D-DIMERS IN THE DIAGNOSIS OF PULMONARY EMBOLISM

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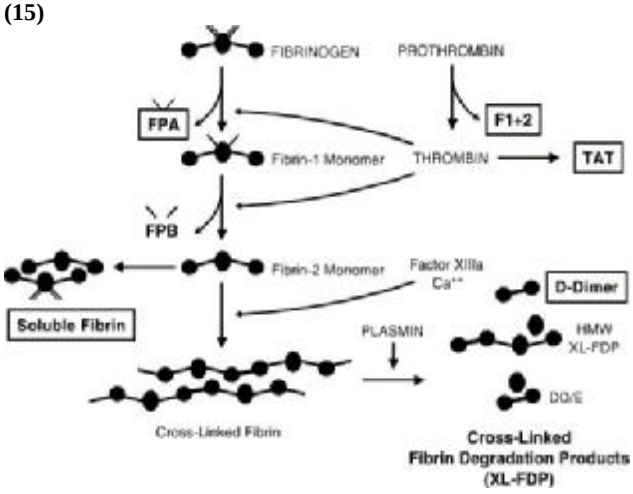
Abstract: *D-Dimers, endogenous fibrinolysis markers, represent the most determined laboratory test of fibrinolysis and coagulation tests. Their role in the diagnosis of pulmonary embolism was extensively discussed and analysed. Currently, there is an important literature which emphasized these markers and which suggests that their clinical indications have not been fully investigated, new utilities to be indicated in the near future. I brought up the main features of D-Dimers, their contribution in the current practice, their limits and future prospects, in the light of the latest literature data.*

Cuvinte cheie: *D-dimeri, trombembolism pulmonar, fibrinoliză*

Rezumat: *D-dimerii, markeri ai fibrinolizei endogene, reprezintă cel mai determinat test de laborator la ora actuală dintre testele de coagulare şi fibrinoliză. Rolul lor în diagnosticul TEP a fost îndelung discutat şi analizat; la ora actuală există o literatură impresionantă ce subliniază importanţa acestor markeri, şi care ne sugerează că indicaţiile lor clinice nu au fost total investigate, urmând ca în viitorul apropiat să ne fie sugerate noi utilităţi ale acestora. Am readus în discuţie principalele caracteristici ale D-Dimerilor, aportul lor în practica curentă, limitele lor şi perspectivele viitoare, în lumina ultimelor date din literatura de specialitate.*

D-dimers (DD) are fibrin degradation products; their plasma levels are increased in the presence of a thrombus formed acutely, consecutively to the simultaneous activation of fibrinolysis and coagulation processes.(5) They are units formed by the action of factor VIII on the monomers and polymers of fibrin, when endogenous fibrinolytic system acts cross-linked on the fibrin present in the body (figure no. 1). The monoclonal antibodies used in the quantification of the DD tests also identify cross-linked degradation fragments of fibrin, which were not lysed by the plasmin. Because 2-3% of plasmatic fibrinogen is physiologically converted to fibrin and then degraded, small amounts of DD are found in plasma of healthy people.(1)

Figure no. 1. Schematic presentation of the DD formation (15)



DD in daily practice

DD grow in all situations which involve increases in levels of fibrin, and subsequently its degradation by plasmin (1), including in nontrombotic disorders: recent major surgery, trauma, pregnancy, hemorrhage, sepsis, neoplasia, inflammation, necrosis, infection, dissection of the aorta or acute arterial thrombosis, which gives DD a low positive predictive value of DD (PPV) low; as a result they cannot be useful in the diagnosis of pulmonary thromboembolism (PE). Rather, a normal level of DD reflects the impossibility of the existence of a deep vein thromboses or pulmonary embolism, having an important predictive negative value (PNV).(5)

The use of DD in emergency compartment for PE diagnosis derives from their characteristic specificity which in turn depends on the particularities of each patient. It has been shown that DD would increase by age, and some studies claim that D-dimers should not be made in patients over 80 years old.(5)

Methods for Quantifying

The quantification of DD levels was possible with the development of monoclonal antibodies that bind to the epitopes on DD fragments, these missing on the non-cross-linked fibrin fragments and on fibrinogen fragments.(1)

There are several methods of determining the DD levels that have different characteristics. In general, qualitative tests offer the advantage that they are simple to perform, have a fast response time and are cheap. Interobservators' reliability was put to doubt in at least three studies, while a fourth has found it to be excellent. However, it is recommended that only trained observers to perform and interpret these tests.(2)

The first tests used were those with latex agglutination test: D-dimers (Diagnostica Stago) and Dimertest Dimertest (Agen biomedical), Minutex (R) (Biopool), Nephelotex (Biopool), and Accuclot (TM) (Sigma Diagnostics). In a study

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of 600 patients, Accuclot had a sensitivity of 90% and a specificity of 70%. However, although the sensitivity of latex agglutination test was indeed increased, their specificity is much smaller, around 45%.(2)

The second types of qualitative tests are blood agglutination tests (SimpliRED (TM), biomedical Agen). SimpliRED is the qualitative assay with most studies based on clinical data. The sensitivity and specificity of the SimpliRED in clinical trials was similar to that of other tests with visual inspection, the sensitivity ranging from 78 to 83% and specificity of 74% to 64.(2)

The second generation of latex tests are quantitative (IL-test, Tinaquant, Liatest) and are generally of greater sensitivity, consistently around 90% and specificity of around 40%, being often framed as moderately sensitive determination methods.

