Controversies in Venous Thromboembolism

Anil Chopra
University Health Network
University of Toronto

Disclosures

Participant in several advisory boards and have received unrestricted education and research grants at UHN:

- Leo, BI, Roche, Sanofi Aventis, Bayer, Janssen, Pfizer, Purdue, Octapharma, CSL Behring

Some Facts…

- Less than 15% pts investigated for DVT or PE in EDs in Canada have the disease
- >50% pts with confirmed DVT have silent PE
- Missed PE: more than half of these pts have subsequent PE (half within a week)

JAMA, 1994:271:223
Thromb Haemost, 2001:86:452

Objectives

- Discuss some controversial issues in the investigation of VTE
- Discuss some controversial issues in the management of VTE

Risk Stratification

- Is clinical judgment as good as the validated clinical instruments?
- Maybe! Experienced ED physicians perform similarly to objective criteria
- Younger, less experienced ED docs tend to underestimate or overestimate risk of DVT or PE (bias)

ACEP Guidelines 2011

VTE Exclusion

- Risk Stratify — Clinical / Validated Tool
- Objective Test

(Sanson,Thromb Haemost 83:199,2000)

Probability and Risk: VTE

- Low Risk: ≤ 1/20 have the disease
- High Risk: ≥ 2/3 have the disease

"PERC Rule"

- "PE Research Consortium" Rule
- Based on a huge data bank by Jeff Kline
- Retrospective "validation" in four academic centres
- Recent prospective validation
- Threshold risk of disease < 2%

Am J EM, 2008:26:181
J Throm Hemast, 2004:2:1247

"PERC Rule"

Eight Criteria
- Age < 50
- Pulse <100
- O2 sats > 94% R/A
- No unilateral leg swelling
- No hemoptysis
- No recent trauma or surgery
- No prior VTE
- No hormone use

→ 1.4% risk of PE

PERC Rule

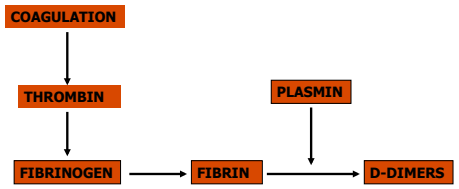
- How can I defend not doing a work-up for PE on low risk patients?
- Is it possible to use clinical criteria to safely rule out PE at the bedside?
- Prevalence of PE in Canadian emerg population investigated < 10 %

D-dimer or D-dummer?

- European studies by Perrier indicate 1/3 of D-dimers negative if all emerg patients investigated for PE had D-dimer (ELISA)
- A positive D-dimer tends to encourage "overinvestigation" of patients

Perrier, Amer J Med, 2004:116:291

D-dimer fragments



D-dimer

Questions

- Should you use the D-dimer as your first test in **all** patients?
- What is the likelihood of it being negative?
- Do you know what type of D-dimer that you have at your hospital?

Diagnosis of VTE: D-dimer

Which D-dimer do you have?

- Latex agglutination
- SimpliRED
- ELISA
- Immunoturbidimetric test

Diagnosis of VTE: D-dimer

- Only useful if negative
- ↑age, pregnancy, surgery, hemorrhage, trauma, malignancy, infection, MI, CVA, CVD, etc.
- First generation latex agglutination not useful (sens < 80%)

STH,2000:26:643-655

D-dimer Testing

- Reliable tests (quantitative):
  - High sensitivity (> 95%)
  - Very high NPV (> 99%)
  - Rapid ELISA (eg. Vidas)
  - Immunoturbidimetric
- Recommended as first test only in non-high risk group
- *Qualitative D-dimer (eg. SimpliRED) shown reliable in low risk patients only (85% sens)

Ann Emerg Med,2003;41:257
Thorax,2003:58:470

Why not D-dimer for everyone?

- 2/3 tests positive: increased costs, particularly with extensive further testing
- Risk of missing VTE in high risk patients
- Lack of detection of alternative disease (Baker's cyst on U/S, mass on CT, etc.)

