Evaluating patients with pulmonary thromboembolism: a retrospective study on the utilization of serum D-dimer assay and CT angiography

**Introduction**

Pulmonary thromboembolism (PTE) is an obstruction by a thromboembolus in any part of the pulmonary arterial circulation usually manifesting clinically as dyspnea, chest pain or collapse. PTE is the third most common acute cardiovascular disease after cardiac ischemic syndromes and stroke [1]. Deep vein thrombosis (DVT) and PTE are both part of a spectrum of one clinical entity, having an annual incidence of 1.0 and 0.5 per 1000 in the Western world, respectively [2]. Based on autopsy data, the incidence of PTE is even greater [3].

The various tests used to evaluate for PTE include D-dimer assay, computed tomographic pulmonary angiography (CTPA), lower limb ultrasonography, conventional angiography, magnetic resonance angiography (MRA) and ventilation-perfusion scintigraphy. In the recent years CTPA has become the standard of care at many institutions across the world for the initial evaluation of patients with suspected pulmonary thromboembolism [4]. CTPA has demonstrated sensitivities of 53%-100% and specificities of 83%-100%. Such wide ranges of accuracies may in part be due to the wide variety of CT scanners in clinical use [4,5].

D-dimer is an inexpensive, and easily performed laboratory test which a direct biomarker of fibrinolysis and an indirect marker of coagulation. Though increased levels of D-dimer occur in various conditions where the coagulation system is activated; its usefulness lies in its ability to safely exclude the presence of venous thromboembolism due to its high negative predictive value. A sensitivity of 96% and specificity of 52% was reported by Kelly et al. [6]. The enzyme linked immunosorbent assay (ELISA) D-dimer method is considered to be the ‘gold standard’ and most widely used. According to a recent study, the use of a screening D-dimer measurement of 1.0 µg/ml or less precludes CTPA in patients with suspected acute PTE [7].

There have been recommendations to triage
Using unlimited gray scale. Lung windows were also available for evaluation of accompanied airway and parenchymal disease, or to detect unsuspected pneumothorax.

A total of 98 cases which were positive for thromboembolism on CTPA were included in this study. The images were interpreted on a picture archiving and communications system (PACS) (eRAD–eRAD Inc. Corporate Headquarters: South Carolina 29607) workstation by at least two American Board certified radiologists experienced in emergency radiology. The radiology reports of our study group generally included details of the pulmonary thromboemboli such as location(s), partial or total vessel obstruction, associated parenchymal changes and other incidental findings (these details are however not included in this article since the reports with positive PTE was only used to define the study group and further to analyze the D-Dimer usage in that group).

We then retrospectively reviewed laboratory data among these patients with positive CTPA to see if serum D-dimer was performed on them and if so their results. We considered values of >500 ng/ml by ELISA method as abnormal/raised levels [6]. The data with number of patients who had D-dimer assay performed (segregated into positive and negative results) and those who did not have the test in various age groups were tabulated and analyzed for their percentage distributions.

### Results

The results are summarized in TABLES 1 and 2. The 98 positive PE cases in this study comprised of 46 (46.9%) men and 52 (53.1%) women. The age of patients in this study group ranged from 17 years to 98 years (mean age of 58.5 years) with a significant number of patients (44.9%) over 60 years of age. A majority of

<table>
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<th>AGE (YEARS)</th>
<th>&lt;20</th>
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<td>FEMALES</td>
<td>TOTAL</td>
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<td>No</td>
<td>D-dimer done</td>
<td>No</td>
<td>D-dimer done</td>
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<td>+</td>
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<td>FEMALES</td>
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</tr>
<tr>
<td>TOTAL</td>
<td>2</td>
<td>15</td>
<td>37</td>
<td>44</td>
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+: Positive D-dimer result
-: Negative D-dimer result
the patients in our study group (73.4%) went directly for CTPA without D dimer assay. Of the 26 patients who were offered a D dimer assay, 20 (76.9%) had elevated values (ranging from 700 to 10540 ng/ml). In patients with high clinical suspicion for PTE (n=90), CTPA was performed without a D-dimer assay; some (n=72) in fact never had a D- dimer assay. In 6 cases (23.1%) though the D-dimer test was negative, CTPA was positive for PTE. The D-dimer positivity varied according to patient age. In the 21 to 40 years age group, 3 patients of 5 (60%) had false negative d dimer results; in the >60 years it was 2 of 12 (16.7%); and in the 41 to 60 years age group 1 of 8 (12.5%). There were no false negatives in the <20 years age group. One of the patients with negative d Dimer results and a positive CTPA is illustrated as example (FIGURES 1 and 2).

