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RESEARCH ARTICLE

DEMOGRAPHIC AND CLINICAL FEATURES IN ACUTE PULMONARY EMBOLISM PATIENTS AND EVALUATION OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION EVOLUTION FREQUENCY

***Erhan Ugurlu, Tarik Sengoz, Ilknur Can, Nese Dursunoglu, Olga Yaylali and Dursun Dursunoglu**

Pamukkale University Medical Faculty, Turkey

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ABSTRACT

Objective: An acute pulmonary embolism is formed sudden obstructions in some pulmonary arterial and thrombus that cause these obstructions comes mostly from deep leg or pelvis veins. Acute pulmonary embolism with incomplete resolution is observed frequently and chronic thromboembolism can result in pulmonary hypertension. Our purpose in this study is to evaluate the frequency and markers of chronic thromboembolism pulmonary hypertension(CTEPH) and the demographic and clinical features of acute pulmonary embolism patients.

Material and Methods: Participants were 127 patients hospitalized due to an acute pulmonary embolism diagnosis between 1 January 2014- 30 April 2015. Patients having any kind deficiency in the D-Dimer blood test, arterial blood gas, computed tomography, lower extremity Doppler ultrasonography, echocardiography, clinical scoring (Wells and revised Geneva) were excluded. 45 patients, whose transcriptions were exact, were included in this study.

Results: The $p0_2$ value is found to be significantly low in submassive patients in comparison with non-massive patients. Values of Geneva scoring were found to be significantly different not only between submassive and massive patients but also between non-massive and massive. Significant difference between non-massive and massive is deteched in the value of D-Dimer. CTEPH was evolved on 10 subjects.

Conclusion: Diagnose acute pulmonary embolism with severe morbidity and mortality, then to start treatment accordingly by determining the severity of the disease are extremely important. Also, physicians need to be aware of CTEPH, which is a preventable complication of acute pulmonary embolism, if they are to predict which patients are likely to develop CTEPH.

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INTRODUCTION

Pulmonary embolism causing the series death and morbidity is common clinical condition (Pollack *et al*., 2011). Acute pulmonary embolism is formed sudden obstructions in some pulmonary arterial and thrombus that cause these obstructions comes from mostly deep leg or pelvis veins. Body fat, weather or amniotic fluid can also cause this situation (Moorjani *et al*., 2013). Venous thromboembolism pathogenesis can be explained as Virchow triad: stasis, endothelial injury and hypercoagulability (Smithburger *et al*., 2013). These three features determine the risk factors of thromboembolism cases. Immobilization, paralysis, atrial fibrillation, long duration trip and venous deficiency are the risk factors for stasis. Hypertension, atherosclerosis, trauma, surgery, catheter are the risk factors for endothelial injury. Malignancy, story of heavy smoking, pregnancy, obesity, estrogens therapy, sepsis, lower extremity traumata or surgery are also the risk factors for hyper coagulopathy (Smithburger *et al*., 2013). Pulmonary embolism and its symptoms are non-specific and because of that clinical diagnosis is not reliable. Although pulmonary angiography in diagnosis of pulmonary embolism has golden standard, since it is invasive operation it is not proper for every patient. Therefore, non- invasive methods with the combination of clinical scoring (Wells and revised Geneva) and laboratory finding are preferred for diagnosis. These non-invasive methods are lower extremity Doppler ultrasonography, ventilation-perfusion scintigraphy, spiral computed tomography angiography (Yetgin *et al*., 2014).

Acute pulmonary embolism with incomplete resolution is observed frequently and chronic thromboembolism can result in pulmonary hypertension. Underlying mechanism is not known on a large scale (Klok *et al*., 2012). Chronic thromboembolism pulmonary hypertension (CTEPH) is partly

Corresponding author: Erhan Ugurlu,
Pamukkale University Medical Faculty, Turkey

preventable, treatable, very frequent and reason of series rate of morbidity and mortality complication (Kayaalp *et al*., 2014). Our purpose in that study is to evaluate frequency and markers of chronic thromboembolism pulmonary hypertension and demographic and clinic attributes of acute pulmonary embolism patients.