Why not image everyone?

- Cost: - cheaper if D-dimer only test done
- Availability at off hours
- V/Q: 2/3 results inconclusive, time consuming
- CT: - can miss small, peripheral clots
  - dye effects, radiation
- Angio: morbidity, mortality
- MRI: not readily available

Case 1

- Pregnant pt with pleuritic CP
- Is D-dimer useful?

- Prevalence of VTE in these patients is 10%
  - For PE, only about 5% !

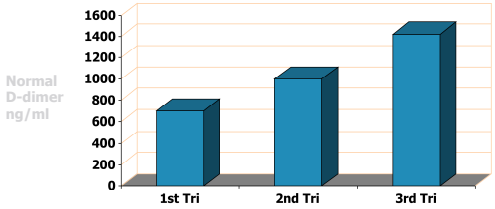
Diagnosis of PE in Pregnancy

D-dimer

- Using variable cutoffs for each trimester is unproven and fraught with error
- NPV in low risk pts nearly 100%
- ATS 2011 guidelines based on "weak evidence, very low quality evidence": don't use D-dimer
- ATS recommendations based on review of pooled data from all three trimesters and desire to avoid additional costs and delays in Dx

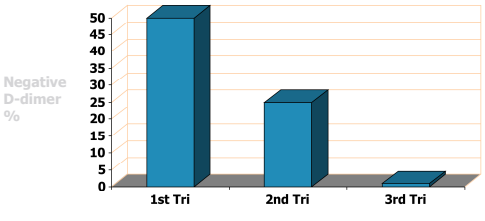
STH,2000:26:643
AJRCCM 2011:184:1200

D-Dimer in Pregnancy



ELISA cutoff = 500 ng/ml

D-Dimer in Pregnancy



Hernandez, Acad Em Med, 11:5:2004

Imaging and Radiation Dose

	Fetal (mGy)	Maternal (mSv)
CXR	0.002	0.1
V/Q	0.32 -0.74	1-2.5
CTPA	0.03-0.66	4-18
DSA	-	7-28

AJRCCM 2011:184:1200

V/Q Scanning in pregnancy

- If CXR normal: diagnostic in 94%
- If CXR abnormal: diagnostic in 40%
- Nearly 100% NPV
- No ability to diagnose alternative pathology

V/Q Scanning in pregnancy

- Only perfusion scan with low dose (half dose of Tc labeled albumin)
- Normal perfusion scan excludes PE
- Abnormal perfusion scan requires addition of ventilation scan (Tc or Xenon)
- Exposure related to radioactivity excreted into the maternal bladder: hydration and frequent urination (Foley)

CT Scan in Pregnancy

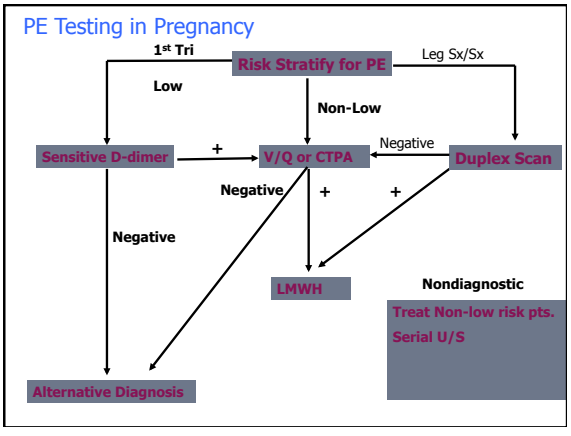
- Low dose protocol preferred with no loss of sensitivity
- NPV near 100%
- 12-13% have alternative diagnosis:
  - Pneumonia
  - Pulmonary Edema

MRI in Pregnancy

- No studies
- MRPA relatively contraindicated: unknown long-term effects of gadolinium on fetus
- Nonpregnant patients:
  - Sensitivity only 78%
  - 25% inadequate studies

