Don't Always Depend on Your D-dimer: An Atypical Case of Pulmonary Embolism

Willhite, Sydney; Betts, Aislinn; Lee, Maya; Juloori, Sangeeta, MD
Indiana University School of Medicine; Indianapolis, Indiana

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

ABSTRACT

Case: A 35-year-old female patient, with current IV drug use and a history of endocarditis warranting tricuspid valve replacement, presented with dyspnea and chest pain. On physical exam, she was found to have scattered wheezes on expiration with no shortness of breath or lower extremity (LE) edema. As the Wells' score for pulmonary embolism (PE) revealed a moderate risk, CTA and D-dimer were obtained. CTA revealed low contrast uptake in the right pulmonary artery, most concerning for a PE. D-dimer and coagulation studies were normal, making deep vein thrombosis (DVT) unlikely and PE questionable. Therefore, there was high suspicion for endocarditis with septic emboli. On day two, transesophageal echocardiogram showed no valvular vegetations or thrombus. With no evidence of endocarditis, DVT was reconsidered. Bilateral LE doppler ultrasounds were negative for DVT. However, a repeat D-dimer was found to be elevated (596 ng/mL). Clinical impression on day three was a PE secondary to a small upper extremity venous thrombosis from IV drug use.

Conclusions: IV drug use is recognized as a risk factor for SVT and DVT due to endothelial damage of injected veins and/or increased coagulation factors. As a LE DVT was ruled out through ultrasound, this patient likely had an UE thrombus with a secondary PE. However, her low D-dimer in the setting of a PE is puzzling considering the test's high sensitivity (95%). Given that her subsequent D-dimer was elevated, this suggests that the initial test may have been inaccurate.

Clinical Significance: D-dimer is considered to be a useful test to rule out DVT and PE in cases of low or moderate probability. However, a few reasons for false-normal D-dimer have been elicited: small emboli, anticoagulant pretreatment, and symptoms ongoing for ≥ 10 days. In this case with moderate probability, the initial falsely low D-dimer decreased suspicion for thrombosis and was most likely due to small emboli. Therefore, the causes of false-normal D-dimer must be well known and considered in order to avoid misdiagnosis.

BACKGROUND

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a leading cause of morbidity and mortality within hospitalized populations.[1] With a reported incidence rate of 29 to 78 per 100,000 person-years,[2] it is clear that occurrence of VTE is burdensome to hospitalizations and the healthcare system.

Intravenous (IV) drug users are known to be at an increased risk for occurance of DVT. It is not clear if IV drug usage predisposes patients to increased risk of specific types of clotting events. However, the likely mechanism for increased incidence of DVTs seen with IV drug use involves reduced blood flow during intoxication, endothelial cell damage, and hypercoagulability from infectious agents entering the bloodstream.[3]

Predisposition to the development of DVT can be evaluated using Virchow's Triad (Figure 1). The three factors implicated in increased risk of DVT are endothelial damage, hypercoagulability, and venous stasis.[4] Repeated endothelial damage may promote friction between blood flow and its vessel, hypercoagulability contributes to clot formation, and finally venous stasis may impact natural anti-coagulation pathway.[4] The overlap between these factors and those that are postulated to contribute to clotting events in the setting of IV drug use further support the increased risk of such events within this population.

If a DVT is suspected, typically emergency departments utilize D-dimer testing as an initial screening due to its speed and cost-effectiveness. However, this screening is not definitive. A patient's risk of having or developing VTE can be assessed separately using methods such as the Wells criteria. While there exist normal and pathological reasons for why a D-dimer may be elevated in an unaffected person,[1] few reasons for falsely-normal D-dimers have been documented including small emboli, anticoagulant pre-treatment, and symptoms ongoing for ≥ 10 days.[5]

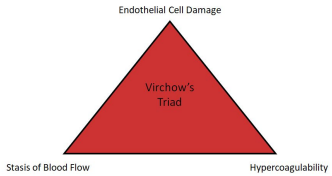


Figure 1. IV drug use has been associated with all three components of Virchow's Triad and thus increases the risk of DVT's.