MATERIALS AND METHODS

Study Population

Ethical approval was obtained from Ethical Board on Human Experiments, with the approval number 60116787-020/28459. 127 patients due to the acute pulmonary embolism diagnosis were hospitalized on the date of between 1 January 2014 - 30 April 2015. Patients having any kind deficiency of D-Dimer blood test, arterial blood gas, computed tomography (CT), lower extremity doppler ultrasonography, echocardiography (ECHO), clinical skoring (Wells and revised Geneva) were excluded from work. 45 patients, whose transcriptions were exact, were included to work. Wells and revised Geneva scores are shown in table 1 and table 2 (Torbicki et al., 2008). Pulmonary artery pressure (PAP) of patients in ECHO was measured in the beginning and 3-6 months period and despite of 3 month anticoagulant treatment were still high (mean PAP ≥ 25 mmHg), so their ventilation/perfusion scintigraphy data was recorded under suspicion of chronic thromboembolic pulmonary hypertension. Ventilation-perfusion scintigraphy parameters which is performed to patients who it is thought to have chronic embolism or owing to reasons of various contraindications could not have CT were recorded. Findings of angiography, which was done to patients that have not falling value of PAP despite of 3 month treatment, were also recorded.

Pulmonary embolism severity index

Subjects having pulmonary embolism are categorized three different part by European Society of Cardiology and American Heart Association. These categories are massive, sub-massive and non-massive. To mean massive pulmonary embolism, systolic blood pressure <90 mmHg or decrease more than >40 mmHg or cardiogenic shock (oliguria, lactic acidose, cold extremity) or syncope connected with circulatory collapse are necessary. In separation of sub-massive and non-massive, ECHO has crucial role. If there is overload on the right into ECHO or symptoms of myocardial injury, that means sub-massive pulmonary embolism can be possible (Torbicki *et al*., 2008). According to these criterions, patients are categorized as massive, submassive and non-massive.

Statistical analysis

Data is analyzed by using SPSS package. Continuous variables, average ± standard deviation and caterogical variables will be given as number and percentage. In comparisons of dependent group, when parametric test hypothesis is provided, significance test between difference of two same sample is used; on the other hand, when parametric test hypothesis is not provided, Wilcoxon paired two sample is used.

RESULTS

9 massive, 22 sub-massive and 14 non-massive patients were accepted to study. These patients were 21 male and 24 female. Patients blood gas, troponin T, D-Dimer, avarage PAP values, Wells and Cenova skoring are indicated in Table 3. $p0_2$ value is found significant low in sub-massive patients in comparison with non-massive patients. Values of Cenova scoring are found significant different not only between sub-massive and massive but also non-massive and massive. When examined measured avarege PAP values in the process of application, significant difference is confirmed between not only submassive and non-massive but also massive and non-massive. Significant difference between non-massive and massive is deteched in the value of D-Dimer.

Table 1. Wells Score

Variable	Points
Previous DVT or PE	1.5
Recent surgery or immobilization	1.5
Cancer	1
Hemoptysis	1
Heart rate >100 beats/min	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Clinical probability (3 level)	Total
Low	0-1
Intermediate	2-6
High	≥ 7
Clinical probability (2 level)	Total
PE unlikely	0-4
PE likely	> 4

DVT: Deep vein thrombosis; PE: Pulmonary embolism

Table 2. Revised Geneva Score

Variable	Points
Age > 65	1
Previous DVT or PE	3
Surgery or fracture within 1-month	2
Active malignancy	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75-94 beats/min	3
Heart rate ≥ 95 beats/min	5
Pain on lower limb deep vein at palpation and unilateral edema	4
Clinical probability (3 level)	Total
Low	0-3
Intermediate	4-10
High	≥ 11
Clinical probability (2 level)	Total
PE unlikely	0-3
PE likely	> 3

DVT: Deep vein thrombosis; PE: Pulmonary embolism

There was a risk factor (malignite, immobilization, story of embolism etc.) on 26 patient and deep vein thrombosis was realized on 18 patient. Chronic thromboembolism pulmonary hypertension (CTEPH) was evolved on 10 patient. The difference between patients having CTEPH and others is indicated in Table 4. 9 of the patients having CTEPH were submassive and one was massive. Even if there was no significant difference, pO_2 and pCO_2 values were found low and avarage PAP values were found high on patients who have CTEPH. Even if it is not important, Well and revised Geneva scores and D-Dimer values were deteched high on group having CTEPH.