### Discussion

CTPA has become established as the primary noninvasive imaging test in clinical practice due to its wide availability, safety, cost-effectiveness and high negative predictive value for the diagnosis of clinically relevant PTE [10]. Our study substantiates this, with almost three fourths of the patients (73%) in the study group having CTPA as the initial or the only diagnostic test for suspected PTE. Besides the direct visualization of intraluminal thrombus, the depiction of cardiac and pulmonary function along with the extent of pulmonary arterial obstruction helps to grade the severity of PTE for further risk stratification and subsequent follow-up to assess the success of thrombolytic therapy because PTE and deep venous thrombosis are two different aspects of the same disease, there is an added advantage of CTPA. CT venography can be performed in conjunction with CTPA, utilizing the same contrast injection. Several studies have reported that a quantitative D-dimer assay was effective in obviating the need for CTPA, and that it had high negative predictive value of about 99.6% [6,8,11]. In spite of this proven fact however, D-dimer screening is not used according to established diagnostic algorithms to determine the need for MDCT in diagnosing acute pulmonary thromboembolism in the emergent setting [12].

### Limitations

Our study design has a few limitations. A major limitation is a selection bias for the study’s
subjects as the clinical index of suspicion was not looked for patients who went directly for CTPA versus D-dimer assay. The cases selected were from different institutions. Thus differences in the CT equipment, the scan protocols (though all confirmed to the minimum ACR-2005 recommendations), and viewing algorithms could potentially create some degree of variability of image quality. However, these differences are to be expected in a multi-institutional study which has the advantage of analyzing the clinical practices and protocols from multiple institutions. A prospective study with matching protocol among all the institutions included in the study would be useful to overcome the limitations mentioned. And a larger study group with more robust statistical analysis of the data would help in forming a better consensus/recommendation.

Our study somewhat points to a relative preference of CTPA over serum D-dimer assay. Furthermore, it is important to note that in our study we found a 23.1% false negative rate for D-dimer assay. Had the CTPAs not been obtained in these patients, appropriate and much needed care would have been denied. This false negative D-dimer results were highest in the 21 to 40 years age group (60%) than in the extremes of age (i.e., <20 and >60 years). Of note, in this age group 2 women underwent D-dimer assay and both were false negative (100%) as shown on subsequent CTPA studies. This may be partly explained by the smaller sample size and differences in laboratory standards; but none the less is an important observation. Thus when clinical suspicion for PTE is high or uncertain, and when other chest pathology is also a clinical possibility, CTPA is a better test than D-dimer as the sole decision making diagnostic tool.

CTPA is now the recommended initial imaging modality for non-massive PTE and patients with a good quality negative CTPA do not require further investigation or treatment for PTE [13].

Nilson et al. in their study also concluded that CTPA has a higher sensitivity and specificity than latex agglutination D-dimer [14]. A recent article by Youssf also states that D-dimer alone cannot exclude or confirm the presence of PE and that a combination of other tests including CTPA is recommended for patients with suspected PE [15].

Conclusion

Our study indicates that there seems to be underutilization of serum D-dimer assay in clinical practice for suspected PTE in spite of the recommendations and guidelines based on previously published reports. The negative D-dimer assay is a significant problem, and should not be used to triage patients with a high clinical index of suspicion for PTE. Furthermore, CTPA also has the added advantage of rapidly diagnosing or excluding other conditions which may clinically mimic PE, many of which are life threatening emergencies.

REFERENCES