NEW DIAGNOSTIC TECHNIQUES FOR PULMONARY EMBOLISM

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MAGNITUDE OF THE PROBLEM

- Five million cases of venous thrombosis/year
- 10% of these will have a PE
- 10% will die
- Correct diagnosis is made in only 10-30% of cases
- Up to 60% of autopsies will show some evidence of past PE
ORIGIN

• 90-95% of pulmonary emboli originate in the deep venous system of the lower extremities
• Other rare locations include
  – Uterine and prostatic veins
  – Upper extremities
  – Renal veins
  – Right side of the heart

Risk Factors

• CHF
• Malignancy
• Obesity
• Estrogen/OCP
• Pregnancy (esp post partum)
• Lower ext injury
• Coagulopathy
• Venous Stasis
• Prior DVT
• Age > 70
• Prolonged Bed Rest
• Surgery requiring > 30 minutes general anesthesia
• Orthopedic Surgery
Virchow’s Triad

- Rudolf Virchow postulated >100 years ago that a triad of factors predisposed to venous thrombosis
  - Local trauma to the vessel wall
  - Hypercoagulability
  - Stasis of blood flow

- It is now felt that pts who suffer a PE have an underlying predisposition that remains silent until a acquired stressor occurs

Symptoms & signs of acute pulmonary embolism

- **Complaints**
  - Dyspnea 73 %
  - Pleuritic chest pain 66 %
  - Cough 37 %
  - Hemoptysis 13 %

- **Signs**
  - Tachypnea 70 %
  - Rales 51 %
  - Tachycardia 30 %
  - S4 24 %
  - Accentuated P2 23 %
  - Circulatory collapse 8 %
Differential Diagnosis

• PE is known as “the great masquerader”
• ACS, MI
• Pneumonia, bronchitis
• CHF
• Asthma
• Costochondritis, Rib Fx,
• Pneumothorax

• PE can coexist with other illnesses!!

DIAGNOSTIC TESTS

WHY???

• Since clinical presentation of PE is variable and nonspecific.

• thus, diagnostic testing is necessary before confirming or excluding the diagnosis of PE.
Routine laboratory findings

• Are nonspecific
• Include:
  – leukocytosis,
  – increased ESR
  – elevated serum LDH or AST (SGOT) with a normal serum bilirubin.

ECG

• ECG suggestive of PE
  – S1Q3T3 pattern,
  – right ventricular strain,
  – new incomplete RBBB
  – are infrequent during acute PE
• However, they are common in massive acute PE & cor pulmonale
• Presence of T-wave inversion in the precordial leads may correlate with RV dysfunction
ECG abnormalities associated with a poor prognosis

- Atrial arrhythmias
- Right bundle branch block
- Inferior Q-waves
- Precordial T-wave inversion and ST-segment changes

Arterial blood gas

- has a limited role
- usually reveal:
  - hypoxemia
  - hypocapnia
  - and respiratory alkalosis.
- Patients with room air pulse oximetry <95 % have increased risk of inhospital complications:
  - respiratory failure
  - cardiogenic shock
  - and death
Brain natriuretic peptide (BNP)

- typically greater in patients with PE compared to patients without PE
- Sensitivity 60% & specificity 62%
- These features limit its usefulness as a diagnostic test.

- The magnitude of the elevation of BNP or its precursor, N-terminal pro-brain natriuretic peptide (NT-proBNP), in patients with PE correlates with the risk of subsequent complications
- Suggesting that BNP and NT-proBNP may have a prognostic role in PE
Serum troponin I and troponin T

- Elevated in 30-50% of patients with a moderate to large PE
- Due to acute RV overload
- Resolve within 40 hours following pulmonary embolism (more prolonged elevation in AMI)
- Not useful for diagnosis
- But are associated with adverse outcomes (prognosis)

D-Dimer

- A specific fibrin degradation product released by a dissolving fibrin clot that can be measured in peripheral blood.
- ½ life of 6 hrs in population with normal renal function
- Non-invasive test
- Relatively low cost laboratory test vs imaging methods
- Aids in ruling out PE
  - High negative predictive value (95%-100%)
  - High sensitivity (90%-100%)
- Subsequent testing is required to rule in or rule out other conditions
D-dimer

- a degradation product of cross-linked fibrin
- in serum using a variety of assays
  - Enzyme-linked immunosorbent assay (ELISA) (>8 hrs)
  - Quantitative rapid ELISA (30 min)
  - Semi-quantitative rapid ELISA (10 min)
  - Qualitative rapid ELISA (10 min)
  - Quantitative latex agglutination assay (10 min)
  - Semi-quantitative latex agglutination assay (in 5 min)
  - Erythrocyte agglutination assay (SimpliRED) (in 2 min)
- >500 ng/mL is usually considered abnormal

