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Selected studies in the diagnosis of pulmonary embolism – review

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ABSTRACT

INTRODUCTION

Pulmonary embolism (PE) is the result of the narrowing or occlusion of the pulmonary artery or its branches by thrombotic material, which are most often thrombi originating from deep veins of the lower limbs or pelvis. Pulmonary embolism very quickly develops life-threatening symptoms, which is why rapid diagnostics and the implementation of appropriate treatment are particularly important.

AIM OF THE STUDY

The aim of the following study is to summarize the state of knowledge about the effectiveness of selected methods in the diagnosis of pulmonary embolism.

STATE OF KNOWLEDGE

In diagnostic strategies regarding pulmonary embolism, the clinical probability of disease, D-dimer concentration, angio-CT examination and lung scintigraphy play a key role. Determining the clinical probability of the disease in combination with the determination of D-dimer concentration allows safe exclusion of pulmonary embolism in a significant percentage of patients. In the analyzed studies, attention was drawn to the large negative predictive value of such a procedure and the necessity to choose an appropriate scale, adjusted to the incidence of PE in a given area.

The dissemination of multi-row computed tomography has made it a method of choice in the assessment of pulmonary vessels in the event of suspected pulmonary embolism. In the analyzed studies, attention was paid to the high negative predictive value of angio-CT, in particular in connection with the determination of clinical probability and the determination of D-dimer concentration. However, it may be controversial to choose a procedure for patients with high clinical probability of PE and a negative result of angio-CT.

Scintigraphy is considered safe for patients due to the significant reduction of exposure to radiation - low enough that this method could be used also in pregnant women. Analyzed studies have proven that scintigraphy is as effective and safe in excluding pulmonary embolism as computed tomography, and its use may result in the development of new, automated methods for diagnosing pulmonary embolism.

SUMMARY

The dissemination of factors predisposing to pulmonary embolism made it one of the main causes of mortality, morbidity and hospitalization in Europe [4]. The increased risk of PE affects people over 40 and doubles in every subsequent decade, which means that, in an ageing European society, both the incidence and mortality will increase [6]. Due to non-specific signs and symptoms, which may indicate other diseases it is vital to introduce fast and safe diagnostics which may confirm or rule out pulmonary embolism.

INTRODUCTION

Pulmonary embolism (PE) is caused by the narrowing or closure of the pulmonary artery or its branches by the thrombotic material. This material is most often thrombi originating from deep veins of the lower limbs or the lesser pelvis. A much less frequent factor may be amniotic fluid,

air, fat tissue or tumour mass. There have also been reports of iatrogenic pulmonary embolism caused by dislocated embolization materials.

Determining the exact epidemiology of pulmonary embolism is difficult for a number of reasons. It may proceed without clinical symptoms and be diagnosed accidentally [1] or immediately manifest as sudden cardiac death [2]. It is also important that PE, along with deep vein thrombosis (DVT) are components of a larger disease entity known as venous thromboembolism (VTE) [3]. In most cases, pulmonary embolism is the result of deep vein thrombosis, which is why most studies analyze epidemiology, risk factors and the natural history of these diseases as a whole [4]

Collective research indicates that venous thromboembolism is the third most common cardiovascular disease and affects 100-200 people per 100,000 per year [3]. It is estimated that in six European Union countries it is the reason of 317,000 deaths. Unfortunately, we do not have reliable statistics on the annual morbidity of VTE and PE in Poland.

The third place among the most frequent cardiovascular diseases, VTE owes to many predisposing factors, related both to the patient and the environment [4]. Venous thromboembolism, and thus pulmonary embolism, may be both idiopathic and caused by a factor that has worked within the last 3 months, up to 6 weeks before the diagnosis [5]. The most powerful factors provoking VTE are extensive trauma, fractures of the lower limbs and neoplastic diseases [6,7]. In women, a special risk factor is taking oral contraception and pregnancy - the risk of pulmonary embolism is greatest in the third trimester of pregnancy and up to 6 weeks after delivery [8].