PATIENT HISTORY and TIMELINE

Patient History: Patient is a 35 year old female with current daily intravenous drug use (IVDU) and a history of MRSA endocarditis s/p bovine tricuspid valve replacement

ED Presentation:

- Patient presents with dyspnea and pleuritic chest pain onset this morning
- CTA of chest reveals no contrast in segmental branches of R pulmonary artery to the upper lobe
- Suspect septic PE based on IVDU and history of valve replacement
- WBC 13.0
- Patient started on low-molecular weight heparin and broad-spectrum antibiotics

Day 1

- With suspicion for septic thrombi caused by bacterial endocarditis, transthoracic echocardiogram (TTE) completed
- TTE with normal mitral valve, poor visualization of prosthetic tricuspid valve and unable to rule out small thrombus or vegetation
- Cardiology consult reports there is a high chance the patient has endocarditis and recommends transesophageal echocardiogram (TEE)
- D-dimer obtained and normal at <200 ng/mL

Day 2

- Patient reports no improvement in symptoms
- Blood cultures with no growth to date
- TEE reveals no vegetations
- As no vegetations seen as cause of emboli, suspicion for blood clot as the culprit now increased
- Lower extremity venous doppler negative for SVT or DVT in both legs

Day 3

- Repeat D-dimer elevated at 596 ng/mL
- New suspicion for upper extremity venous thrombosis as the cause of PE
- Patient voices she wants to leave upon learning that her pain and SOB is unlikely cardiac related
- Patient is advised to stay inpatient while awaiting final blood culture results, as there is not a safe plan for discharge regarding PCP follow-up and insurance coverage for anticoagulation is in process
- Patient leaves AMA

D-DIMER

D-dimer is a small protein fragment produced by fibrin degradation[6] that is utilized in screening for thrombosis caused by serious health conditions such as deep venous thrombosis, pulmonary embolism, and disseminated intravascular coagulation.

D-dimer is commonly used as a screening test. This is because of its high sensitivity and moderate specificity.

- **Sensitivity: 97%**
- **Specificity: 61-64%.**[6]

In a typical case of suspected PE, a normal d-dimer effectively rules out PE while an elevated D-dimer reveals a need for further testing including imaging. However, this case had a multitude of factors in play, including IVDU and previous endocarditis warranting valve replacement. Initial D-dimer was within the normal range, whereas repeat D-dimer was elevated (Figure 2).

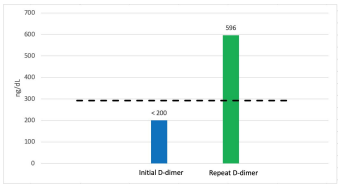


Figure 2. Initial and repeat d-dimer compared to the upper limit of normal for d-dimer in patient <50 years old, at 292 ng/dL (black dotted line).

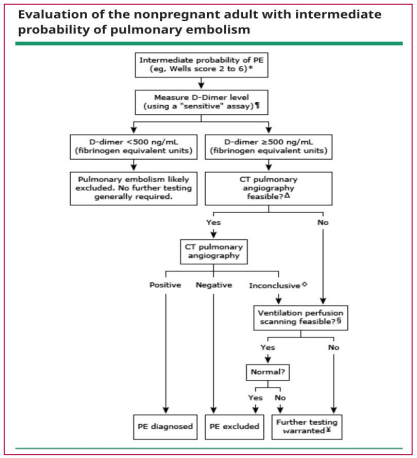
Causes of false positives:[6]

- Liver disease
- High rheumatoid factor
- Malignancy
- Trauma
- Inflammation
- Pregnancy
- Advanced age

Causes of false negatives:[5]

- **Small emboli**
- Anticoagulant pretreatment
- Symptoms ongoing ≥ 10 days

STANDARD ALGORITHM



*When the D-dimer level is <500 ng/mL, no further testing is typically required. However, some experts will proceed with diagnostic imaging in select patients. For example, imaging may be considered in patients who have limited cardiopulmonary reserve [7]

