Investigation of relationship between the D-dimer and ischemia-modified albumin levels with the radiological imaging-based pulmonary embolism severity score in acute pulmonary embolism

Akut pulmoner embolizmde D-dimer ve iskemi modifiye albümin değerleri ile radyolojik görüntüleme-esaslı pulmoner embolizm şiddet skoru arasındaki ilişkinin incelenmesi

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ABSTRACT

Objective: To investigate possible relationship between the D-dimer and ischemia-modified albumin (IMA) levels and radiological imaging-based severity scores in pulmonary embolism (PE) based on two different radiological characteristics; the pulmonary arterial obstruction index (PAOI) and the right ventricle/left ventricle (RV/LV) ratio.

Methods: In this prospective cohort study, forty-seven patients presenting to the emergency department and definitively diagnosed with PE using spiral computerized tomography (CT) were initially enrolled in the study. Levels of IMA and D-dimer were assessed colorimetrical and immuno-turbidimetric methods, respectively. The PAOI and RV/LV ratios were calculated from CT images. The levels of biochemical parameters between the groups were compared with use of Mann-Whitney U and Kruskal-Wallis tests and relationship between the radiological scores were assessed using the Spearman correlation test.

Results: Analysis of the calculated PAOI and RV/LV ratio revealed a significant correlation between them (r=0.36, p=0.023). D-dimer levels differed considerably among the mild (<40%), moderate (40%-60%) and severe (60%) groups constituted on the basis of PAOI (p=0.039). This difference stemmed from those in D-dimer levels in the mild group, PAOI <40 % and the severe group, PAOI 60% (p=0.02; Z= -2.328). In addition, D-dimer levels and PAOI revealed a positive correlation, but no similar correlation was determined between D-dimer levels and RV/LV. There were no significant correlations between IMA and D-dimer levels, PAOI and RV/LV ratios.

Conclusion: In the biochemical determination of severity of PE based on radiological characteristics, D-dimer may be a more relevant marker than IMA, which has been proposed as a new marker. *(Anadolu Kardiyol Derg 2010; 10: 346-52)*

Key words: D-dimer, ischemia-modified albumin, pulmonary embolism, pulmonary arterial obstruction index, radiological severity, spiral computed tomography

ÖZET

Amaç: İki farklı radyolojik parametre, pulmoner arter obstrüksiyon indeksi (PAOI) ve sağ ventrikül/sol ventrikül oranı (RV/LV) temel alınarak, radyolojik görüntüleme-esaslı pulmoner embolizm şiddet skoru ile D- dimer ve iskemi modifiye albümin (IMA) düzeyleri arasındaki muhtemel ilişkiyi incelemek.

Yöntemler: Bu prospektif kohort çalışmasında, acil servise başvuran ve spiral bilgisayarlı tomografi (CT) ile PE kesin tanısı konulan kırk yedi hasta çalışmaya dahil edildi. D-dimer ve IMA düzeyleri sırasıyla immuno-turbidimetrik ve kolorimetrik metodlarla belirlendi. Bilgisayarlı tomografi görüntülerinden PAOI ve RV/LV oranları hesaplandı. Biyokimyasal parametrelerin gruplar arasındaki seviyeleri Mann-Whitney U test ve Kruskal-Wallis test kullanılarak karşılaştırıldı ve radyolojik skorlar ile ilişkileri Spearman korelasyon testi kullanılarak belirlendi.

Bulgular: Hesaplanan PAOI ve RV/LV oranlarının analizi aralarında belirgin bir ilişki olduğunu yansıttı (r=0.036, p=0.023). PAOI temelinde oluşturulan hafif (< %40), orta (%40 - %60) ve şiddetli (> %60) PE grupları arasında D-dimer düzeyleri göze çarpan oranda farklıydı (p=0.039). Bu fark hafif grup, PAOI< %40, ile şiddetli grup, PAOI> %60 arasındaki D-dimer seviyelerindeki farklılıktan kaynaklanıyordu (p=0.02; Z= -2.328). Aynı zamanda, D-dimer düzeyleri ile PAOI pozitif bir korelasyon gösteriyordu, fakat D-dimer düzeyleri ile RV/LV oranı arasında benzer bir korelasyon yoktu. İskemi modifiye albümin düzeyleri ile D-dimer düzeyleri, PAOI ve RV/LV oranı arasında anlamlı bir korelasyon yoktu.