Duplex not recommended

- Prevalence of PE in pregnant patients tested
  = 5%
- If 1/3 have positive Duplex, # of + scans per 100
  = 1 to 2
- Unless patient has signs/symptoms of DVT:
  = 5-10 % positive scans
  (highest yield in first trimester)



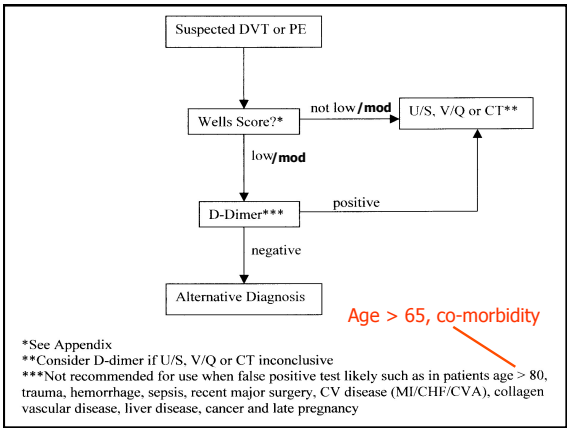
Very low negative D-dimer rate with increasing age …

- Age 80: 5-10% negative
- Age <40: 60% negative

Righini,J Am Geriatr Soc,2005:53:1039

Reasonable use of D-dimer

- Young patients
- Low risk patients without comorbidity
- 1st trimester pregnancy
- Following inconclusive tests (eg. nondiagnostic V/Q in patient with contrast allergy)



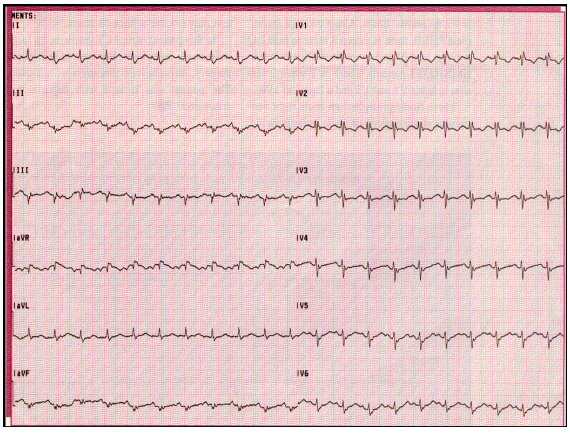
Case 2

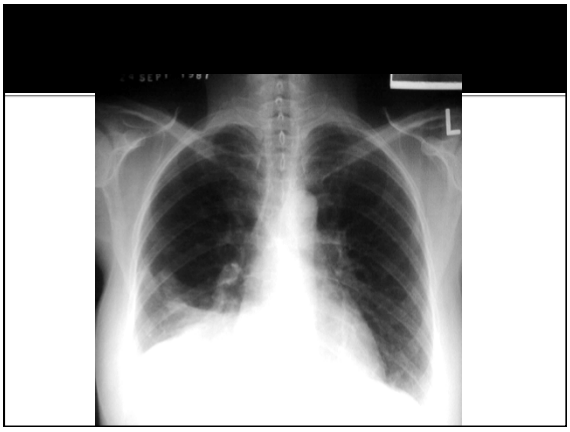
- 29 y.o. healthy female on OCP with unexplained pleuritic chest pain

A negative, sensitive D-dimer excludes PE
(less than 1/100 chance of missing this disease)

Case 3

- 72 y.o. male with recent back surgery with unexplained dyspnoea
- Noted to be tachycardia, tachypnoea, hypertensive with O2 sats 95% on R/A





Which Test to Choose?

