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Research article

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A new parameter for the determination of normal right ventricular function in patients with acute pulmonary embolism

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Ethics Committee Approval
The study was approved by the ethics committee of the Kahramanmaras Faculty of Medicine, and a decision was made. 2018/22.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The performance of the right ventricular myocardium is crucial in various pathological states and the right ventricular dysfunction has a prognostic value in pulmonary embolism. We sought to bring out which parameters were helpful in predicting a normal right ventricular function in patients with acute pulmonary embolism.

Methods: Consecutive 100 acute pulmonary embolism patients, who were hospitalized and confirmed by computed tomography angiography, were enrolled in this cohort study. All patients' demographics, symptoms on admission, risk factors, electrocardiography and laboratory findings, and hemodynamic parameters were assessed. Echocardiography was performed in the first 24 hours. The study group of pulmonary embolism patients was divided into two groups based on their basic characteristics: Patients with normal right ventricular function and patients with right ventricular failure.

Results: The average age of the patients was 63 (16) years, with 48 (48%) of them being male. Twenty three patients (23%) had normal RV functions. According to the multiple logistic regression analysis, age (P=0.041, OR: 1.174, 95% CI: 1.007 to 1.368), oxygen saturation (P=0.026, OR: 1.372, 95% CI: 1.039 to 1.812) and heart rate (P=0.049, OR: 1.160, 95% CI: 1.001 to 1.346) were independent predictors of normal RV function. The setting in which all three parameters (Age, Heart rate, Oxygen saturation) were positive was considered AHO index=1, with a positive predictive value of 100% a sensitivity of 44%, a negative predictive value of 85.6% and a specificity of 100% (AUC: 0.717, 95% CI: 0.619 to 0.803) for normal RV function.

Conclusion: In acute pulmonary embolism patients who were younger than 53 years of age with a heart rate of ≤118 bpm and an oxygen saturation of >90% (AHO index=1), right ventricular functions were normal. Accordingly, without the need of computed tomography angiography or echocardiography, the clinician may predict normal right ventricular function with available demographic and noninvasive hemodynamic parameters.

Keywords: Acute pulmonary embolism, Right ventricular function, Age, Heart rate, Oxygen saturation

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Introduction

Although acute pulmonary embolism (PE) is a life-threatening cardiopulmonary disease, an important decrease in its morbidity and mortality has been accomplished over the years through early diagnosis, risk assessment and recently developed treatment methods [1-4]. The development of shock or hypotension, right ventricular (RV) dysfunction and myocardial damage are the most important prognostic risk factors for acute PE patients which undertake a critical role in determining the optimal strategy of treatment [5-7].

The presence of right ventricular dysfunction indicators such as dilatation of RV in an echocardiographic image, hypokinesia or extreme pressure loading, RV dilatation in spiral BT, increase in BNP or NT-Pro BNP and increased cardiac pressure in right cardiac catheterization indicate a medium-risk PE group [8-12]. Patients with no evidence of RV dysfunction or myocardial damage are considered the low-risk PE group. With the detection of low-risk PE patients, performing outpatient follow-up and treatment will be possible [1].

In this study, we sought to bring out which hemodynamic parameters were helpful in predicting a preserved RV function in the PE population.

Materials and methods

A total of 100 participants were hospitalized after being admitted to the emergency room and subsequently diagnosed with acute PE by tomographic angiography