Sonuç: Radyolojik parametreler temelinde PE'nin şiddetinin biyokimyasal olarak belirlenmesinde D-dimer, yeni bir marker olarak önerilen IMA'ya göre daha uygun bir marker olabilir. *(Anadolu Kardiyol Derg 2010; 10: 346-52)*

Anahtar kelimeler: D-dimer, iskemi modifiye albümin, pulmoner embolizm, pulmoner arter obstrüksiyon indeksi, radyolojik ciddiyet, spiral bilgisayarlı tomografi

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Introduction

Pulmonary embolism (PE) is a common and potentially fatal cardiovascular disorder. The severity ranges from clinically unimportant, incidental cases, to life threatening massive embolism with higher mortality (1). None of the existing laboratory tests can reliably exclude the diagnosis and clinicians must therefore rely on diagnostic imaging methods. Improvement of the computerized tomography (CT) technique with the introduction of spiral CT has made this a commonly used method in recent years (2).

Even when PE is properly treated with anticoagulant therapy, the mortality rate in hemodynamically stable patients ranges from 2% to 7% (3). Parameters such as hypotension, right ventricular dysfunction and elevated troponin levels are associated with adverse prognosis and poor outcome (4, 5). These patients may require more intensive treatment and usually benefit from thrombolytic therapy (6). Two radiological characteristics have been shown to be associated with poor outcome and high in-hospital mortality: a high pulmonary arterial obstruction index (PAOI) and an increased right ventricle/left ventricle (RV/LV) ratio (7). In a recent study, using these radiologic characteristics Ghanima et al. (8) demonstrated that the level of D-dimer is related to the severity of PE.

During acute ischemic conditions the metal binding capacity of albumin is modified and generates a metabolic variant of protein with reduced transition metal binding. This change is quantifiable and commonly known as ischemia modified albumin (IMA). Recently, IMA measurement has been proposed as a sensitive marker for the diagnosis of myocardial ischemia presenting with typical acute chest pain (9). However, IMA levels are also known to increase in other ischemic conditions, as well as being an indicator of oxidative stress, and may not be specific for cardiac ischemia. Recently, Türedi et al. (10) showed that the level of IMA may be of use in the diagnosis of PE, another ischemic condition.

We carried out this study in the light of this new information aiming at investigating the relationship between the D-dimer and IMA and radiological imaging-based severity scores utilizing the PAOI and the RV/LV ratio in acute pulmonary embolism.

Methods

Study Design

This prospective cohort study was performed in the Emergency Department of Karadeniz Technical University Faculty of Medicine. The protocol for the study was approved by the hospital's local ethical committee and the agreement of each patient enrolled was obtained. The inclusion period was from January 2007 to June 2007.

Study population

Forty-seven patients presenting to the emergency department and definitively diagnosed with PE using spiral CT were enrolled in the study. Exclusion criteria were: (i) other ischemic diseases, such as acute coronary syndrome, acute myocardial infarction or ischemia, acute cerebrovascular disease, acute peripheral vein occlusion or acute mesenteric ischemia; (ii) an abnormal serum albumin level making the determination of IMA levels impossible (normal level 3.5-5.5 mg/dl); (iii) advanced liver, kidney or heart insufficiency; (iv) age < 18 years; (v) allergy to contrast material; (vi) venous thromboembolism or PE in the previous six months; or (vii) refusal to participate in the study.

Data collection and processing

Emergency physicians completed a form requesting details of medical history (such as risk factors), physical examination, chest x-ray and ECG signs. Ischemia modified albumin, D-dimer and arterial blood gas analyses were performed for all patients before tomographic examination. After spiral CT examination, PAOI and the RV/LV ratio were calculated.

