Two Great Tests for Shortness of Breath: BNP & D-Dimer

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Objectives

• Explain why different reference limits should be used for BNP/NTproBNP in the ER

• Define the situations in which D-Dimer should be used in the Emergency Room

• List 2 benefits of offering D-Dimer testing in the ER

COPD, Pneumonia, or CHF?

A 65 year old man arrives at the Emergency Room because of worsening shortness of breath over the past week.

Two weeks ago, he had a URI, with a mild fever, but he seemed to recover from that. His history is notable for smoking 1 pack of cigarettes a day for the past 30 years.

His physical examination is unremarkable, except for some mild wheezing in his right lung fields.

Among several blood tests ordered, his NTproBNP returns with a value of 600 pg/mL (reference interval <125 pg/mL).
Role of Natriuretic Peptides

- In Congestive Heart Failure (CHF), the pumping action of the heart is compromised, and the heart expands.
- In addition, the body retains additional sodium, which can result in fluid accumulating in tissues (legs, lungs).
- The stretching of the heart muscle not only helps the pumping action (Starlings Law) but also results in secretion of natriuretic peptides, which increase urinary sodium excretion.
- A balancing act.

Nomenclature of Natriuretic Peptide

- Atrial Natriuretic Peptide (ANP)
  - discovered first; isolated from atria of heart
- Brain Natriuretic Peptide (BNP)
  - isolated from brain; hence the name
  - later, isolated from ventricles of heart, too
  - more stable than ANP, easier to measure
  - re-named "B-Type Natriuretic Peptide"
- "Metabolism of BNP"
  - with stretch, heart muscle cells release proBNP, which is cleaved into NT-proBNP and BNP in equimolar amounts.

"Metabolism" of BNP

- preproBNP (134 aa)
  - proBNP (108 aa)
    - signal peptide (26 aa)
      - myocyte
      - secretion
      - NT-proBNP (1-76) (Inactive)
      - BNP (77-108) (Active)
    - vascular lumen
    - T1/2=90 min
    - T1/2=18 min
    - Vasodilatation, natriuresis
A Superb Lab Test

The New England Journal of Medicine


NTproBNP Performance in CHF
(Roche Package Insert Data)

Bottom Line: Excellent Negative Predictive Value
i.e., can be used to rule out CHF reliably

NTproBNP Performance in CHF
(Roche Package Insert Data)

Bottom Line: Loose Association with NYHA Class
Implications for Use in ED?
Other Uses for BNP/NT-ProBNP

- A few related clinical issues
- Natrecor™ Infusion Clinics™ controversy
- Screening for CHF?
- Can these assays be used to distinguish TRALI from TACO?
Additional Issues Related to Natriuretic Peptides

• Renal insufficiency
  – may cause mild elevations, but not to levels used in ED

• Frequency of measurement
  – Not more than once per week - This is not like troponin or CK-MB

• What constitutes a significant change?
  – CV of <10%
  – Intra-individual differences much larger
  – Probably require 2-fold change to be significant

2005 Controversy – Infusion Clinics

The fact that NTproBNP could distinguish between endogenous secretion and infused BNP was little comfort.

CHF: A Serious Disease

• 5 year mortality comparable to many cancers!

• increasing in prevalence because of advances in treatment of MI’s

• Therapies are available to improve outcomes, especially if initiated early

• Diagnosis by physical exam is poor

• Screening with cardiac ultrasound is expensive
Screening for CHF with BNP?

McDonagh TA et al. Lancet 1998;351:9-13

Pulmonary Edema With RBC Transfusion

TRALI: Transfusion Related Acute Lung Injury
- cause: antibodies to HLA antigens in donor blood
- fluid therapy helps
- diuretics hurt
- mortality: 5%
- test donor for HLA antibodies

TACO: Transfusion Associated Circulatory Overload
- cause: volume overload in patients with CHF
- fluids help
- diuretics hurt
- additional transfusions to be administered slowly
- no consequences for donor

some data to suggest that TRALI is much more likely if BNP is low or increases <50% over baseline

COPD, Pneumonia, or CHF?

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Two weeks ago, he had a URI, with a mild fever, but he seemed to recover from that. His history is notable for smoking 1 pack of cigarettes a day for the past 30 years.

His physical examination is unremarkable, except for some mild wheezing in his right lung fields.

Among several blood tests ordered, his NTproBNP returns with a value of 600 pg/mL (reference interval <125 pg/mL).

Even though this NTproBNP is elevated (indicating the patient may have mild CHF), it is not high enough to account for his shortness of breath at rest.

Other causes are more likely.
Is It or Isn’t PE/DVT?

A 28 year old woman arrives at the Emergency Room with acute shortness of breath occurring just after arriving in Philadelphia after an overnight flight from Europe.

She is a very healthy individual, who sees her primary care physician annually. Of note, she takes oral contraceptives.

His physical examination is unremarkable, except for some mild wheezing in his right lung fields.

Among several blood tests ordered, her D-Dimer value is reported as 250 ng/mL (reference interval <500).

Understanding What D-Dimer Is

These molecules do **not** originate from clot

Heterogeneous collection of molecules occurring in differing combinations

[Diagram: Generation of D-dimer from cross-linked fibrin]

http://ahdc.vet.cornell.edu/coag/test/D-dimer.gif
Similarities to Bone Turnover Markers

- In the old days, bone resorption markers included calcium, phosphate, collagen, etc., none of which were specific for bone destruction. In that sense, they were like FDPs.