? PE

V/Q scan or Spiral CT

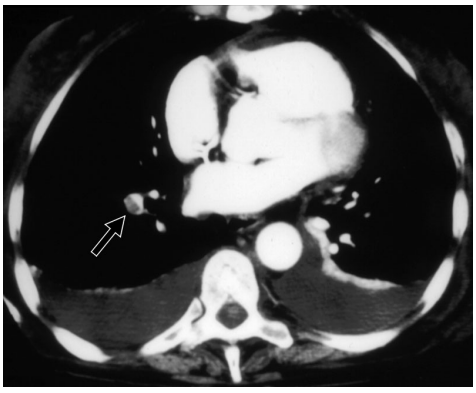
Choose V/Q Scan	Choose Spiral CT
1. Normal CXR	1. Abnormal CXR
2. Otherwise healthy	2. Respiratory disease
3. Renal Insufficiency	3. Critical care patient
4. Contrast allergy	4. Suspect massive PE

Diagnosis of PE: V/Q Scan

Advantages	Disadvantages
Availability	Majority inconclusive (60%)
No Contrast	Time consuming (2 hours)
Considerable experience	No alternative diagnosis

Case 3

- Wells: intermediate prob (>20%)
- D-dimer most likely to be positive
- V/Q unlikely to be normal (10% high) and unable to give alternative etiology
- CT chest best initial test if creatinine not significantly elevated



Diagnosis of PE: CT

Benefits

- Direct visualization of clot or alternative Dx (25%)
- MDCT: nearly 100% sensitive for central clots and >90% for all clots (NPV 99%)
- High specificity: >91%
- Useful in pts with significant lung disease (COPD, fibrosis, metastases)
- Cheaper than V/Q scan
- < 10% nondiagnostic (vs. 60% for V/Q)

JAMA,2005:293:2012
Int Med,2003:307,322

Controversies in the Management of DVT and PE

When to treat calf DVTs

- Extend proximally 20% of time
- Extension usually within a week
- Nonextending calf DVT rarely causes PE

- Always treat if high risk of extension:
  - Previous VTE
  - Persistent immobility
  - Persistent hypercoagulable state

Below Knee DVT

- RCT of 51 isolated calf thromboses
- 23 pts treated for 3mons with heparin and warfarin (INR 2.5-4.2) and stockings
- 28 pts treated heparin (few days) and stockings
- Outcomes: recurrence, extension and PE at 3 mons and 1 yr

Lagerstedt et al LANCET 1985

Outcomes

WARFARIN	NO TREATMENT
At 3 mons: 0% recurrences, extensions or PE	At 3 mons: 29% (8/28)
At 1 yr: 1/23 pts had a recurrence	8 recurrences including 5 extensions and 1 PE
	•At 1 yr: 9/29 had a recurrence

Lagerstedt et al LANCET 1985

ACCP Guidelines

- ACCP recommend treatment of symptomatic isolated calf DVT with anticoagulation
- Authors felt preventing recurrent thromboembolic events more important than bleeding or cost

Chest 2008: 133

LMWH

What dose in the very obese patient?

dalteparin:	200 u/kg sc ?max 18,000 U
enoxaparin:	1.5 mg/kg sc ?max 180 mg
tinzaparin:	175 u/kg sc ?max 18,000 U

LMWH for very obese patients

- clinics routinely exceed upper limits:
  30-32,000 Unit maximum (180 Kg)
- option to divide up the dosing into bid for enoxaparin and dalteparin
  eg. up to enoxaparin 150 mg sc bid
- measure anti-Xa levels 4-6 hrs post dose
  (0.7 – 1.0 IU/ml)

Hainer,Throm Haemost, 2002:87:817

LMWH

What to do with dischargeable patients with elevated creatinine?

- Admit
- use tinzaparin as least affected by poor renal function (?half dosage if CrCl < 30)
- UFH 5,000 U iv bolus, then 17,500 U bid sc and follow heparin level
- UFH 333 U/kg sc, then 250U/kg sc q12h

Kearon,JAMA,2006:296:935
Buller,Chest,2004:126:401s

New Oral Anticoagulants

- Dabigatran (Pradax): direct thrombi inhibitor (DTI)
- Rivaroxaban (Xarelto): anti-Xa
- Apixaban (Eliquis): anti-Xa