Acta clin Croat 2001; 40:255-258 Original Scientific Paper

D-DIMERS IN THE DIAGNOSIS OF THROMBOEMBOLIC DISEASES

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SUMMARY – Every suspicion of thromboembolic disease requires urgent therapy decision because of the potential life-threatening complications. Routine measurement of plasma D-dimer levels has alleviated this delicate problem. In this study, D-dimers were measured in 49 out of 121 patients admitted to the Department of Medicine from 1997 till 1999 for suspected thromboembolic disease. The selection of these 49 patients was based on the high probability of pulmonary embolism on ventilation/perfusion lung scan or clinical signs of deep venous thrombosis and positive isotope venography. Increased D-dimer levels were found in all 49 cases. The patients were classified according to the extension of the thrombotic incident. Higher D-dimer values were recorded in patients with massive or submassive pulmonary embolism (mean 5.6 ng/L) as compared to those with segmental pulmonary embolism (mean 2.6 ng/L). D-dimer levels in patients with ileofemoral thrombosis were much higher (mean 5.2 ng/L) than in patients with calf thrombosis (mean 1.6 ng/L). One patient with calf thrombosis had a borderline level of 0.3 ng/L (normal value: up to 0.3 ng/L). Although a positive correlation between thrombus size and D-dimer levels has been demonstrated, other factors may also influence test results, e.g., disseminated intravascular coagulation, intensity of fibrinolysis, and simultaneous thrombosis of unrecognized localization.

Key words: *Fibrin – fibrinogen degradation products, analysis; Pulmonary embolism, diagnosis; Venous thrombosis, diagnosis*

Introduction

In spite of the progress in medical technology, pulmonary embolism (PE) and deep venous thrombosis (DVT) remain a serious diagnostic problem[1]. In severe forms of thromboembolic disease (TED), diagnostic procedures cannot be performed at a rate at which pulmonary embolism may threaten the patient's life. For the same reason, clinicians are quite frequently forced to make the diagnosis only on the basis of history data, clinical manifestations, and routine laboratory tests. In such an emergency, PE and DVT may clinically resemble several other diseases, thus making therapeutic decision more difficult[2]. The introduction of D-dimer assays into clinical practice was widely welcome and accepted by physicians because of its remarkable contribution to accurate diagnosis of TED.

Our first trials in the determination of D-dimer levels were initiated in the late 1994. We started to use enzyme-linked immunosorbent assay (ELISA) in collaboration with Dr. Godec from the Croatian Institute of Transfusion Medicine from Zagreb. At the time, preliminary results indicated that the test reliability was considerably influenced by sample transportation and processing speed. The introduction of this method at our own coagulation laboratory provided an opportunity for fast and safe sample processing with reliable results. It opened up the possibility of D-dimer detection and evaluation in TED, which was precisely the aim of the present study.

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Received June 25, 2001, accepted in revised form December 2, 2001

Patients and Methods

In the period between January 1997 and July 1999, 121 patients were admitted to the Department of Medicine for suspected TED. The diagnosis of PE or DVT was made in 49 patients (30 women and 19 men, mean age 63.2 and 62.5 years, respectively). Only patients with acute symptoms of illness lasting for not more than 72 hours were included. Routine laboratory tests were performed on admission (ECG, acid-base balance, chest x-ray). A high probability of PE on ventilation/perfusion (V/P) lung scan was found in 25 patients. Typical clinical signs and isotope venography performed by sodium pertechnetate Te 99m were sufficient for the diagnosis of DVT in 24 patients. Both PE and DVT were found in 12 patients. The patients were classified according to predominant clinical manifestations and laboratory data into PE and DVT group. In the PE group, 11 patients had massive or submassive PE, and 14 had segmental PE. In the DVT group, calf thrombosis and ileofemoral thrombosis was detected in 14 and ten patients, respectively.