(CTA). The existence of RV dysfunction is considered when classifying patients with acute PE. Group I consisted of patients with RV failure (n: 77) and group II consisted of patients with normal RV function (n: 23). The following data were collected: Symptoms and time of admission to the emergency room, susceptibility conditions, history of coronary artery disease, diabetes, hypertension and chronic obstructive pulmonary disease (COPD), vital signs at the time of admission to the hospital, blood gas analysis, admission blood parameters, and the results of an electrocardiogram (ECG), transthoracic echocardiography, lower extremity Doppler ultrasound, contrast-enhanced computed tomography and ventilation perfusion imaging and other diagnostic procedures. Within the first 30 minutes after presenting to the emergency room, vital signs and blood samples were collected. Hypertension is defined as having two or more blood pressures ≥140/90 mmHg during the measurement period or taking antihypertensive medications. A fasting blood glucose level of 126 mg/dl or higher, or taking antidiabetic medications, is defined as diabetes. An abnormal stress test result, the evidence of ischemia, or a coronary angiography confirming >50% coronary artery stenosis, or a clinical history of coronary artery disease are used to determine the coronary artery disease. S1Q3T3, right bundle branch block pattern, and right preventricular T wave variation are the rhythm and ECG results related to the right ventricular load. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Kahramanmaras Faculty of Medicine with the decision numbered 2018/22.

Echocardiography was performed within 24 hours after admission. Using 2.5 to 5 MHz probes, the Vivid 7 system (GE Healthcare, Wauwatosa, WI, USA) was used to evaluate all inspections at all participating sites. According to contemporary guidelines [13], the modified Simpson method is used to calculate ejection fraction with a defined chamber size. Echocardiography is used to evaluate RV dysfunction, RV dilation, increased tricuspid regurgitation jet rate, and pulmonary artery systolic pressure (SPAP). In addition, right ventricular dilation (right ventricular size> 3.4 cm in the basal plane or> 3.8 cm in the median plane) is associated with RV dysfunction, as is the presence of McConnell's sign [13]. According to the recommendations [14], the intensity of the color blood jet Doppler signal is combined with the width of the venous contraction to identify severe tricuspid regurgitation. The calculation of pulmonary artery systolic pressure was performed as previously described [15].

Statistical analysis

Continuous variables with a non-normal distribution were presented as mean, standard deviation (SD), or interquartile range (IQR), while categorical variables are expressed as percentages. As a measure of the test accuracy, the area under the curve (AUC) was estimated. The investigators compared AUCs using the Z test. Patients with acute PD were divided into two groups: Group A, including patients with right ventricular failure, and group B, including patients with normal right ventricular function.

When the distribution was skewed, the 2-test was used to compare categorical variables, the independent sample t-test, to evaluate normally distributed continuous data, and the Mann-Whitney U test, to compare the patient groups. The Pearson or Spearman correlation tests were used to determine the correlation between variables. To quantify the relationship between the factors and the complete RV function, we used univariate analysis. Variables that were significant in univariate analysis and other potential confounders were used in the multiple logistic regression model using forward progressive techniques to assess independent prognostic factors of maintained RV function.

Results

Of all enrolled 100 consecutive patients, the mean age was 63 (16) years. The study group was gender balanced (52% female, 48% male).

Table 1 shows the differences in hemodynamic, electrocardiographic, echocardiographic, and laboratory results between the two groups of patients with acute PE, as well as their concomitant diseases. Except for age, a history of chronic obstructive pulmonary disease, and recent surgery history, both groups had similar baseline characteristics. The group with a preserved right ventricle function (Group B) was younger and had fewer patients with COPD and a previous surgery. In physical examination, Group B patients' heart rate was significantly slower and oxygen saturation was significantly better than those in Group A. In electrocardiographic parameters, group B tended to have slightly but significantly fewer patients with atrial fibrillation. Group B also had significantly better creatinine and alanine aminotransferase levels.