Methods of measurement

i. IMA measurement: Blood samples were taken from the brachial vein using the venopuncture technique at time of presentation. Vacutainer tubes without anticoagulants were used to obtain serum. Serum specimens were obtained following 15 minutes of centrifugation at 3000 rpm. Specimens to be used for measuring IMA blood concentrations were pipetted into Eppendorf tubes and stored at -80 °C.

Reduced cobalt to albumin binding capacity (IMA levels) was analyzed using the rapid and colorimetric method developed by Bar-Or et al. (11). The results were reported as absorbance unit (ABSU).

ii. D-dimer measurement: D-dimer was assayed using the quantitative, immuno-turbidimetric STA-Liatest D-dimer assay kit (Diagnostica Stago, Asnieres, France) run an automated coagulation analyzer (STA-compact, Diagnostica Stago) in a routine setting.

iii. CT imaging: All patients underwent spiral CT within 12 hours, using a 16 detector spiral CT scanner (Siemens Somatom Sensatio, Germany). A total volume of 120-150 ml non-ionic contrast medium (Iemeron, Bracco, Milan, Italy) containing 300 mg iodine/ml was injected intravenously at a rate of 4 ml/sec and with a scan delay of 10-15 sec.

iv. CT image interpretation: Definitive diagnosis of PE was established using spiral CT, the scans being reviewed by different blinded radiologists experienced in reviewing spiral CT. The spiral CT criterion used to diagnose PE consisted of direct visualization of non-occlusive endoluminal thrombus (central filling defect or partially outlined by contrast agent) or of complete occlusion by thrombus in normal sized or enlarged vessels including the main pulmonary arteries, lobar arteries, segmental arteries and sub-segmental vessels.

Scanning was performed from the top of the diaphragm to a level slightly above the aortic arch during a single 30-sec breath hold. Film hard-copy images were obtained at standard mediastinal and lung settings. Pulmonary arterial obstruction index was calculated on the basis of degree of obstruction and the location of the thrombus at CT according to the method described by Qanadli et al. and the RV/LV ratio calculated by computing the ratio between the width of the right and left ventricular cavities assessed on axial images obtained at the maximal plane distances between the ventricular endocardial free wall and the interventricular septum, perpendicular on the long axis, by one or other blinded radiologist (12). Fig. 1A and 1B show sagittal and transverse sections from one of the patients we used in calculating PAOI, and Fig. 2 shows a transverse tomography section belong to one of the patients we used in calculating RV/LV levels.

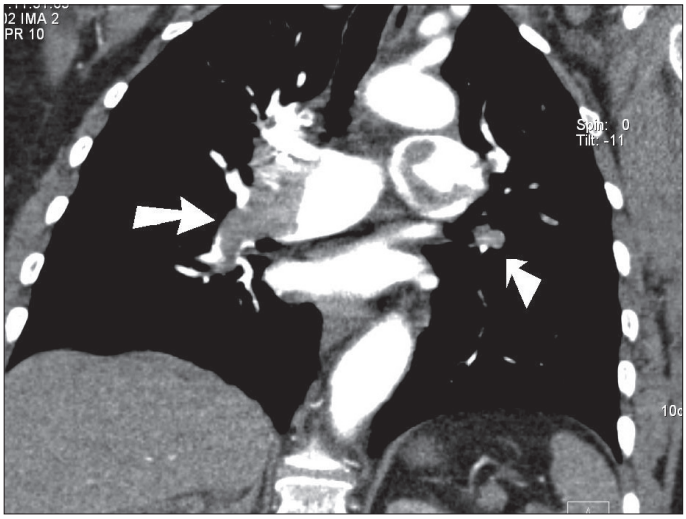

Figure 1A. Pulmonary embolism image at examination of sagittal tomography section used in calculating PAOI
PAOI-pulmonary artery obstruction index

