When More May Be Less
The Lessons Learned from CTPA

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Learning Objectives

• To discuss the relevant literature concerning the evolution of CT to diagnose acute pulmonary embolism
• To list the evidence for overdiagnosis of pulmonary embolism using CT pulmonary angiography
• To highlight current trends in the treatment of acute PE
CT Angiography for PE

- First publication in 1992
- Rapid advances in technology over 20 years

Stein P. Pulmonary Embolism, Blackwell Futura 2007 Chapter 58, p.261
Diagnostic Performance of CTPA

• Based on studies mostly done with 4 detector CT or less and compared with suboptimal gold standard
• Reported sensitivities between 83-100% and specificities between 89-97%
• Outcome studies good

Outcome Studies of MDCTA for PE

• Meta-analysis of 15 studies
  – 3500 patients with negative CTPA
  – 3 month incidence of PE = 1-2.8%
  – Negative predictive value ≈ 99%

• Similar to conventional invasive pulmonary angiography

• Similar to V/Q scan

Quiroz et al. JAMA 2005; 293(16):2012-2017
Advantages of CTPA in Suspected PE

✓ Available
✓ Fast
✓ Alternative diagnosis in 11-85%
✓ Ancillary information
Background

- Normal function of pulmonary capillary bed to filter small clots formed in systemic venous circulation and protect the systemic circulation*
- Capillary endothelium has complete complement of fibrinolytic enzymes to break down clot without clinical effect*
- Incidental pulmonary emboli
  - >50% autopsies¹ in patients who died of other causes
  - 4% contrast-enhanced CTs²
  - 17% inpatient CTs > 80 yo³
  - 24% trauma CTs⁴

Growing evidence of overdiagnosis for CTPA

²Goodman LR. Radiol 2005;234(3):654-58
³Storto ML et al AJR 2005;184(1):264-67
⁵Schultz DJ et al. J Trauma 2004;56:727-31;discussion 731-33
Outline

- Overdiagnosis
- False positive diagnosis
- Limited negative studies
- Subsegmental PE management
Overdiagnosis

• Definition
  ✓ Diagnosis of clinically unimportant disease
• Does not mean diagnosis is WRONG
• CT frequently depicts “pathology” of uncertain significance
  ✓ Lung nodules, atherosclerosis, pancreatic, liver, adrenal and thyroid lesions
  ✓ Hence development of management guidelines
• Paradox of improved CT spatial and temporal resolution
Evidence for Overdiagnosis
Randomized Controlled Trial

• Anderson DR et al.  JAMA 2007
  – Randomized controlled trial comparing utility of CTPA and V/Q
  – Greater # of PE diagnosed with CTPA than V/Q
  – Rate of VTE at 3 months identical in untreated patients

Additional PE cases on CTPA clinically unimportant
Evidence for Overdiagnosis
Cohort Studies

- PE dx doubled over time without relationship to PE risk factors
- PE mortality stable
- No association between increased PE dx and mortality

Evidence for Overdiagnosis
Cohort Study: Time Trends in PE Diagnosis

72% increase in incidence of PE as primary diagnosis
No change in mortality
36% decrease in case fatality

National inpatient cause-of-death databases
Additional cases of PE may be associated with a lower severity of illness

Evidence for Overdiagnosis
Cohort Studies

- 2087 patients with PE dx at single urban center identified from hospital database and Social Security Death Index between 2000-2007

PE diagnosed with CTPA 50% less lethal than if Dx with V/Q (OR 0.54 CI 0.31-0.92)

Sheh SH et al. AJR 2012;198:1340-5
Evidence for Overdiagnosis
Meta-analysis

22 clinical trials

• Subsegmental PE (SSPE) diagnosis 4.7% for single vs 9.4% for MDCT
• False negative (FN) rate - 0.9% vs 1.1% respectively
• CTPA increases diagnosis of SSPE without change in FN rate → SSPE may not be clinically relevant

Carrier M et al. J Thromb Haemosst 2010;8:1716-1722
When a Test is Good

When a Test is Too Good

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Pulmonary Embolism per 100,000 US Adults</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>Effective Test</td>
<td>Nonfatal</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td>Nonfatal</td>
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<tr>
<td>Case-Fatality</td>
<td>Depressed</td>
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<tr>
<td>Mortality</td>
<td>Nonfatal</td>
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<tr>
<td>Apparent Incidence</td>
<td>Diagnosed PE</td>
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<tr>
<td>Apparent Incidence</td>
<td>Increased</td>
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<tr>
<td>Mortality</td>
<td>Decreased</td>
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<tr>
<td>Case-Fatality</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

More sensitive test detects more pulmonary emboli, and new cases benefit from treatment -> fewer deaths.

More sensitive test detects more pulmonary emboli, and new cases do not benefit from treatment (mild disease).

Outline

• Overdiagnosis
• False positive diagnosis
• Limited negative studies
• Subsegmental PE management
All Dots are not Clots
Evidence for False Positive CTPA

• PIOPED II\textsuperscript{1}
  • Positive predictive value for SSPE only 25%

  • 91 positive CTPA, 4 detector row CT
  • Retrospective review by three board certified radiologists
    and two 2\textsuperscript{nd} year residents
  • $k=0.38$; 95% CI, 0.0-0.89 for SSPE

\textsuperscript{1}Stein PD et al. NEJM 2006;354:2317-327
All Dots are Not Clots
Evidence for False Positive CTPA

  - 70 patients with SSPE on 64 detector CTPA
    » Academic center
    » Reviewed by one thoracic radiologist
    » $k=0.51$; 95% CI, 0.39-0.64
    » 11% false positive
All Dots are not Clots
Evidence for False Positive CTPA

