D-dimer for Suspected Pulmonary Embolism

Whom Should We Test?

After > 10 years of intensive research, plasma d-dimer measurement is increasingly accepted as a first-line test in patients with suspected pulmonary embolism. Adoption of d-dimer was faster in suspected deep venous thrombosis, probably because clinicians are less fearful of a false-negative result in that context than when a potentially fatal disease such as pulmonary embolism is suspected. Nevertheless, as carefully reviewed in a recent editorial in CHEST by Kelly and Hunt, and in a recent review of outcome studies in suspected pulmonary embolism, the evidence is now convincing: highly or even less sensitive d-dimer assays combined with clinical probability assessment are safe instruments to rule out pulmonary embolism. However, it is now well recognized that d-dimer assays are not a homogeneous group and exhibit vastly different characteristics: they recognize different epitopes of d-dimer and use different technologies (latex, enzyme-linked immunosorbent assay [ELISA], immunoturbidimetry) that impact on the diagnostic characteristics and performance of each individual assay. The safety of ruling out pulmonary embolism based on a d-dimer concentration below the predefined cutoff value depends on the sensitivity of the test, ie, the proportion of patients with pulmonary embolism in whom d-dimer is elevated. Indeed, if that proportion approaches 100% (the true figure lies between 96% and 99% for ELISA and immunoturbidimetric assays), the probability of a false-negative test result is very low, and a negative test result is strong evidence that the patient does not have pulmonary embolism. However, although d-dimer is highly specific for cross-linked fibrin, fibrin is generated and degraded in a wide variety of clinical situations. Therefore, the specificity of highly sensitive d-dimer assays for pulmonary embolism is only approximately 40% in outpatients. This has two consequences. First, a d-dimer result above the threshold value is of no value for ruling in pulmonary embolism. More importantly, since only negative d-dimer results are useful for clinical decision making, the proportion of patients with a negative result among those without a pulmonary embolus (ie, specificity) determines the clinical usefulness of the test. Consider a prevalence of pulmonary embolism of 20%, a usual figure in the published literature. In a hypothetical cohort of 100 patients, 80 patients would not have the disease. If the specificity of d-dimer is 40%, d-dimer will be negative in 32 patients. Therefore, the number of
patients who must be tested in order to rule out one pulmonary embolism among the entire cohort would be three. In contrast, if the specificity decreases to 12%, only 10 patients will benefit and the number needed to test will rise to 10. Hence, if the specificity of d-dimer varies across patient subgroups, the clinical usefulness of that test may depend on the patient population in whom it is being used.

The article by Rathbun et al in this issue of CHEST (see page 851) highlights that property of d-dimer. They measured d-dimer levels by a quantitative latex assay in 125 patients with a clinical suspicion of pulmonary embolism and a nondiagnostic ventilation-perfusion lung scan. Pulmonary embolism was ruled out by the combination of a negative d-dimer result and normal compression ultrasonography, or in case of a positive d-dimer test result, normal serial compression ultrasonography followed by angiography only in patients with inadequate cardiorespiratory reserve. Although restricting d-dimer measurement to patients with a nondiagnostic scan may not be the most cost-effective approach, the main finding is the lower clinical usefulness of d-dimer in inpatients. Indeed, the cohort included a mix of inpatients and outpatients and d-dimer results were negative in only 11 of the 103 inpatients (11%) compared with 7 of the 22 outpatients (32%), a significant difference despite the small outpatient sample. This confirms a previous series in which only 5 of 114 inpatients (4%) suspected of pulmonary embolism had a negative ELISA d-dimer result. Hence, using a highly sensitive d-dimer assay, the number needed to test would be in the range of 10 to 25, clearly indicating a reduced clinical usefulness compared to outpatients.

This is not restricted to inpatients, and a variety of patient subgroups exhibit very low d-dimer specificities.7-10 D-dimer increases with age; therefore, the specificity of d-dimer decreases steadily with age in suspected pulmonary embolism. In a series of outpatients with suspected pulmonary embolism, the specificity of an ELISA d-dimer assay was 67% in patients ≤ 50 years old compared with only 10% in patients > 50 years old.11 Many cancers, particularly at the disseminated stage, are associated with an elevation of d-dimer. Data are not yet available on the performance of d-dimer in cancer patients with suspected pulmonary embolism. In suspected deep venous thrombosis, however, two outpatient series have demonstrated a significantly lower specificity in patients with cancer (29% compared with 51% in patients without cancer in one series,10 and 48% compared with 82% in the other study).12 Those unusually high figures for specificity are due to the characteristics of the assay used in those series, the SimpliRED assay (Agen; Brisbane, QLD, Australia), a whole-blood agglutination test that has a low 85% sensitivity but a higher specificity than more sensitive immunoturbidimetric and ELISA assays. Finally, pregnancy is another situation in which d-dimer may have a reduced clinical usefulness because its levels increase throughout pregnancy.10,14 Nevertheless, in a series of 144 women in whom d-dimer was assayed serially during pregnancy, d-dimer was below the cut-off value in 75% of women up to week 14 and 50% up to week 19 of pregnancy.