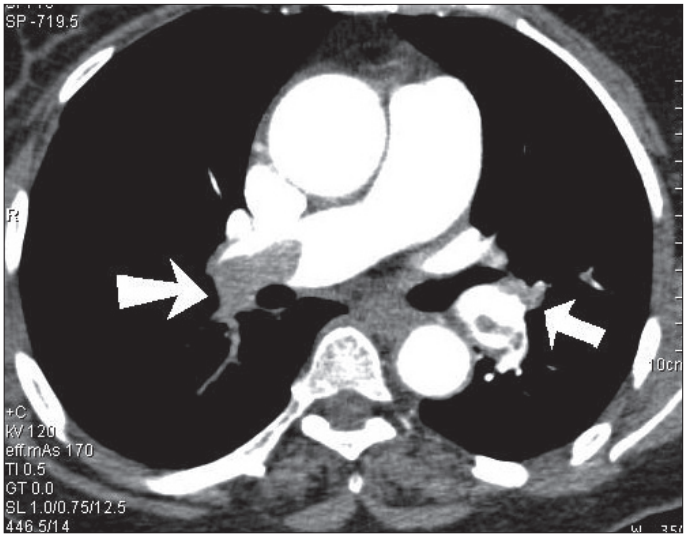

Figure 1B. Pulmonary embolism image at examination of transverse tomography section used in calculating PAOI
PAOI-pulmonary artery obstruction index

Statistical Analysis

Statistical analyses were performed using SPSS for Windows 11.0 (SPSS, Chicago, IL, USA). Our data were heterogeneous, and data normality was assessed using the Kolmogorov-Smirnov normality test. The levels of biochemical parameters between the groups were compared with use of Mann-Whitney *U* and Kruskal-Wallis tests and relationship between the radiological scores were assessed using the Spearman correlation test. Statistical significance was assumed at a level of $p<0.05$.

Results

A total of 47 consecutive patients with PE were initially enrolled in the study. Eight patients were excluded under predefined criteria; acute coronary syndrome (n=3), paradoxical embolism (n=1), advanced kidney insufficiency (n=1), or peripheral arterial occlusion (n=2), and one patient refused to participate (n=1).

The clinical characteristics of the remaining 39 PE patients are summarized in Table 1.

Analysis of PAOI and RV/LV data revealed a positive correlation between them (r=0.6, p=0.0001). Additionally, D-dimer levels and PAOI exhibited a positive correlation (r=0.36, p=0.02), but no similar correlation was determined between D-dimer levels and RV/LV ratio (r=0.26, p=0.1). There were no significant correlations between IMA and D-dimer levels (r=-0.06, p=0.7), PAOI (r=0.04, p=0.8) and RV/LV ratios (r=-0.1, p=0.5).

We classified severity of PE on the basis of PAOI as mild (<40%), moderate (40-60%) or severe (>60%). Average IMA and D-dimer levels for the groups determined according to this classification are shown in Table 2. According to these results, D-dimer levels differed considerably among the mild (<40%), moderate (40%-60%) and severe (60%) groups based on PAOI (p=0.039). This difference stemmed from the difference in

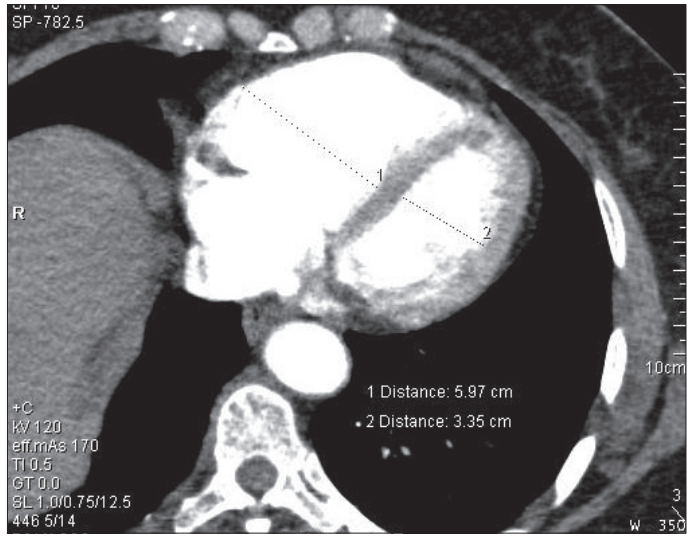

Figure 2. Calculation of RV/LV level at transverse tomography section examination
RV/LV -right ventricle/left ventricle