The blockage of the pulmonary artery causes the failure of the right ventricle, which disturbs both blood circulation and gas exchange. In order to increase the pressure in the pulmonary artery (PVR), more than 30-50 percent of the cross-sectional area of the pulmonary arteries must be blocked [9]. An increase in PVR results in an increase in pressure in the right ventricle, which causes it to stretch and lengthens the contraction time. At the same time, neurohumoral activation causes constriction of systemic vessels which temporarily stabilizes the circulatory system [10]. In the case of prolongation of right ventricle contraction to early left ventricular diastole, desynchronization of ventricular contraction occurs, impeding left ventricular filling, reducing cardiac output (CO) and contributing to hypotension and haemodynamic destabilization [11]. As a consequence of haemodynamic instability and low CO, there is desaturation of mixed venous blood. The zones of reduced flow in the pulmonary vessels connected to the zones of normal blood supply lead to an imbalance between ventilation and perfusion. Nearly one-third of patients may experience right-to-left leakage through the patent

oval duct, resulting in severe hypoxia and increased risk of paradoxical stroke or embolism [12].

Life-threatening changes in pulmonary embolism develop very quickly, causing a sudden deterioration of the patient's health, which is why it is necessary to quickly diagnose the disease and apply appropriate treatment. Thus the aim of the study is to summarize the state of knowledge on the effectiveness of selected diagnostic techniques in the diagnosis of pulmonary embolism.

STATE OF KNOWLEDGE

CLINICAL PROBABILITY

The sensitivity and specificity of the signs and symptoms are limited but combined with the results of the basic additional tests and the appropriate assessment by the physician, allows to determine patient’s pre-test probability (PTP) of the occurrence of confirmed PE. The probability of confirming pulmonary embolism depends not only on the properties of the diagnostic test (eg angio-CT) but also on the pre-test probability, therefore its determination is the basis in the diagnostic algorithms for PE [4].

The value of the probability assessment has been confirmed in numerous studies. The analysis carried out by Douma et al in seven Dutch hospitals compared the likelihood estimates of pulmonary embolism in four scales (Wells scale, simplified Wells scale, modified Geneva scale and simplified modified Geneva scale). The study included 807 patients, 23% were confirmed with pulmonary embolism. In 62% (Wells simplified scale) up to 72% (Wells scale) of patients, the probability of pulmonary embolism was defined as low. In conjunction with the D-Dimer concentration assay, this allowed embolism to be eliminated in 22-24% of patients. What's more, the incorrect assessment at the PTP connection and the D-Dimer marking was similarly common (1 patient, 0.5% to 0.6%) [13].

A meta-analysis by Ceriani et al, comparing different scales determining the likelihood of pulmonary embolism, included 29 trials and 31,215 patients. In the case of three-point scales, the probability results were: small 6-13%, moderate 23-25% and large 49-76%. For two-stage scales: PE unlikely - 6-8% and PE probable - 23-34%. Meta-analysis results indicate the similar accuracy of scales determining the probability of pulmonary embolism. However, the authors of the study concluded that the different results of assessments are forcing physicians to choose the most appropriate scale, which should be dictated by the prevalence of PE in a given area, the type of patients (hospital or outpatient patients) and the D-dimer assay method [14].

Similar conclusions have been drawn by Lucassen et al in their meta-analysis of 52 studies and 55 268 patients. They indicate that using the scales for determining the pulmonary embolism probability conjoined with D-dimer assay can safely rule out, the occurrence of PE. However, it is important to choose the right scale and methods for the determination of D-dimers depending on PE prevalence in a given area. [15]

D-DIMER

D-dimers are a product of clot decay and can be detected in the patient's blood by means of appropriate tests. In the presence of an acute thrombus, their concentration increases due to simultaneous activation of the coagulation system and fibrinolysis. The ESC guidelines for the diagnosis and management of acute pulmonary embolism indicate a high negative predictive value (NPV) of ELISA (or derivative) tests, which means that the correct concentration of D-dimer indicates a low probability of acute DVT or PE. Due to numerous conditions causing the production of fibrin (including tumours, inflammation, bleeding, surgery), the positive predictive value of this parameter is low [4].

