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Washington University Emergency Medicine Journal Club
D-Dimer in the Diagnosis of Aortic Dissection

Vignette

You are moonlighting in a local community ED one afternoon—making serious bank and contemplating what to spend on that money on—when you encounter a forty-year old male patient with chest pain. He has a history of hypertension for which he takes lisinopril, but is otherwise completely healthy. He was watching TV earlier in the day, eating nachos, when he developed a fairly abrupt onset of dull pain in the center of his chest.

As you continue your HPI, you learn that the pain does, in fact, radiate into his back, but is not ripping or tearing. He has no neurologic deficits, has symmetric blood pressures in both arms, and has stable vitals (BP130/85, HR 79, RR 12, SpO2 98%).

You order and ECG, CXR, cardiac enzymes, a BMP, and CBC, all of which come back normal.

You are still considering an acute aortic dissection as part of your differential, given the radiation of pain to the back, but would prefer not to expose your patient to the risks of radiation and contrast unless absolutely necessary. Your suspicion is fairly low. You wonder if a D-dimer would be a reasonable test to rule aortic dissection in this patient. In the end, you get a CT scan, which is negative for dissection, and admit the patient for a stress test. When you get off work, you decide to search the evidence and see what you can find.

PICO Question
Population: Adult ED patients with suspected aortic dissection
Intervention: D-dimer
Comparison: CT aortic angiogram, MRI
Outcome: Diagnostic accuracy (sensitivity, specificity, likelihood ratios)

Search Strategy

MedLine was searched via PubMED, using the strategy "D-dimer AND aortic dissection" resulting in 117 citations (http://tinyurl.com/omohgdl). Of these, one meta-analysis and 3 primary research articles were selected for inclusion.

Article 1: Asha SE, Miers JW. A Systematic Review and Meta-analysis of D-dimer as a Rule-out Test for Suspected Acute Aortic Dissection. Ann Emerg Med. 2015 Oct; 66(4):368-78. Answer Key.

Article 2: Suzuki T, Distante A, Zizza A, et al; IRAD-Bio Investigators. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic

Dissection Substudy on Biomarkers (IRAD-Bio) experience. Circulation. 2009 May 26;119(20):2702-7. Answer Key.

Article 3: Nazerian P, Morello F, Vanni S, Bono A, Castelli M, Forno D, Gigli C, Soardo F, Carbone F, Lupia E, Grifoni S. Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection. Int J Cardiol. 2014 Jul 15;175(1):78-82. Answer Key.

Article 4: Gorla R, Erbel R, Kahlert P, Tsagakis K, Jakob H, Mahabadi AA, Schlosser T, Eggebrecht H, Bossone E, Jánosi RA. Accuracy of a diagnostic strategy combining aortic dissection detection risk score and D-dimer levels in patients with suspected acute aortic syndrome. Eur Heart J Acute Cardiovasc Care. 2015 Jul 16. Answer Key.

Bottom Line

Aortic dissection, while a relatively rare disease, carries with it a high mortality rate. Mortality for type A dissection is around 25% when managed with surgery, and this rate increases to nearly 60% when managed non-operatively (Hagan 2000). Mortality has been shown to increase substantially for every hour treatment is delayed (Mészáros 2000), making prompt diagnosis and management a key to a good outcome. Diagnosis of aortic dissection typically requires CT angiography, MRI, or trans-esophageal echocardiography (TEE). MRI and TEE are both time-consuming modalities, and TEE is typically quite invasive. While CT is relatively quick and noninvasive, it carries risks associated with both radiation exposure and with the administration of iodinated contrast dye. Therefore the possibility of a noninvasive, rapid screening laboratory test to rule-out aortic dissection is quite appealing.

D-dimer has been proven to accurately rule-out pulmonary embolism, but only when used properly. Low and possibly moderate-risk patients, as determined by a clinical decision rule such as the modified Well's score or the Geneva score, with a negative D-dimer are felt to be at sufficiently low risk of PE that further testing is not needed (ACEP Clinical Policy).

D-dimer has also been proposed as a means of ruling out aortic dissection. A prior journal club on this topic found that D-dimer had a low negative likelihood ratio (0.06) and negative predictive value, but concluded that there was an absence of clinical decision rules (CDR's) to determine pre-test probability, and hence to determine which patients could be accurately ruled out for dissection with a negative D-dimer alone. We therefore sought to determine if such CDR's existed, and if an algorithm could be devised to used D-dimer to exclude aortic dissection in a subset of patients.

The aortic dissection detection (ADD) risk score, introduced in the American Heart Association 2010 guidelines, is a prospectively validated CDR, in which low-risk patients (ADD score = 0) have been shown to have a risk of disease of around 6%. Combined with a negative likelihood ratio of 0.05, as demonstrated in a recently published meta-

analysis from the Annals of Emergency Medicine, a patient with an ADD score of 0 and a negative D-dimer would have a post-probability of disease of 0.3%. Of note, a large, prospective, multicenter trial found a similar negative likelihood ratio (0.07). A retrospective study out of Germany sought to evaluate this approach, and found that out of 376 patients being evaluated for aortic dissection, 127 (34%) had an ADD score of 0 and a negative D-dimer . None of these patients were found to have an aortic dissection. In a similar study from Italy, a prospectively collected registry was used to retrospectively evaluate the ADD score combined with D-dimer testing. Out of 1035 patients being evaluated for aortic dissection with a D-dimer level available, 92 (8.9%) had both an ADD score of 0 and a negative D-dimer, and none of these patients were found to have an aortic dissection. Among 152 patients with an ADD score of 1 and a negative D-dimer, only 2 (0.2%) were found to have an aortic dissection.

While these data are promising, suggesting that patients with an ADD score of 0 (and possibly 1) and a negative D-dimer are at extremely low risk of having an aortic dissection, some issues remain. To date, no prospective studies have evaluated the accuracy or safety of this approach, and should be conducted prior to more widespread implementation. Additionally, the test threshold—the probability of disease below which further testing is likely to cause more harm than benefit, but above which further testing is warranted—should be calculated in order to determine the cut-off at which we can safely exclude patients with a negative D-dimer alone. The Pauker and Kassirer method for calculating test and treatment thresholds is shown in figure 1, and relies on knowing the diagnostic test characteristics of more definitive testing, and the risks associated with the test, and the risks associated with treatment of the disease. Once this test threshold is known, and once the combined use of the ADD score and negative D-dimer has been prospectively shown to identify a subset of patients at sufficiently low risk of aortic dissection, an algorithm can be set in place to reliably exclude the disease without the risks of more definitive testing.

Figure 1. The Pauker and Kassirer Method of Calculating Test and Treatment Thresholds

$P_{pos/nd}$ = probability of a positive result in patients without disease = 1-specificity
$P_{neg/nd}$ = probability of a negative result in patients without disease = specificity
R_{rx} = risk of treatment in patients without disease
R_t = risk of diagnostic test
$P_{pos/d}$ = probability of a positive result in patients with disease = sensitivity
$P_{neg/d}$ = probability of a negative result in patients with disease = 1 – sensitivity
B_{rx} = benefit of treatment in patients with disease