Does this imply that the diagnostic yield of d-dimer is so low in those patient subgroups that it should no longer be measured? Consider testing 100 patients with a low or intermediate clinical probability of pulmonary embolism by d-dimer (US $30) followed by helical CT ($300) in case of a positive result. If the d-dimer result is negative in 32 patients, the expected figure for an average 40% specificity and a 20% prevalence, the total costs of testing will be $24,000. However, if the d-dimer result is negative in only 10 of those patients (specificity, 12%), total costs will be $30,000, equivalent to those of performing CT in all patients without measuring d-dimer. Admittedly, those calculations are extremely crude, but they illustrate that for low specificity values, d-dimer is no longer cost saving but it does not significantly add to total costs. In addition, the diagnostic yield of imaging techniques may also be lower in the same patient groups who have a low d-dimer specificity. Elderly patients and patients with lung cancer have a higher proportion of nondiagnostic lung scans. Elderly and hospitalized patients have a higher prevalence of renal failure that might be worsened by contrast-enhanced CT. Lastly, every effort should be made to protect pregnant women from unnecessary irradiation. Therefore, since d-dimer is so convenient, one might argue that even one negative result out of each 10 assays performed is still clinically useful. However, the threshold of clinical usefulness below which d-dimer should no longer be assayed remains arbitrary and a matter of clinical judgment.

In summary, specificity of d-dimer is lower in various patient subgroups than the average specificity observed in outpatients admitted to the emergency department for suspected pulmonary embolism. This results in a lower clinical usefulness, defined as the number of patients who must be tested to rule out one pulmonary embolism. In contrast, sensitivity does not seem to be affected by those patient characteristics. Whether the diagnostic yield of d-dimer is too low to warrant its use in hospitalized patients, patients with cancer, elderly patients, and pregnant women is controversial in the absence of an accepted clinical usefulness threshold.
Empirically, clinicians might consider that even a 1-in-10 chance of a negative result is still clinically useful in such patients; therefore, they would measure d-dimer in those with only one of those features. However, some of these patient characteristics are likely to be additive, and the probability of a negative d-dimer result in an elderly patient suspected of pulmonary embolism during the course of inpatient treatment for active cancer is probably so low that d-dimer testing would be considered a waste of time and resources. Hence, a decision on a case-by-case basis by clinicians aware of the characteristics of d-dimer in subgroups appears to be more reasonable than a general rule to abstain from testing in patients in whom a low d-dimer specificity is to be expected.

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Portable Monitoring for Diagnosing Obstructive Sleep Apnea

Not Yet Ready for Primetime

Obstructive sleep apnea (OSA) is a highly prevalent disease with estimates that 20% of white men and women with body mass index between 25 and 28 kg/m² have an apnea-hypopnea index (AHI) of ≥ 5.1 In recent years, OSA has been associated with a number of common morbid conditions, including heart disease, stroke, diabetes, and motor vehicle accidents. These links and the fact that the disease is readily treatable with nasal continuous positive airway pressure (CPAP) have accelerated the need for prompt and accurate diagnosis. The current standard clinical workup includes a history, a physical examination, and a referral to a sleep disorders laboratory for an overnight complete polysomnogram. If OSA is found, a second overnight polysomnogram with nasal CPAP is performed. Given the length of time, the costs and technical expertise required, along with the advances in computer technology, a move toward less complicated techniques in the home has gained popularity. In a recent issue of CHEST, an extensive evidence-based review of the current status of portable monitoring for the diagnosis of OSA was published.2 A subsequent publication in Sleep used this evidence review to develop clinical practice guidelines.3 The outcome of these articles suggests that portable monitoring for the diagnosis of OSA is not quite “ready for prime-time.” The evidence review was based on 49 articles in the peer-reviewed literature. The authors of the evidence review systematically evaluated each article with the help of an evidence practice center to determine its quality. The evidence was used to generate a practice parameter, which states that