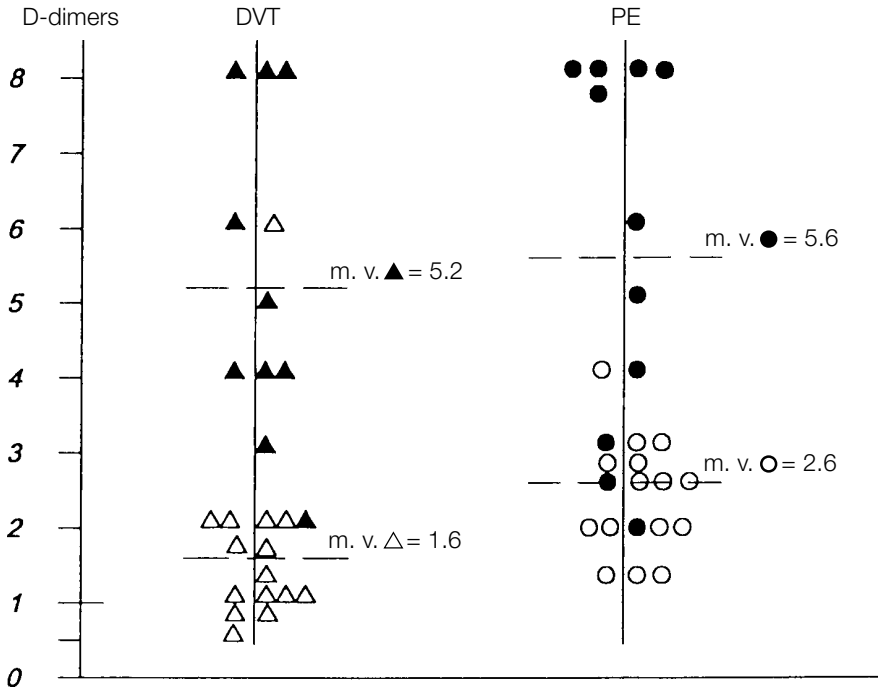
D-dimers were measured on admission in citrated platelet-free plasma by rapid immunoassay (Nyco-Card D-Dimer, Axis-Shield PoC AS, Oslo, Norway) and results were read off by the NycoCard Reader (measuring range 0.1-20.0 mg/L; measuring intervals 0.1 mg/L). Monoclonal antibodies specific for neoantigen on D-dimer structure are used in the test. Normal values stated by the manufacturer and at our laboratory were up to 0.3 ng/L.

Patients with extremely rapid or extremely slow fibrinolysis on admission were excluded from the study.

Results

D-dimer levels in patients with different TEDs are shown in Fig. 1. Patients with massive, submassive or segmental PE, and those with calf or ileofemoral thrombosis are specially marked.

Increased plasma D-dimer levels were found in all 49 patients with PE or DVT. Only one patient with calf thrombosis had a borderline D-dimer value (0.3 ng/L).



DVT=deep venous thrombosis; ileofemoral ▲ ;
calf thrombosis △ ;
pulmonary embolism massive or submassive ● ;
segmental ○

Fig. 1. Scatterplot of D-dimer levels in patients with different thromboembolic diseases.

Most of the patients with massive or submassive PE had D-dimer levels ranging from 2 to 8 ng/L, mean 5.6 ng/L, and those with segmental PE from 1.5 to 4 ng/L, mean 2.6 ng/L. Patients with ileofemoral thrombosis also had elevated D-dimer levels, ranging from 2 to 8 ng/L, mean 5.2 ng/L as compared to those with calf thrombosis, in whom they ranged from 0.5 to 6 ng/L, mean 1.6 ng/L.

Discussion

The study showed pathologic, increased D-dimer levels in all patients with acute TED except for one borderline case (0.3 ng/L). The results of the study are consistent with those reported elsewhere[3-7]. However, although highly sensitive, the methods used in PE and DVT diagnosis are much less specific. Therefore, only patients with a high probability of PE on V/P lung scan were selected for the study. Clinically suspect DVT was verified by isotope venography.

Considerably higher values were recorded in patients with massive or submassive PE as well as in those with ileofemoral thrombosis. These observations require further evaluation, although a proportional correlation between thrombus size and degradation product levels may be expected. This correlation was demonstrated by Hansson *et al.*[8] in 28 patients with proximal and distal DVT. A definite advantage of measuring D-dimer levels was shown by Goldhaber *et al.*[9]. They report on 45 patients with pulmonary embolism verified by angiography. Increased D-dimer levels were present in 42 cases. Nonsignificant D-dimer values were found in the remaining three patients. Two of them had residual pathologic changes of previous DVT but there was no proper explanation in the third patient. Ginsberg *et al.*[10] report on 197 patients with verified PE. The sensitivity of D-dimer levels was 84.4%, however, the specificity was much lower, i.e. 68.4%. The authors point out that normal venous plethysmography and D-dimer level do not require any additional diagnostic procedure. Perrier *et al.*[11] have suggested a diagnostic algorithm in the following order: clinical manifestations and D-dimer level together with venous ultrasonography and/or V/P lung scan.

A very simplified approach has been proposed by Egermayer *et al.*[4]. Normal D-dimer findings, pO_2 >80 mm Hg, and respiratory rate <20/min exclude PE with a high significance. Bradley *et al.*[12] showed a high D-dimer sensitivity (97.7%) in patients with DVT verified by ultrasonography. Just one false-positive test was found.