Table 3. The demographic and clinical parameters of the participants are shown

	Submassive(n=22)	Massive(n=9)	Nonmassive (n=14)	P
Age	64.45 ± 11.35	65.67 ± 18.01	62.14 ± 12.81	0.804
pH	7.45 ± 0.06	7.46 ± 0.03	7.44 ± 0.05	0.82
$PaCO_2$(*mm/Hg*)	29.26 ± 5.47	31.74 ± 3.51	31.66 ± 5.97	0.319
PaO_2(*mm/Hg*)	58.14 ± 19.19	63.11 ± 16.05	86.86 ± 25.13	0.001
Wells score	4.8 ± 2.38	6.39 ± 2.27	4.57 ± 2.21	0.156
Revised Geneva score	7.14 ± 1.75	7.11 ± 1.27	4.39 ± 1.11	0.0001
Mean PAP(*mm/Hg*)	49.5 ± 15.46	45.11 ± 19.9	20.55 ± 2.02	0.0001
TroponinT(μg/l)	0.04 ± 0.05	0.1 ± 0.2	0.04 ± 0.06	0.267
D-dimer(ng/ml)	3483.09 ± 4034.61	5572.44 ± 3221.38	2721.5 ± 3693.25	0.032

PaO_2: Partial pressure of oxygen, $PaCO_2$: Partial pressure of carbon dioxide, PAP: Pulmonary arterial pressure

Table 4. The demographic and clinical parameters of CTEPH and no CTEPH are shown

	CTEPH(n=10)	No CTEPH (n=35)	P
Age	62.8 ± 13.97	64.31 ± 12.99	0.751
Gender (M/F)	4/6	17/18	0.792
pH	7.46 ± 0.03	7.44 ± 0.05	0.453
$PaCO_2$(*mm/Hg*)	29.34 ± 5.47	30.84 ± 5.34	0.44
PaO_2(*mm/Hg*)	59.8 ± 25.65	70.43 ± 23.35	0.111
Wells Score	5.15 ± 2.32	5.01 ± 2.4	0.875
Revised Geneva Score	6.7 ± 1.83	6.16 ± 1.98	0.442
Mean PAP	44.6 ± 13.01	39.84 ± 20.38	0.192
Troponin T(μg/l)	0.03 ± 0.01	0.06 ± 0.11	0.475
D-Dimer(ng/ml)	5713.8 ± 5449.54	3100 ± 3058.11	0.175

PaO_2: Partial pressure of oxygen, $PaCO_2$: Partial pressure of carbon dioxide, PAP: Pulmonary arterial pressure, CTEPH: Chronic thromboembolic pulmonary hypertension