Univariate analysis was performed to the parameters in Table 1 to quantify any relationship with normal right ventricular function (Table 2). The statistically significant parameters were included in the multiple logistic regression analysis (Table 3), which showed that age (P=0.041, OR: 1.174, 95% CI: 1.007 to 1.368), oxygen saturation (P=0.026, OR: 1.372, 95% CI: 1.039 to 1.812) and heart rate (P=0.049, OR: 1.160, 95% CI: 1.001 to 1.346) were independent predictors of preserved right ventricle function. ROC analysis brought out the cut-off values of these parameters for normal right ventricular function: For saturation it was >90% (60% sensitivity, 86.2% specificity, AUC: 0.750, 95% CI, 0.645 to 0.838, Figure 1) and for heart rate it was ≤ 118 bpm (100% sensitivity, 51.6% specificity, AUC: 0.803, 95% CI, 0.702 to 0.881, Figure 2). The cut-off value for age was ≤ 53 years (65.2% sensitivity, 88.3% specificity, AUC: 0.788, 95% CI, 0.695 to 0.864, Figure 3). The setting in which all three parameters were positive was considered AHO index=1, with a positive predictive value of 100%, a sensitivity of 44%, a negative predictive value of 85.6% and a specificity of 100% (AUC 0.717, 95% CI 0.577 to 0.857, figure 4) for normal right ventricle function.

Table 1: Baseline characteristics of groups

	Patients with right ventricular failure (n:77)	Patients with normal right ventricular function (n:23)	*P*-value
Mean age, years	67(14)	49(16)	<0.001
Gender, female, n, %	38 (49%)	14 (61%)	0.232
Hypertension, n, %	36 (47%)	6 (26%)	0.062
Diabetes mellitus, n, %	22 (29%)	3 (13%)	0.105
Coronary artery disease, n, %	22 (29%)	4 (17%)	0.195
COPD, n, %	22 (29%)	2 (9%)	0.040
Admission symptoms			
Dyspnea, n, %	54 (70%)	13 (57%)	0.167
Chest pain, n, %	17 (22%)	9 (39%)	0.088
Hemoptysis, n, %	7 (9%)	0 (0%)	0.150
Syncope, n, %	8 (10%)	2 (9%)	0.585
Symptom duration			
< 6 hours, n, %	3 (4%)	1 (4%)	0.655
6-12 hours, n, %	8 (10%)	1 (4%)	0.339
12-24 hours, n, %	16 (21%)	5 (22%)	0.564
> 24 hours, n, %	50 (65%)	16 (70%)	0.442
Immobilization, n, %	16 (21%)	3 (13%)	0.309
Previous history of PE, n, %	5 (7%)	1 (4%)	0.580
Previous history of DVT, n, %	4 (5%)	2 (9%)	0.420
Previous history of surgery, n, %	11 (14%)	8 (35%)	0.033
Systolic blood pressure, mm Hg	104(19)	110(17)	0.243
Diastolic blood pressure, mmHg	64(15)	68(14)	0.300
Heart rate, beats/minute	116(20)	98(13)	0.009
Oxygen saturation, %	82(9)	89(11)	<0.001
Electrocardiography parameters			
Atrial fibrillation, n, %	26 (34%)	3 (13%)	0.044
Right bundle branch block, n, %	30 (39%)	5 (22%)	0.100
S1Q3T3, n, %	18 (23%)	2 (9%)	0.102
T wave changes, n, %	33 (43%)	7 (30%)	0.206
Deep venous thrombosis, %	30 (40%)	5 (22%)	0.093
Laboratory findings			
Hemoglobin, gr/dl	13(2)	12.8(1.7)	0.643
Albumin, gr/dL	3.0(0.6)	3.2(0.7)	0.210
Creatinine, mg/dL	1.3(1.0)	0.8(0.4)	0.017
Alanine aminotransferase, IU/L	99(209)	40(36)	0.024
Troponin I, ng/mL	0.16(0.4)	0.08(0.16)	0.458
D-Dimer > 1500 ng/ml, n,%	52 (77%)	10 (56%)	0.137

COPD: Chronic obstructive pulmonary disease, DVT: Deep venous thrombosis, PE: pulmonary embolism