Table 1. Clinical characteristics of the 39 PE patients

Age, years	67.2±13.5
Body temperature, C°	36.6±0.7
Pulse, beat/min	101.2±19.6
Systolic blood pressure, mmHg	120.6±34.1
Diastolic blood pressure, mmHg	75.8±19.5
Respiratory rate, breath/min	26.8±5.9
Sex, n(%)	
Male	11 (28.2)
Female	28 (71.8)
Clinical presentation, n (%)	
Dyspnea	12 (30.7)
Chest pain	8 (20.5)
Hemoptysis	6 (15.3)
Syncope	1 (2.5)
Symptoms of deep vein thrombosis	8 (20.5)
Asymptomatic	4 (10.2)
Risk factors, n (%)	
Surgery within the previous 1 month	5 (12.8)
Immobilization	14 (35.8)
Cancer	4 (10.2)
Previous deep vein thrombosis	4 (10.2)
Trauma	1 (2.5)
Chronic obstructive pulmonary disease	1 (2.5)
Cardiac failure	1 (2.5)
Laboratory	
Glucose, mg/dl	130.2±50.5
Blood urea nitrogen, mg/dl	21.9±11.7
Creatinine, mg/dl	0.9±0.2
Alanine aminotransferase, U/L	29.4±24.6
Aspartate aminotransferase, U/L	30.0±19.5
Treatment applied, n (%)	
Conventional therapy	35 (89.8)
Thrombolytic therapy	4 (10.2)

Data are presented mean±SD and proportions/percentages
PE-pulmonary emboli, SD-standard deviation

D-dimer levels in the mild group, PAOI <40 % and the severe group, PAOI 60 % (p=0.02; Z= -2.328). There was no significant correlation between IMA levels and severity groups constituted on the basis of PAOI (p=0.338).

We also classified severity of PE according to RV/LV ratios; mild (RV/LV ratio <1), moderate (RV/LV ratio 1.1-1.4), or severe (RV/LV ratio >1.5). Average IMA and D-dimer levels for the groups determined according to this classification are shown in Table 3. No significant difference was determined between RV/LV ratio and D-dimer or IMA levels (for D-dimer, p=0.06; for IMA, p=0.99).

Discussion

In the present study we investigated whether there is a correlation between PE severity and IMA. We determined higher IMA levels with increasing PAOI. In addition, there was no significant correlation between IMA and RV/LV ratios and PAOI. Otherwise, the higher D-dimer values correlate with a higher PAOI; but there was no similar correlation between RV/LV ratio and D-dimer.

PE is a potentially fatal disorder. Mortality is thought to be caused in part by pressure overload of the right ventricle secondary to acute pulmonary arterial hypertension caused by PE. This initially results in right ventricular dysfunction, which may progress to right ventricular failure and circulatory collapse (13). One study demonstrated that a substantial proportion (40%) of normotensive patients with acute PE presents with echocardiographic signs of right ventricular dysfunction and that the presence of right ventricular dysfunction is a marker for adverse clinical outcomes such as a high rate of PE related shock or in-hospital mortality (14).

In the literature, the ratio of right ventricle to left ventricle short axis diameters (RV/LV) has been proposed as an accurate sign for the presence of right ventricle dysfunction (15). CT scans were considered to show no right ventricle dysfunction if the ratio of RV/LV was 1.0 or less, moderate right ventricle dysfunction if the ratio was greater than 1.0 but less than or equal to 1.5 and severe right ventricle dysfunction if the ratio was greater than 1.5; as recommended in the literature (16).