DISCUSSION

Looking at the results of our study, pO_2 values were significantly lower in submassive patients than non-massive patients. The average value of pO_2 in submassive patients is 58.14±19.19 mmHg. In Sergio fasulla and colleagues' study, in which heparin and thrombolytic are compared in the treatment of submassive emboli patients, pO_2 values are respectively founded 61.8±8 and 62.3±9 mmHg (Fasullo *et al*., 2011). These values are similar to those values in our study. Although hypoxia does not help in distinction of massive and submassive, it may help to distinguish of non-massive patients. PO_2 average value of non-massive patients in our study is 86.86 ± 25.23 mmHg and these values are similar to values in people who are not sick. When we looked at Wells and revised Geneva risk scores for the risk classification for pulmonary embolism, it is seen that although there is no significant difference between the groups for Wells, there is significant difference between massive and non-massive, sub-massive and non-massive in revised Geneva. In the study done by Babak and colleagues with 54 pulmonic emboli and 32 control patients Wells scores did not show significant differences between two groups (Sharif-Kashani *et al*., 2012). In Kanbay and colleagues' study about comparing Wells score and EKG values to estimate the severity of PE, it is not seen a significant difference severe and mild groups (Kanbay *et al*., 2007). These results are similar to our study results. However, looking at recent studies, it is shown that Wells score gives more accurate results than revised Geneva score (Di Marca *et al*., 2015, Shen *et al*., 2016, Guo *et al*., 2015 and Gruettner *et al*., 2015). In these studies, and meta-analysis, they compare these scores in the diagnosis of pulmonary embolism, not compare according to severity of pulmonary embolism. Plasma levels of D-dimer is a marker of fibrinolysis, and in acute thromboembolic and many clinical cases, the level rises. Sensitivity of D-dimer test is too high (95-100 %) but specificity is moderate (43-93 %)(Stein *et al*., 2004). If becoming <500 μg^{-1} of the negative predictive value of D-dimer test is tought as low probability pulmonary embolism clinically, it allows exclusion of this diagnosis (van der Hulle *et al*., 2016). D-dimer levels increase with age. In patients over 50 years of age-dependent D-dimer cut-off value determined as: age*10μg^{-1} and it was confirmed in large prospective studies (Douma *et al*., 2010 and Righini *et al*., 2014). In our study, D-dimer levels were significantly lower in patients with non-massive than patients with massive. It is expected that in non-massive patients who have less embolism charge have less D-dimer levels. When examining the literature, as we know, there is no a comparison between D-dimer values and the severity of pulmonary embolism (massive, submassive and non-massive). CTEPH, despite anticoagulant treatment at least 3 months, the presence of signs to chronic thromboembolic disease in CT angiography and miss-match defects in the ventilation perfusion lung scan is defined as precapillary pulmonary hypertension (mean pulmonary artery pressure ≥25 mmHg with a pulmonary capillary wedge pressure ≤ 15 mmHg) (O'Connell C *et al*., 2015). CTEPH incidence in pulmonary embolism patients is between 0.5% and 9% (Pengo *et al*., 2004, Becattini *et al*., 2006 and Lang *et al*., 2014). In our study, the incidence is shown 7.8% similar to the literature.

In patients with CTEPH, pO_2 and pCO_2 values lower than other embolism patients, mean PAP values founded not significantly but higher. Again, Wells and revised Geneva score and D-dimer values were not founded significant but higher in groups with CTEPH. The study of Koyama and colleagues, in which compared the saturation values of CTEPH patients, patients' pO_2 and pCO_2 values were similar to our study (Kohyama *et al*., 2015). Klok and colleagues' study to distinguish CEPHT during acute pulmonary embolism and develop a simple non-invasive diagnostic algorithm, they seperate patients two groups with CEPHT and without CEPHT. It is looked at N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP), GDF-15, CRP, Urate, FVIII:C ve D-dimer in this two groups. They identified significant

differences on results except D-dimer (Klok *et al*., 2011). There is not significant D-dimer levels in our study, too. In the literature, to our knowledge, there is not any study that compares patients' with CTEPH and other embolism patients' these parameters: pO_2, pCO_2, Wells ve revised Geneva score.The only curative and standard treatment for CTEPH is Pulmonary Endarterectomy (PEA). However, with 30% to 50% of patients may be operated (Olsson *et al*., 2014). All patients should receive anticoagulants lifelong and there is not enough evidence to recommend new generation oral anticoagulants. Another new treatment option is pulmonary balloon angioplasty (O'Connell *et al*., 2015). 3 of our 10 patients with CTEPH had been ex after 1 month from diagnose and 4 patients take only anticoagulant treatment because of PEA contraindicated, 2 of them are unknown fate for the arrival of the patient controls and we had only 1 patient with PEA, PA pressure has returned to normal and it is under our control. The major limitations of our study are the small number of patients and the lack of record keeping. As a result; to diagnose acute pulmonary embolism with severe morbidity and mortality, and after diagnosis, to start the treatment accordingly by determining the severity of the disease is extremely important. Also, it is needed to be aware of CTEPH, which is a preventable complication of acute pulmonary embolism, to estimate in which patients CTEPH may develop, and to follow close patients with CTEPH.

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