Causes of increased D-dimer

1. Arterial thromboembolic disease
2. Myocardial infarction
3. Stroke
4. Acute limb ischemia
5. Atrial fibrillation
6. Intracardiac thrombus
7. Venous thromboembolic disease
8. Deep vein thrombosis
9. Pulmonary embolism
10. DIC
11. Preeclampsia and eclampsia
12. Abnormal fibrinolysis; use of thrombolytic agents
13. Cardiovascular disease, congestive failure
14. Severe infection/inflammation
15. Surgery/trauma
16. Systemic inflammatory response syndrome
17. Vasoocclusive episode of sickle cell disease
18. Severe liver disease (decreased clearance)
19. Malignancy
20. Renal disease
21. Nephrotic syndrome (eg, renal vein thrombosis)
22. Acute renal failure
23. Chronic renal failure and underlying cardiovascular disease
24. Normal pregnancy
25. Venous malformations
**Ventilation-perfusion scanning**

- It visualizes:
  - Ventilation (gas exchange) using Xenon 133
  - and perfusion using technetium 99m-labeled albumin aggregates.

**RESULTS:**

- High probability.
- Intermediate probability.
- Low probability

* Normal

**V/Q Scan**

- Useful if the results are normal or near normal, or if there is a high probability for PE
  - As many as 40% of pts with high clinical suspicion for PE and low probability scans have a PE on angiogram
High Probability V/Q Scan

This V/P scan demonstrates:
multiple segmental defects and normal ventilation in those areas
Lower extremity venous ultrasound

- **The rationale** is that venous thrombosis detected by ultrasound is treated similar to confirmed PE.
- **Limitations:**
  - False positive studies are common
  - False negative (29%)
Venous Ultrasonography

- Relies on loss of vein compressibility as the primary criterion
- About 1/3 of pts will have no imaging evidence of DVT
  - Clot may have already embolized
  - Clot present in the pelvic veins (U/S usually inadequate)
  - Workup for PE should continue even if dopplers (-) in a pt in which you have a high clinical suspicion

- **Color-flow Doppler imaging and compression ultrasonography have:**
  - a high sensitivity (89-100%)
  - and specificity (89-100%) for detection of proximal DVT in symptomatic patients. However, has a low sensitivity (38%) and a low positive predictive value (26%) in patients without symptoms of DVT.
  - Patients with positive findings for DVT can be anticoagulated
  - other patients must have more investigations performed to definitively rule out pulmonary embolism.
**Echocardiogram**

- Useful for rapid triage of pts
- Assess right and left ventricular function
- Diagnostic of PE if hemodynamics by echo are consistent with clinical hx

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**Echocardiography**

- has limited accuracy in the diagnosis of pulmonary embolism.
- TEE may identify central pulmonary embolism, with a sensitivity 82%.
- Overall sensitivity and specificity for central and peripheral pulmonary embolism is 59% and 77%.
- Echocardiography may demonstrate RV dysfunction in acute pulmonary embolism, predicting a higher mortality and possible benefit from thrombolytic therapy.
Pulmonary Angiogram

• Most specific test available for diagnosis of PE
• Can detect emboli as small as 1-2 mm
• Most useful when the clinical likelihood of PE differs substantially from the lung scan result or when the lung scan is intermediate probability

• Pulmonary angiography remains the criterion standard for the diagnosis of pulmonary embolism.
• Following injection of iodinated contrast, anteroposterior, lateral, and oblique studies are performed on each lung.
• Positive results consist of a filling defect or sharp cutoff of the affected artery.
• Nonocclusive emboli are described to have a tram-track appearance.
• Angiography generally is a safe procedure.
• Negative pulmonary angiogram findings, exclude clinically relevant pulmonary embolism.
PULMONARY CTA
• CT angiography (CTA) is the initial imaging modality of choice for stable patients with suspected pulmonary embolism.

• The ACR considers chest CTA the current standard of care for the detection of pulmonary embolism.

• In patients with a negative CTA, the likelihood for subsequent thromboembolic events is extremely small.

• CTA can visualize:
  – main
  – Lobar
  – and segmental pulmonary emboli

• sensitivity >90%.

• CTA can detect emboli as small as 2 mm affecting up to the 7th division of pulmonary artery.

• CTA results may suggest an alternative diagnosis in up to 57% of patients.