The extent of PE is commonly expressed by indicating the

Table 2. D-dimer and IMA levels in PE severity groups established on the basis of PAOI

Variables	Mild (PAOI: <40%) n=16		Moderate (PAOI: 40-60%) n=9		Severe (PAOI: >60%) n=14	
	Mean±SD	Range (Median)	Mean±SD	Range (Median)	Mean±SD	Range (Median)
D-dimer, µg/ml *	8.36±7.24**	23 (5.69)	14.33±9.95	27 (13.4)	17.72 ±12.65**	43 (13.7)
IMA (ABSU)	0.315±0.069	0.241 (0.300)	0.316±0.061	0.161 (0.319)	0.357±0.113	0.515 (0.343)

* Kruskal - Wallis test, p= 0.039 for difference in D - dimer levels between the PAOI groups
** Mann Whitney U test, p=0.02, Z= -2.328 for the difference in D - dimer levels between the mild, <40% PAOI group and the severe, 60% PAOI group*** Kruskal - Wallis test, p= 0.338 for IMA
ABSU - absorbance unit, IMA - ischemia modified albumin, PAOI - pulmonary artery obstruction index, PE - pulmonary emboli, SD- standard deviation

Table 3. D-dimer and IMA levels in PE severity groups constituted on the basis of RV/LV levels

Variables	Mild (RV/LV ratio <1)		Moderate (RV/LV ratio 1.1-1.4)		Severe (RV/LV ratio >1.5)	
	n=19		n=8		n=112	
	Mean±SD	Range (Median)	Mean±SD	Range (Median)	Mean±SD	Range (Median)
D-dimer, µg/ml*	10.67±9.50	30 (7.09)	9.29±9.48	28 (5.75)	18.95±11.82	39 (15)
IMA, ABSU**	0.325±0.058	0.213 (0.319)	0.355±0.175	0.515 (0.333)	0.323±0.055	0.185 (0.323)

* Kruskal - Wallis test for D - dimer, p=0.06 ** Kruskal - Wallis test for IMA, p=0.99
ABSU - absorbance unit, IMA - ischemia modified albumin, PE - pulmonary emboli, RV/LV - right ventricle/left ventricle, SD - standard deviation

anatomic level of the most proximal vessel affected by a clot (17). We calculated the vascular obstruction index using the scoring system described by Qanadli et al (12). In order to determine the CT obstruction index (PAOI), the arterial tree of each lung was regarded as having 10 segmental arteries (three belonging to the upper lobe, two to the middle lobe and to the lingual, and five to the lower lobe). The presence of embolus in a segmental artery scored 1 point, and embolus in the most proximal arterial level was given a value equal to the number of segmental arteries arising distally. To provide additional information about the residual perfusion distal to the embolus, a weighting factor was assigned to each value, depending on the degree of vascular obstruction. This factor was equal to zero when no thrombus was observed; 1, when partially occlusive thrombus was observed; or 2, with total occlusion. Isolated subsegmental embolus was regarded as a partially occluded segmental artery and was assigned a value of 1. Thus, the maximal CT obstruction index was 40 per patient. The percentage of vascular obstruction was calculated by dividing the patient score by the maximal total score and multiplying the result by 100 (12).

Vander Meer et al. (3) demonstrated that there was increased risk of death from PE for patients with an obstruction index of 40 % or higher. Kucher et al. (18) showed that PE patients with higher PAOI levels also have higher D-dimer values. In addition, Galle et al. (19) showed that D-dimer correlates with the extent of PE assessed using ventilation-perfusion scan. In our study, we demonstrated that the higher D-dimer values correlated with a higher PAOI; but that there was no similar correlation between RV/LV ratio and D-dimer. This situation may be due to biochemical and tomography sampling in the acute PE patients constituting the study group being performed on presentation and the period up until then, the embolic focus leading to high PAOI, being too short for morphological changes in the right ventricle to form in such a way as to produce a significant alteration in the RV/LV ratio. There is no information in the literature regarding presence of such a time-dependent difference in the development of PAOI and the RV/LV ratio.