For the above-mentioned reasons, the research is focused on the usefulness of D-dimer assays to exclude PE. A prospective study conducted by Wells et al on a group of 930 consecutive patients with suspected pulmonary embolism confirmed the high negative predictive value of the D-dimer assay together with the determination of the pre-test probability of PE. Of the 437 patients in whom the probability of PE was defined as low and with a negative result of D-dimers, only one patient developed the pulmonary embolism (NPV = 99.5%). The authors of the study point out that segregation of patients based on PTP and the D-dimer assay is safe for patients and reduces the need for costly imaging [16]. On the other hand, the basic role of D-dimers as a parameter excluding pulmonary embolism is also increasingly being questioned. Complicated and demanding experience in the use of D-dimers in clinical practice increases the importance of research on finding a different, perhaps more specific parameter. In other studies the correlation between some f the routinely marked blood parameters, such as PCT, MCHC, RDW, PDW and INR, and confirmation of pulmonary embolism in the angio-CT has been found [29].

A meta-analysis by Carrier et al summarized the results of seven studies (six prospective and one randomized trial) estimating a 3-month risk of thromboembolism. In 5622 patients with PTP of pulmonary embolism defined as "low / moderate" (according to the Geneva scale) or "unlikely" according to the Wells scale, the concentration of D-dimers was determined. Based on these two factors, the pulmonary embolism was ruled out in 2,248 patients and treatment

was discontinued. The three months observation showed that the risk of thromboembolism in untreated patients was 0.14% (3 people in 2166). The authors of the analysis concluded that with appropriate PTP determination and D-dimer concentration, it is possible to safely and effectively exclude pulmonary embolism in a large proportion of patients with suspected PE. [17]

Other studies indicate limitations of D-dimer tests. Their specificity decreases with age of the patient and in people above 80 years of age is only about 10% [18]. The ADJUST-PE inter-center study, under the direction of Righini, tested the suitability of the age-modified cut-off point for D-dimer concentrations. The analysis included 3346 patients with suspected pulmonary embolism. Adapted to the age cut-off point in patients over 50 years of age was determined from the formula: age x 10μg / l. 337 patients with a D-dimer concentration above 500 μg / L, but below the age-appropriate cut-off point, were selected from the study group. In a three-month observation, only one of 331 patients had PE (0.3%). Significant results were also obtained in the group of patients over 75 years of age in whom PTP was defined as "non-high" (673 people). The application of the age-modified cut-off point allowed to increase the number of patients who had excluded pulmonary embolism from 43 (6.3%) to 200 (29.7%) without false negative results. The authors of the study concluded that using an age-adjusted cut-off point for D-dimers can increase the number of patients who will be excluded from pulmonary embolism without unnecessary additional tests.

COMPUTED TOMOGRAPHY OF LUNGS

The dissemination of multi-row computed tomography (MDCT), which is characterized by the good quality of arterial vascular contrast and high both temporal and spatial resolution, made CT angiography the clinical method of choice in the assessment of pulmonary vessels in the event of suspected pulmonary embolism. [4] Previous studies [19,20] suggest that computed tomography provides sufficient visualization of pulmonary arteries at least to the level of segmental arteries, whereas there are controversies regarding patients with negative CT and high clinical probability of PE, in which thrombus may be present at the level of arteries not measurable in MDCT [4].

The study conducted by Goodman et al was to check the possibility of PE exclusion with MDCT in patients with various PTPs. The analysis conducted on a group of 711 patients confirmed the high negative predictive value of the negative CT result in patients with low and moderate pulmonary embolism (96% and 89% respectively), whereas in patients with high probability it was only 60%. At the same time, in patients with moderate and high PTP pulmonary embolism,

the positive predictive value was 92% and 96%, respectively, while it was significantly lower in patients with low probability (58%) [21].