UPPER EXTREMITY THROMBOEMBOLISM

- DVT occurs in approximately 1 in 1000 people per year; though lower extremity (LE) DVT is much more common, **4-10% of cases** are a result of upper extremity (UE) DVT.[8]
- **Malignancy and insertion of venous catheters**, especially central venous catheters, are common culprits of UE DVT.[8]
- UE DVT are associated with higher mortality than LE DVT, though it is believed this is due to a higher incidence of cancer in this group.[9]

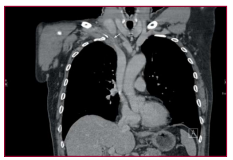


Figure 3. CT of an UE DVT at the junction of the right subclavian vein and superior vena cava (Heil)

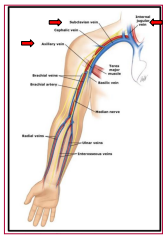


Figure 4. Veins of the upper extremity, with arrows denoting most commonly affected veins in UE DVT[10]

- There following veins are most commonly affected: subclavian, axillary, and jugular (Figure 4).[8,10]
- Symptoms of UE DVT are nonspecific and may include pain and swelling, **but 33-60% of patients are asymptomatic.**[8]
- Commonly used algorithms are of limited use in UE DVT
- The gold standard for diagnosis is UE doppler ultrasound.[8]
- Treatment of UE DVT is no different than that of the LE and involves anticoagulation with heparin followed by oral anticoagulants.[8]

BIASES REGARDING IVDU IN WOMEN

It is notable that the patient in this case left AMA and without planned follow-up. This raises questions as to why the patient made this decision: Was it a lack of understanding as to the severity of a PE? Was it due to feeling uncomfortable in the hospital setting?

In thinking about this second possibility, we looked into biases regarding female intravenous drug users. Most of these biases have been shown to be specifically linked to pregnant females. Though this patient was not pregnant, she is a mother. It is vital to be aware of all possible biases in order to provide the best possible care.

Below are some studied and known biases related to this case:

- Studies in addiction have found that both providers and the public view pregnant females with substance abuse more harshly than other patients.[11]
- A study revealed 76% of nurses felt "angry" toward mothers experiencing substance abuse.[11]
- A study compared provider biases before and after training. Training centered around biases linked to substance abuse. On a scale of 1-5, providers' knowledge about "gender difference with addiction" (ex. women less likely to seek treatment) was self-rated as such:
  - pre-training knowledge was rated a 2.6
  - post-training knowledge was rated a 4.5 ($p < 0.001$).[11]

With this in mind, it is crucial that healthcare workers receive training regarding gender differences in substance abuse as well as training to make individuals aware of preconceived biases.

SUMMARY and CONCLUSIONS

- Though D-dimer is simply a screening test with a high sensitivity, there are a multitude of reasons why it can be misleading.
- Small emboli, anticoagulant therapy, and symptoms lasting greater than 10 days can lead to a false negative D-dimer. In patients with IV drug use, it is possible that a small emboli could be the cause of a falsely normal D-dimer. A thorough history and medication review is thus recommended when working up a patient with symptoms of a PE.
- Use of Well's criteria and the algorithm for possible PE to guide work-up is extremely useful in a patient with a LE DVT; it is unfortunately not as valuable in a patient with an UE DVT and thus when one has high suspicion for thromboembolism this possible diagnosis cannot be forgotten.
- An upper extremity thromboembolism can be the culprit of a PE, especially when there is no evidence of a low extremity DVT. While this is typically seen in patients with malignancies and venous catheters, it is possible that IV injection of illicit drugs leads to endothelial cell damage in upper extremity veins and thus increases the risk of UTE's.
- Biases toward female patients, especially mothers, with drug abuse have been associated with harsh treatment, patient distrust, and poor outcomes. It is important that providers recognize their biases and receive training regarding gender differences in addiction in order to provide comprehensive and compassionate care.

REFERENCES

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