During acute ischemic conditions, the metal binding capacity of albumin is modified and reduces transition metal binding, generating a metabolic variant of protein. This change is quantifiable and commonly known as IMA (20). Recently, IMA measurement has been proposed as a sensitive marker for the diagnosis of myocardial ischemia presenting with typical acute chest pain. IMA, which appears to be an indicator of oxidative stress, may not be specific for cardiac ischemia. Studies have demonstrated that many conditions may elevate IMA levels, such as mesenteric ischemia, peripheral arterial occlusion, deep venous thrombosis, stroke and acute cardiac arrest, and that IMA may be a diagnostic biomarker for these conditions (21-25). There are only a few reports in the literature about the diagnostic value of IMA in the diagnosis of PE. Türedi et al. (10) recently examined the serum IMA levels of 60 individuals, consisting of 30 PE patients who had been definitively diagnosed via spiral CT angiography and 30 healthy volunteers, and suggested that IMA levels may be useful as a discriminative marker to exclude PE. In the another study, Türedi et al. (26) showed that IMA was 93% sensitive and 75% specific in the diagnosis of PE. PPV was 79.4% and NPV was 78.6%. The authors suggested that IMA is a good alternative to D-dimer in PE diagnosis in terms of both cost and efficiency.

Ours is the first study to investigate whether there is a correlation between PE severity and IMA. Right ventricular myocardial ischemia and injury contribute to right ventricular dysfunction and failure during acute pulmonary embolism. An acute rise in pulmonary artery and right ventricular pressures and subsequent dilatation of the right ventricle may cause regional right ventricular ischemia and injury (27). We hypothesized that severe right ventricular pressure overload and dilatation due to PE might cause RV ischemia and increase IMA levels without necrosis. But our results did not support this hypothesis. We determined higher IMA levels with increasing PAOI, but this increase was not significant. In addition, there was no significant correlation between IMA and RV/LV ratios according to our results. This may be due to the fact that IMA levels are influenced significantly by a wide array of physiological variables, including exercise and hydration. They may also be elevated in a number of other diseases and oxidative conditions (28). During our patient selection, we eliminated patients with advanced liver, kidney or congestive heart failure, which can alter IMA levels. We were not able, however, to check for all variables, which could possibly influence IMA levels and these correlations.

Biochemical markers reduce many invasive and costly procedures used in determining disease diagnosis and course. Although it is easier, thanks to multi-sectional tomography, that has entered clinical practice, to diagnose PE and determine the severity of the disease radiologically, such processes, and especially those requiring contrast, cannot be applied to these patients. In addition, repetition of these procedures in respect of course of the disease raises costs and also exposes the patient to the extra burden imposed by radiation and contrast. In that regard, although tomography examination sensitivity provides a high level of information as specified by the physician, there is still a need for reliable biochemical markers to reflect the clinical course as much as the diagnosis of the disease. In these terms, D-dimer levels have a relative correlation with tomography findings, while IMA, under investigation as a possible new marker in the diagnosis of PE, appears less effective in that regard.

Study Limitations

The definitive diagnosis of PE was made using s-CTPA. The sensitivity and specificity of s-CT ranges from 53% to 100% and from 81% to 100%, respectively, when pulmonary arteriography is used as the standard for diagnosis of PE (29). In addition, due to the conditions in the center in which the study was performed, the tomography device used was a 16-detector one. Tomography devices with a greater number of detectors are used in similar studies under current conditions. For that reason, sub-segmental or micro embolisms invisible under s-CTPA may have been present.

Since our study was planned solely around the analysis of the correlation between radiological severity parameters and biochemical markers, it does not include such clinical parameters of PE severity as mortality, length of hospitalization, the need for intensive care or vasopressor support. In these terms, no definitive comment on the course of the disease can be made.

Conclusion

D-dimer, which is still used in PE diagnosis in the biochemical determination of severity based on PE radiological characteristics, may be a more suitable marker than IMA, which has been proposed as a new alternative. However, there is a need for wider studies in the light of the restricted nature of our own research and the importance of the subject matter.

Conflict of interest: None declared.

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