Quantitative method ELISA (enzyme-linked immunoabsorbent assay) -ELISA tests such as VIDAS Biomerieux have demonstrated greater sensitivity, to an average of 97-98% and a specificity of about 40%; these methods can be used to exclude patients with PE and low/moderate pre-test probability In the Emergency Department, a negative result in the ELISA DD, may exclude the PE to about 30 percent of the patients without imposing additional tests. The safety of PE exclusion was not validated in patients that associate moderate clinical pre-test probability if classification was done using a probability scheme structured on three levels. But if it was used, Wells rule which classify patients in 2 categories: with improbable PE or possible PE, determination methods with moderate sensitivity are valued as safe for the exclusion of the PE to patients with improbable PE (for example, a score = 4 points). Assessment of the need for a determination of the value DD in a situation, remains a matter of clinical choice.(5)

Recent developments in managing patients with suspicion of PE, improved accuracy in diagnosis and management algorithms made them safer and more affordable. Clinical trials are evaluating the diagnostic processes and are trying to make them even simpler and less costly. Patients with low risk of PE, with a negative DD test can avoid imaging tests; those with moderate risk, with a negative quantity DD test, the may have excluded diagnosis without the need for imaging tests.

Limits and new perspectives

There still are under discussion all the situations where the DD tests are positive and when we cannot exclude deep venous thrombosis (DVT) or PE, such as post surgery, cases, pregnancy and the postpartum period, in patients with DVT or PE in history, in the case of malignancies and in old people.

In a study performed on a hospitalized population, patients in surgical and medical wards, with suspicion of PE, ELISA DD test proved to be negative only in 5% of cases (5 patients from 73).(6)

Radel et al. analyzed the value DD in a population of 1208 patients, divided into 6 age classes, and demonstrated the uselessness of applying the test in patients over 80 years; the test ruled out PE in 2 of 3 patients up to 70 years, but only 5% of those aged over 80 years;(7) Other authors have tried to raise the limit, the cut-off from 500 to 600 or 700ng/l. The study made by Linghini et al. showed that in order to increase the specificity of the test to the entire cohort the cut-off should be 900ng/l, value at which sensitivity is of 95%, but the number of false-negative cases is growing up quickly, which makes this strategy to be uncertain and risky.(8)

Studies made in patients with malignancies and suspicion of PE, although few, have shown that DD evaluation in these patients was absolutely meaninglessness. Radel et al. studied a group of 1721 patients with neoplasia, and with suspicion of PE. The results were: DD below the 500ng/ml in 494 (32%) of those 1,554 patients without a history of neoplasia, compared to only 18 (11%) of the 169 patients with known malignant pathology, which illustrates the low specificity of the assay in the case of malignancies.(9) Hence, we conclude that evaluation of DD in the Emergency Department is useful to exclude PE in patients with malignancies although its utility is low due to the fact that approximately 1 in 10 patient will have the DD test result in normal limits.

Another challenge is to diagnose DVT/recurring PE; studies have shown that in patients with high risk of recurrence, values of plasmatic DD are also maintained elevated. The usefulness of the test is also found as a test that makes the exclusion of venous thromboses, but, as in the case of neoplasia, the number of patients with recurring negative tests is very small. Diagnostic strategies must include clinical pretest probability assessment and both DD and imaging tests.(10,11)

It is known that DD levels increase in pregnancy, along with its evolution, bringing about the decrease of tests specificity and limiting their usefulness. A study that analyzed the evolution of fibrinolysis markers in pregnancy showed that 39 percent of pregnant women have presented values of DD in normal limits, before 30 weeks of gestation, and 25% have maintained negative tests until week 42. As there are studies which show that although the specificity is low, test sensitivity is also influenced, in the case of pregnant women, it is probably safer not to treat a suspected DVT/PE if DD values are in the normal range.(1,12)

There are studies that have examined the usefulness of the DD, as a prognostic factor in PE, side by side with right cardiac dysfunction markers and with prognostic and clinical factors. It has been demonstrated that patients who died had high levels of DD compared to those who have survived. Therefore, it is believed that patients with confirmed PE and DD values < 1500ng/ml show lower mortality risk.(13)

The use of DD was studied to identify patients at high risk of recurring PE, which require long-term anticoagulant therapy, without reaching a concrete result. Patients with high values of DD, at one month after discontinuation of treatment, show high incidence recurrence, which may be lowered through the continuation of therapy; in patients with normal values of DD, the optimal duration of anticoagulant therapy was not established.(14)

As a result of these studies, we conclude that the high sensitivity that they have, DD evaluation tests represent a good way for the exclusion of PE/TVP; on the other hand, their low specificity makes them not capable to confirm the diagnosis of PE. Because most patients with suspicion of PE, finally do not have this pathology, it is reasonable to use DD as a first-line tests, after evaluating the clinical probability. In the Emergency Department, DD test dictates the subsequent management in 1 of 3 patients with suspicion of PE.(2)

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