On the other hand, specificity was only 48.9%, with 45 false-positive findings. According to Ryn *et al.*[13] and other sources, the sensitivity of elevated D-dimer levels in the diagnosis of PE ranges from 73% to 100%. The specificity varies widely, depending on the assay used and the patient studied. A specificity of 30% to 70% was recorded in larger studies. A recent prospective study using 5 different latex agglutination assays showed a normal D-dimer level to have a high negative predictive value of 94% - 100% in excluding PE[14]. Most authors[6-9] consider D-dimer test very useful when clinical suspicion of thromboembolism is low or moderate. Conversely, when high clinical suspicion of TED is present, a negative D-dimer test should be ignored. An interesting question was raised by Romero-Garcia *et al.*[15]. Their study indicates the prognostic benefit of measuring D-dimer levels in obstetric patients with thrombosis risk factors. As shown by these results, a moderate increase in D-dimer levels (up to twofold upper normal limit) was recorded in 78% of pregnant women with a history of TED. The same increase was observed in 60% of cesarean deliveries, 37% of hypertensive and 23% of diabetic pregnancies. Pregnant women with a fourfold D-dimer level increase developed clinical manifestations of TED. However, these results were not confirmed by some other authors[16]. According to Fischbach[17], an expert in laboratory diagnosis, these data should be taken with some reserve. Higher D-dimer levels are normally present in late pregnancy and postpartal period. Therefore, their prognostic value in such a period is questionable. Additional diagnostic procedures in pregnant women with high D-dimer levels and a high risk of thrombotic factors appear to be reasonable. In his manual of laboratory tests[17], Fischbach points out very clearly that D-dimers are more specific for disseminated intravascular coagulation (secondary fibrinolysis) but are useful in TED as well. The level of D-dimers will also be higher in malignancies, inflammatory diseases (sepsis), primary fibrinolysis, cardiac insufficiency, and in elderly patients. Fischbach also points out that D-dimers can be false-positive if a high rheumatoid factor titer or high CA-125 tumor marker value (ovarian cancer) is present.

As shown by Shorr *et al.*[18], critically ill patients often have elevated concentrations of D-dimers in the absence of TED.

Conclusion

We found increased D-dimer levels in all patients included in the study, had they PE or DVT. Generally, more

extensive local thrombosis or thromboembolism was associated with higher D-dimer levels. However, the possibility of asymptomatic thrombotic incidents of other localizations should be considered at the same time as well. Segmental PE or calf thrombosis induced lower or borderline values, which makes this useful test less reliable.

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Sažetak

D-DIMERI U DIJAGNOSTICI TROMBOEMBOLIJSKIH BOLESTI

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Svaka sumnja na tromboembolijsku bolest zahtijeva hitno odlučivanje o terapiji zbog mogućih komplikacija opasnih za život. Rutinsko mjerenje razina D-dimera u plazmi ublažilo je ovaj delikatan problem. U ovom su ispitivanju D-dimeri mjereni u 49 od 121 bolesnika primljenih na Kliniku za unutarnje bolesti između 1997. i 1999. godine zbog sumnje na tromboembolijsku bolest. Ovih je 49 bolesnika odabrano na osnovi visoke vjerojatnosti plućne embolije utvrđene prigodom ventilacijsko/perfuzijskog snimanja pluća ili prema kliničkim znacima duboke venske tromboze i pozitivne izotopne venografije. Povišene razine D-dimera nađene su u svih 49 bolesnika. Bolesnici su razvrstani prema razmjeru trombotskog ispada. Više vrijednosti D-dimera zabilježene su u bolesnika s masivnom ili submasivnom plućnom embolijom (srednja vrijednost 5,6 ng/L) u usporedbi s onima sa segmentnom plućnom embolijom (srednja vrijednost 2,6 ng/L). Razine D-dimera u bolesnika s ileofemoralnom trombozom bile su znatno više (srednja vrijednost 5,2 ng/L) nego u bolesnika s trombozom potkoljenice (srednja vrijednost 1,6 ng/L). Jedan je bolesnik s trombozom potkoljenice imao graničnu vrijednost od 0,3 ng/L (normalna vrijednost: do 0,3 ng/L). Iako je dokazana pozitivna korelacija između veličine tromba i razina D-dimera, postoje i drugi čimbenici koji mogu utjecati na razultate pretrage, a to su diseminirana intravaskularna koagulacija, intenzitet fibrinolize i istodobna tromboza nepoznate lokalizacije.

Ključne riječi: *Proizvodi razgradnje fibrina – fibrinogena, analiza; Plućna embolija, dijagnostika; Venska tromboza, dijagnostika*