  Telopeptides are the like the “D-Dimer” of bone, in that they can form only after bone is destroyed.

- There may be more on this topic later in the course.

- Also, note that alkaline phosphatase is a marker of bone formation.

A Typical Immunoturbidimetric Assay

“Wells Criteria” & PE/DVT

Derivation of a Simple Clinical Model to Categorize Patients Probability of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Wells Criteria</th>
<th>PE/DVT</th>
</tr>
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<tbody>
<tr>
<td>Risk Factors</td>
<td>Score</td>
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<tr>
<td>Female</td>
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<tr>
<td>Male</td>
<td>0</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>2</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>1</td>
</tr>
<tr>
<td>History of DVT</td>
<td>2</td>
</tr>
<tr>
<td>History of MI</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
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<table>
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<tr>
<th>Wells Criteria</th>
<th>PE/DVT</th>
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<tbody>
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<td>Score</td>
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<tr>
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<tr>
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<td>Intermediate</td>
</tr>
<tr>
<td>5-7</td>
<td>High</td>
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</table>
The D-Dimer assay should NOT be used to exclude venous thromboembolism (VTE) in hospitalized patients since they often have co-morbid diseases associated with elevated D-Dimer levels. Doing so will lead to false positive results and prompt further unnecessary testing.

The current literature only supports the use of this assay to exclude VTE among outpatients with a LOW PRETEST PROBABILITY of disease who are being evaluated in the Emergency Department or Ambulatory setting.

**BIDMC OnLine Lab Manual: D-Dimer**

Cross-linked fibrin degradation product generated by lysis of fibrin (and not fibrinogen).

**BIDMC Implementation**

"High Sensitivity" Assay <500 ng FEU/mL

**BIDMC Experience**

(Sanchez L et al Acad Emerg Med 2011:18:317-321)

- 6-month study, encompassing 25,917 ED visits
- 859 D-Dimers ordered (565 females, 294 males)
  - 346 < 500 ng/mL → discharged without imaging
  - 219 > 500 ng/mL
    - 187 had imaging
    - 17 (9.1%) had PE
- effects on resource utilization
  (compared to previous high sensitivity D-Dimer assay)
  - decreased ED length of stay by 45 minutes
  - decreased radiation exposure (CTAs decreased 16%)
  - higher yield (4.2% to 9.1%), same number of positives
"High Sensitivity": An Increasingly Used Term

- Implies greater precision at low concentrations
- Assays affected:
  - CRP vs hs-CRP
  - 3rd generation TSH
  - D-Dimer
- Original D-Dimer assays
  - used in DIC (disseminated intravascular coagulation)
  - designed to detect very high levels
  - cannot be used to categorize values for DVT/PE
  - check your package insert to be sure it’s approved for use in DVT/PE

Units: Not As Easy As You’d Think

- email from a colleague working in the Emergency Room at a different hospital in our “network”:
  “How should I interpret a value of 350 ng/mL?”
- lab report indicates values >237 ng/mL are abnormal, but he’s used to our assay with a threshold of 500 ng/mL
- 2 units (both, unfortunately, in ng/mL):
  - Fibrinogen Equivalent Units (FEU)
  - D-Dimer Units (DDU)
  - 1 DDU ~ 2 FEU, so the threshold are equivalent
  - most labs use FEUs for DVT/PE

CAP Accreditation Checklist
Final Words on D-Dimer

• Use D-Dimer to rule out DVT/PE only when suspicion is low (Wells criteria)

• If suspicion is moderate or high, imaging is absolutely "necessary", regardless of D-Dimer result

• Make sure the D-Dimer assay is high sensitivity and that you know which units are used

Is It or Isn’t PE/DVT?

A 28 year old woman arrives at the Emergency Room with acute shortness of breath occurring just after arriving in Philadelphia after an overnight flight from Europe.

She is physically fit.

This patient has a low Wells score, so it was totally appropriate to order the D-Dimer.

The value is below 500 FEU ng/mL.

She does not need an imaging study and can be safely discharged home.

Among several blood tests ordered, her D-Dimer value is reported as 250 ng/mL (reference interval <500).

Final Words on Shortness of Breath in the ED

• BNP (or NTproBNP) and D-Dimer are superb tests, among the best assays in Clinical Chemistry

• They are used daily by Emergency Department physicians across the country to make critical decisions about their patients
Self-Assessment Question 1

Why should higher thresholds be used for BNP (and NTproBNP) in ER patients with shortness of breath than for diagnosing CHF?

A) COPD causes shortness of breath
B) ER patients are older
C) CHF can exist without shortness of breath
D) Anxiety can raise BNP (and NTproBNP) levels

Self-Assessment Question 2

Which of the following patients can be screened with D-Dimer levels as a means of ruling out DVT or PE?

A) A hospitalized patient
B) A patient with history of DVT and heart rate > 100
C) A patient with a swollen, tender leg
D) A patient on chemotherapy for breast cancer

Self-Assessment Question 3

Which of the following is an advantage of offering D-Dimer testing in the Emergency Room?

A) Increased numbers of patients admitted to hospitals for thorough examinations
B) Decreased numbers of patients exposed to radiation
C) Increased revenue to radiologists for performing CTAs
D) No need for physicians to carefully evaluate patients