• Limitation of CTA: small subsegmental emboli may not be detected.
MSCT Pulmonary

- Sensitivity 90-100%
- Specificity 89-94% for detection of PE
- down to the level of subsegmental arteries.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td>Specificity</td>
<td>Reader expertise required</td>
</tr>
<tr>
<td>Availability</td>
<td>Expense</td>
</tr>
<tr>
<td>Safety</td>
<td>Not portable</td>
</tr>
<tr>
<td>Relative rapidity of procedure</td>
<td>Need contrast bolus comparable to angiogram</td>
</tr>
<tr>
<td>Diagnosis of other disease entities</td>
<td>Poor visualization of certain regions</td>
</tr>
<tr>
<td>Retrospective reconstructions</td>
<td>Contraindications</td>
</tr>
<tr>
<td>Advancing technology</td>
<td>Contrast allergy</td>
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</tbody>
</table>
CT revealing pulmonary infarct

CT revealing emboli in pulmonary artery.
Perfusion CT

- Thin slice MSCT Pulmonary artery
- Quantitative maps of pulmonary arterial perfusion with custom-made software (basama Perfusion; [http://www.basama.net/perfusion/index.htm](http://www.basama.net/perfusion/index.htm))
- Also quantifies the amount of blood flow.
CT shows thromboembolic material in the right pulmonary artery.

Perfusion CT image clearly shows perfusion deficit of the right lower lobe.

. SPECT using Tc-99m-macroaggregated albumin (MAA) shows perfusion deficit of the right lower lobe.

Perfusion CT image shows perfusion deficit of the right lower lobe. LLung 1.24 ml/min/ml, & R Lower lobe s 0.10 ml/min/ml.
Magnetic resonance imaging

- evidence of PE may be detected by using standard or gated spin-echo techniques.
- Pulmonary emboli demonstrate increased signal intensity within the pulmonary artery.
- MRA is performed following intravenous administration of gadolinium.
- MRI has a sensitivity of 85% and specificity of 96% for central, lobar, and segmental emboli.
- MRI is inadequate for the diagnosis of subsegmental emboli.

PULMONARY EMBOLISM ???
Clinical Probability Score

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Symptoms and signs of deep vein thrombosis</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Recent immobilization or surgery (&gt;4 wk)</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous deep vein thrombosis or pulmonary embolism</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemophagia</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.0</td>
</tr>
<tr>
<td>Pulmonary embolism more likely than alternative diagnosis</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Low score (<2.0) or intermediate score (2.0–6.0) → d-Dimer assay (highly sensitive) → Positive → Multidetector CT → No pulmonary embolism/Pulmonary embolism confirmed → Do not treat/Treat

High score (>6.0) → Multidetector CT → No pulmonary embolism/Pulmonary embolism confirmed → Do not treat/Treat

CT immediately available?

No → Echocardiography → Direct or indirect signs of pulmonary embolism → Search for another cause of hypotension or shock

Yes → Multidetector CT → Positive → Consider immediate thrombolysis or embolectomy → Search for another cause of hypotension or shock

Negative → Search for another cause of hypotension or shock
Imaging Pregnant Patients with Suspected Pulmonary Embolism: What the Radiologist Needs to Know

Radiographics May-June 2009 29:639-654;

- Pregnancy is associated with a 5X increase in the prevalence of venous thromboembolism,
- PE is a leading cause of maternal death.
- Diagnosis of PE during pregnancy is challenging.
- Concerns about exposure of the fetus & IV administered contrast material, as well as potential medicolegal issues.
- Although diagnostic imaging plays an important role there are no widely accepted guidelines.
- Radiologists should know advantages & disadvantages of imaging modalities, methods for dose reduction, radiation risks, medicolegal risk and management guidelines.
Flowchart shows use of quantitative rapid D-dimer ELISA in combination with clinical assessment.

Stein P D et al. Radiology 2007;242:15-21

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Low Probability Clinical Assessment
Positive D-dimer Rapid ELISA

CT Angiography or
CT Angiography/CT Venography

CT Angiogram Negative, NPV 96%
CT Angiogram/CT Venogram
Negative, NPV 97%

No Treatment

CT Angiogram Positive, PPV 58%
CT Angiogram/CT Venogram
Positive, PPV 57%

Segmental PPV 68%
Subsegmental PPV 25%

Options:
• Repeat CT Angiogram or CT Angiogram/CT Venogram if Poor Quality
• If CT Angiography only, Ultrasound or MRI Venography
• Pulmonary Scintigraphy
• Digital Subtraction Angiography
• Serial Ultrasound

Main or Lobar Pulmonary Embolism
PPV 97%

Treat

Suspect Pulmonary Embolism

Clinical Low or Moderate

D-Dimer Rapid ELISA
Negative
No Treatment

Clinical High

D-Dimer Rapid ELISA
Positive
Further Tests

Further Tests

Radiology
**Moderate Probability Clinical Assessment**
Positive D-dimer Rapid ELISA

- CT Angiography or
- CT Angiography/CT Venography

- CT Angiogram Negative, NPV 89%
- CT Angiogram/CT Venogram Negative, NPV 92%
  - No Treatment
  - Option if
  - CT Angiography only,
  - Ultrasound or MRI Venography