• 728 positive CTPA interpreted by community radiologists retrospectively reviewed by 4 academic thoracic radiologists

• 27% of 177 SSPE indeterminate

• 15% of 177 SSPE false positive

• Most common cause of false positive study → breathing artifact (50%)

All Dots are not Clots
Evidence for False Positive CTPA

• 174 positive CTPA on 64 detector CT
  – Interpreted by mixed specialty radiologists in tertiary care university hospital
  – Reinterpreted by 3 thoracic radiologists with >10 years experience
  – Discordance in 25.9%
    • 26.8% segmental PE
    • 59.4% SSPE
  – Most common cause → breathing artifact (42.2%)

Hutchinson BD et al. AJR 2015;205:271-277
Outline

- Overdiagnosis
- False positive diagnosis
- Limited negative studies
- Subsegmental PE management
Impact of Limited Negative CTPA on Clinical Outcomes

Retrospective cohort study

• Definition of limited negative study
  – Report impression stated negative study but also stated limitation

• Primary outcome
  – 90-day incidence of VTE (false negative CTPA)

• Secondary outcome
  – Additional imaging
  – Initiation of anticoagulation
  – Bleeding complications

Yu S. et al. JAMA Intern Med 2015(3);447
Impact of Limited Negative CTPA on Clinical Outcomes

2553 CTPA for suspected PE
Baseline patient characteristics for limited negative similar to definitely negative vs. positive

Yu S. et al. JAMA Intern Med 2015(3);447
Impact of Limited Negative CTPA on Clinical Outcomes

- Primary outcome
  - 1.4 vs. 1.8% 90-day VTE for limited vs. definitely negative study

Yu S. et al. JAMA Intern Med 2015(3);447
Impact of Limited Negative CTPA on Clinical Outcomes

- Patients with limited negative CTPA have similar outcomes to definitely negative CTPA
- These patients receive more radiation and are more frequently anticoagulated
- Emphasis on study limitations may be detrimental

Yu S. et al. JAMA Intern Med 2015(3);447
Outline

• Overdiagnosis
• False positive diagnosis
• Limited negative studies
• Subsegmental PE management
Overdiagnosis and False Positive Studies Lead to Overtreatment

- Accepted practice to treat **ALL** patients with PE with anticoagulation
- Majority diagnosed with SSPE on CT **ARE** anticoagulated
- Majority with probable SSPE on V/Q (low or intermediate prob) **ARE NOT** anticoagulated

Donato AA et al. Thromb Res 2010;126:e266-70
Eyer BA et al. AJR 2005;184:623-38
Overtreatment May Lead to Harm

71% increase post-CTPA

Evidence for Safety of Withholding Anticoagulants for SSPE Based on Studies Using V/Q

- PIOPED I – 17% low prob V/Q had SSPE
- Prospective management cohort studies
  - Pts with low or intermed prob V/Q, low pre-test prob and negative serial leg vein U/S ➔ safe to withhold anticoagulation (recurrent VTE = 0.5%, same as pts with neg CTPA = 1.7%)
- We feel comfortable not treating patients with low or intermediate probability V/Q. Why not CTPA?

Perrier A et al. Lancet 1999;353:190-95
Evidence for Safety of Withholding Anticoagulants for SSPE using CTPA

Donato AA et al. 2010

- 93 patients with isolated subsegmental PE without DVT
- 3-month clinical outcomes (anticoagulation use, recurrence, death, hemorrhage)
  - 24% observed – no recurrent PE, no deaths
  - 76% treated – 5.3% major hemorrhage, no deaths

Donato AA et al. Thrombosis Research 2010;126 ;e266–e270
Isolated SSPE on CTPA Treatment vs. No Treatment

- Meta-analysis - over 60 patients
- 0% rate of recurrent VTE at 3 months
- 7% incidence of major bleeding on anticoagulants

SSPE: Who Not to Treat

- Adequate cardiopulmonary reserve
- No evidence of DVT
- Major risk factor for PE no longer present, i.e., surgery, trauma, and no continuing risk factor
- No history of central venous catheterization
- No history of atrial fibrillation
- Compliant and trustworthy patient who would return for serial noninvasive leg tests
What is the Future of SSPE Management?

Outcome Trial

• Prospective management cohort study (NCT01455818)
  – Canada, France, Switzerland
  – Anticoagulation withheld
    • Patients with SSPE diagnosis on CTPA
    • No DVT on serial leg vein ultrasound
What are the Guidelines Recommending?

• ACCP 2016
  • Isolated SSPE and no proximal DVT who have a low risk for recurrent VTE, we suggest clinical surveillance over anticoagulation (Grade 2C)

• European Society of Cardiology 2014
  • Individualized decision about anticoagulant therapy in patients with isolated SSPE and negative leg ultrasound

Komstantinides SV et al. Eur Heart J 2014;35:3033-73
Conclusion

- Development of MORE robust technology and overuse of this technology has resulted in LESS benefit to some patients as a result of overdiagnosis.
- Even with improved technology, FALSE POSITIVE diagnosis of small PE still common.
- Management of SSPE is changing.
What is the Radiologist’s Role?

- Recommend V/Q in patients with normal CXR?
- Double read limited negative scans or SSPE scans?
- SSPE diagnosis on CTPA only when certain
  - May recommend leg vein ultrasound in limited negative CTPA for added safety
- Limit comments about uncertainty about subsegmental PE in technically limited negative studies

“Placing the responsibility for overtreatment on the users rather than the providers of diagnostic information amputates the clinical importance and value of radiologists”

Jha S. Radiol 2014;270(2):628-29
Questions?

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