venous thromboembolism (VTE), obtain a high-sensitive D-dimer measurement as the initial diagnostic test; don’t obtain imaging studies as the initial diagnostic test.

In patients with low pretest probability of VTE as defined by the Wells prediction rules, a negative high-sensitivity D-dimer measurement effectively excludes VTE and the need for further imaging studies.

These items are provided solely for informational purposes and are not intended as a substitute for consultation with a medical professional. Patients with any specific questions about the items on this list or their individual situation should consult their physician.

How The List Was Created

Sources
American College of Radiology

View all recommendations from this society

Released April 4, 2012

Don’t image for suspected pulmonary embolism (PE) without moderate or high pre-test probability of PE

While deep vein thrombosis (DVT) and PE are relatively common clinically, they are rare in the absence of elevated blood d-Dimer levels and certain specific risk factors. Imaging, particularly computed tomography (CT) pulmonary angiography, is a rapid, accurate and widely available test, but has limited value in patients who are very unlikely, based on serum and clinical criteria, to have significant value. Imaging is helpful to confirm or exclude PE only for such patients, not for patients with low pre-test probability of PE.

These items are provided solely for informational purposes and are not intended as a substitute for consultation with a medical professional. Patients with any specific questions about the items on this list or their individual situation should consult their physician.

How The List Was Created

Sources

www.choosingwisely.org/clinician-lists
American College of Chest Physicians and American Thoracic Society

View all recommendations from this society

Released October 27, 2013

Don’t perform chest computed tomography (CT angiography) to evaluate for possible pulmonary embolism in patients with a low clinical probability and negative results of a highly sensitive D-dimer assay.

Clinical practice guidelines for pulmonary embolism indicate that the cost and potential harms of CT angiography (including radiation exposure and the possibility of detecting and treating clinically insignificant pulmonary emboli with anticoagulation) outweigh the benefits for patients with a low pre-test probability of pulmonary embolism. In patients with a low clinical prediction score (e.g., Wells or Geneva score) followed by a negative D-dimer measured with a high sensitivity test (e.g., ELISA), pulmonary embolism is effectively excluded and no further imaging is indicated for pulmonary embolism evaluation.

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www.choosingwisely.org/clinician-lists
American College of Emergency Physicians

View all recommendations from this society

October 27, 2014

Avoid CT pulmonary angiography in emergency department patients with a low-pretest probability of pulmonary embolism and either a negative Pulmonary Embolism Rule-Out Criteria (PERC) or a negative D-dimer.

Advances in medical technology have increased the ability to diagnose even small blood clots in the lung. Now, the most commonly used test is known as a CT pulmonary angiogram (CTPA). It is readily available in most hospitals and emergency rooms. However, disadvantages of the CTPA include patient exposure to radiation, the use of dye in the veins that can damage kidneys and high cost.

Studies have demonstrated that certain findings in a patient’s medical history put them at very low risk for having a blood clot in the lung. In some cases, a blood test called a D-dimer may be additionally used to screen for the possibility of a clot. If patient historical factors and physical examination findings are negative, along with a negative D-dimer (if the physician chooses to order it), evidence shows that the risk of an undiagnosed blood clot is the same as if the patient had a negative CTPA. Such a strategy saves the risk of radiation, kidney injury and the high cost of a CTPA.

These items are provided solely for informational purposes and are not intended as a

www.choosingwisely.org/clinician-lists
WHO WILL TELL THE EMPEROR HE HAS NO CLOTHES?