- CT Angiogram Positive, PPV 92%
- CT Angiogram/CT Venogram Positive, PPV 90%
  - Treat

**High Probability Clinical Assessment**

- CT Angiography or
- CT Angiography/CT Venography

- CT Angiogram Negative, NPV 60%
- CT Angiogram/CT Venogram Negative, NPV 82%

- CT Angiogram Positive, PPV 96%
- CT Angiogram/CT Venogram Positive, PPV 96%
  - Treat

Options:
- Repeat CT Angiogram or CT Angiogram/CT Venogram if Poor Quality
- If CT Angiography only, Ultrasound or MRI Venography
- Pulmonary Scintigraphy
- Digital Subtraction Angiography
- Serial Ultrasound
Other conditions elevating D-Dimer

- Age
- Coronary disease
- Pregnancy
- Peripheral arteriopathy
- Bleeding disorders
- Thrombolytic treatment
- Cancer
- Liver disease
- Infection
- Inflammation
- Hematoma

Diagnosis

- Serum Studies
  - D-dimer
    - Elevated in more than 90% of pts with PE
    - Reflects breakdown of plasmin and endogenous thrombolysis
    - Not specific: Can also be elevated in MI, sepsis, or almost any systemic illness
    - Negative predictive value
  - ABG—contrary to classic teaching, arterial blood gases lack diagnostic utility for PE
A-a Gradient

– Alveolar arterial oxygen gradient
– $148-1.2(PaCO_2) - PaO_2$
– Gradient > 15-20 is considered abnormal.
– Done at Room air.

Diagnosis

• CXR
  – Usually reveals a non specific abnormality. 14% normal
  – Classic abnormalities include:
    • Westermark’s Sign - focal oligemia
    • Hampton’s Hump - wedge shaped density
      – Enlarged Right Descending Pulmonary Artery (Palla’s sign)
PE which appears like a mass.

PE with hemorrhage or pulmonary edema
Imaging Pregnant Patients with Suspected Pulmonary Embolism: What the Radiologist Needs to Know

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ABSTRACT

Pregnancy is associated with a fivefold increase in the prevalence of venous thromboembolism, and pulmonary embolism is a leading cause of maternal death. However, the diagnosis of pulmonary embolism during pregnancy is challenging because classic clinical symptoms are often absent and physiologic changes during pregnancy can mimic pulmonary embolism. Concerns about exposure of the fetus to ionizing radiation and intravenously administered contrast material, as well as potential

PE with effusion and elevated diaphragm
**Objective**

We sought to determine whether the magnitude of the d-dimer correlates with a higher likelihood of a pulmonary embolus (PE).

**Methods**

- An electronic chart review was performed at an academic, tertiary care center with an annual ED census of over 100,000 patients and a 3-year residency program.
- All patients with a chest CT scan with

<table>
<thead>
<tr>
<th>D-dimer Level</th>
<th>N</th>
<th>PE Dx (%)</th>
</tr>
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<tbody>
<tr>
<td>0-0.58</td>
<td>182</td>
<td>8 (4.4%)</td>
</tr>
<tr>
<td>0.58-1.0</td>
<td>194</td>
<td>9 (4.6%)</td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>188</td>
<td>23 (12.2%)</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>177</td>
<td>22 (12.2%)</td>
</tr>
<tr>
<td>5.0-20</td>
<td>34</td>
<td>21 (53.3%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>11</td>
<td>5 (45.5%)</td>
</tr>
</tbody>
</table>

**Results**

- 726 subjects (27% male; mean age 52.0 years) were identified over 7.5 years that had both a chest CT scan performed and a d-dimer level obtained in the ED.
- 79 subjects (10.9%; mean d-dimer 3.99) were diagnosed with PE and 747 (89%; mean d-dimer 1.57) did not have a PE.
- The positive predictive value (PPV) of pulmonary embolus for d-dimer level cutoffs of 0.58: 1.0, 2.0, 5.0.

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**Modified Wells criteria: clinical assessment for pulmonary embolism**

| Clinical symptoms of DVT (leg swelling, pain with palpation) | 3.0 |
| Other diagnosis less likely than pulmonary embolism          | 3.0 |
| Heart rate >100                                              | 1.5 |
| Immobilization (23 days) or surgery in the previous four weeks| 1.5 |
| Previous DVT/PE                                              | 1.5 |
| Hemoptysis                                                   | 1.0 |
| Malignancy                                                   | 1.0 |

**Probability**

<table>
<thead>
<tr>
<th>Traditional clinical probability assessment</th>
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<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Simplified clinical probability assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>PE likely</td>
</tr>
<tr>
<td>PE unlikely</td>
</tr>
</tbody>
</table>

*Data from van Belle, A, et al. JAMA 2006; 295:172*