Another study tested the safety of exclusion of pulmonary embolism based on the determination of the D-dimer concentration in the patient's blood in combination with multi-row CT. The analysis included 3306 patients with suspected PE. On the basis of computed tomography, pulmonary embolism was excluded in 1505 patients, of whom 1,393 patients were withdrawn from anticoagulant treatment. In a three-month follow-up, pulmonary embolism was found in 1.3% of people from the mentioned group, whereas pulmonary embolism could be the cause of the death of seven patients (0.5%) with a negative CT result. Based on this data, the authors concluded that PTP, D-dimer concentrations and CT can be used to safely exclude pulmonary embolism based on the PTP determination [22].

The dissemination of computed tomography and its performance from other indications (chest cancer, paroxysmal atrial fibrillation, heart failure) results in frequent random diagnoses of pulmonary embolism. A meta-analysis conducted by Chiu and O'Conell on a group of 10,000 patients indicates that PE is accidentally detected in 2.6% of patients. In groups of risk of pulmonary embolism, this percentage is even higher (3.1% in people with cancer, 4.0% in hospitalized patients, 7.6% in patients of intensive care units) [23]. There have been no reliable studies on the management of such patients [4], however, the literature provides recommendations for anticoagulant therapy in patients with thrombi in lobular or more proximal arteries and in patients with cancer [4,24].

LUNG SCINTIGRAPHY

Lung scintigraphy is a diagnostic method that uses radioactive isotopes to assess perfusion and lung ventilation. Intravenous administration of 99m technetium-labelled molecules enables evaluation of the patency of pulmonary vessels. To increase the specificity of the study, ventilation tests using markers such as xenon 133 or technetium 99m are also used. [25] The minimum amount of contrast medium used for the test reduces exposure to radiation - in the case of lung scintigraphy, it is 1.1 mSv for an average adult (for comparison, spiral computed tomography causes exposure to about 2 to 6 mSv) [26]. Such low radiation doses make this method safe even for pregnant patients [4].

A prospective study conducted on a group of 1417 patients with suspected PE proved that scintigraphy is as effective in excluding pulmonary embolism as computed tomography. Patients were divided into two groups according to the applied study, followed by 3 months observation. Of the 701 patients examined with MDCT, 133 (19,2%) were diagnosed with PE. Out of 561 people with negative results, PE developed in 2 (0.4%) patients. By means of

scintigraphy, embolism was confirmed in 101 (14.2%) patients, but it was excluded in 611. In 6 patients from the second group, PE developed, which resulted in one fatal case [27].

The use of scintigraphic methods may also result in the objectification and automation of pulmonary embolism diagnosis. A study conducted in Aachen on a group of 53 patients checked the possibility of using automated diagnostic algorithms using the SPECT method. The diagnosis made by the algorithm was compared with the diagnosis made by two experienced doctors. Sensitivity and specificity of the conventional method were 0.91 and 0.97, respectively, while in the automatic method - 0.95 and 0.84. In the second case, the percentage of false positive results caused by image artefacts increased. This was caused by image artefacts. The combination of both methods and the visual removal of artefacts led to a sensitivity of 0.95 and specificity of 1.0, which may be the reason for the development of new strategies [28].

SUMMARY

The dissemination of factors predisposing to pulmonary embolism made it one of the main causes of mortality, morbidity and hospitalization in Europe [4]. The increased risk of PE affects people over 40 and doubles in every subsequent decade, which means that, in an ageing European society, both the incidence and mortality will increase [6].

Early clinical diagnosis of pulmonary embolism remains an issue. Due to non-specific signs and symptoms, it may not be recognized. In some cases, the symptoms may be indicative of myocardial ischaemia, acute coronary syndrome or aortic dissection. The need to exclude these conditions may result in prolonged diagnosis and pose a danger to the patient, thus, it is important to know the factors predisposing to the PE and determine its clinical probability, as well as perform appropriate imaging tests that will help confirm or rule out the disease [4]

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