Table 2: Univariate predictors of normal right ventricular function

	P-value	OR	(95% CI)
Mean age, years	<0.001	0.931	0.899-0.963
Heart rate, beat/minute	0.001	0.947	0.916-0.979
Creatinine, mg/dL	0.005	0.079	0.013-0.466
Oxygen saturation, %	0.014	1.092	1.018-1.172
History of surgery, %	0.033	0.313	0.107-0.911
COPD, n,%	0.066	0.238	0.051-1.102
Atrial fibrillation, n,%	0.066	3.399	0.924-12.498
Hypertension, n,%	0.084	2.488	0.886-6.988
D-Dimer > 1500 ng/ml, n,%	0.084	0.385	0.130-1.139

All the variables from Table 1 were examined and only those significant at P<0.1 level are shown. CI: Confidence interval; OR: Odds ratio, Abbreviations in Table 1.

Table 3: Multiple predictors of normal right ventricular function

	P-value	OR	(95% CI)
Oxygen saturation, %	0.005	1.377	1.104-1.716
Heart rate, beat/minute	0.008	0.887	0.812-0.970
Mean age, years	0.010	0.867	0.777-0.967

Multiple logistic regression analysis including P<0.05 level from Table 2.
CI: Confidence interval; OR: Odds ratio

Figure 1: ROC curve for Oxygen saturation

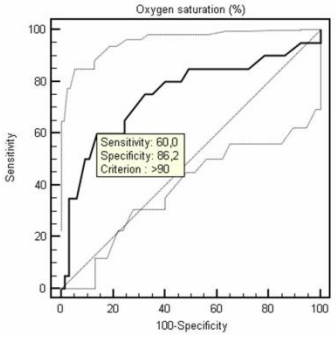


Figure 2: ROC curve for Heart rate

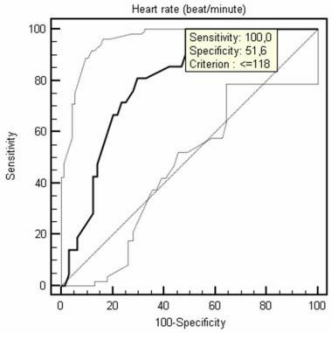


Figure 3: ROC curve for age

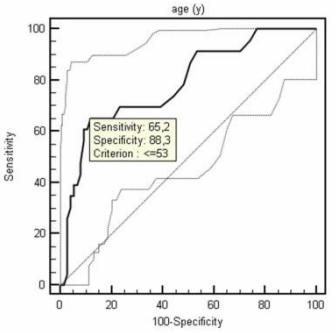
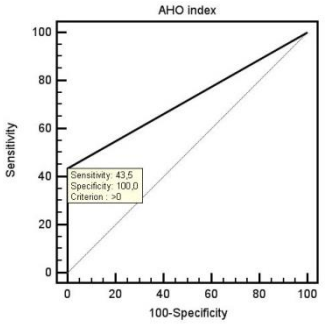


Figure 4: ROC curve for AHO index=1



Discussion

To the best of our knowledge, this is the first study demonstrating that an index comprising three quantitative parameters, age and heart rate and oxygen saturation, significantly predicts preserved RV functions in patients with sudden onset PE.

Acute PE is a complex cardiopulmonary disease and rapid risk stratification has become the most important part of treatment. A great variety of clinical, echocardiographic, and blood markers are used in this classification. Hypotension or the presence of shock is still the most important prognostic factor. Guidelines suggest the prognostic use of troponin and natriuretic peptides [1]. In addition, several laboratory parameters such as gamma glutamyl transferase [16], red cell distribution width [17], uric acid [18], heart-type fatty acid-binding protein (H-FABP) [19], copeptin, and mid-regional pro-adrenomedullin (MR-proADM) [20], were shown to be associated with mortality in PE, without adequate sensitivity and specificity.

In acute PE, it is well known that mortality is higher in patients who exhibit compromised RV functions. Right heart failure is a critical part in the vicious cycle of death in embolism: Occlusion of pulmonary arterial branch, increased pulmonary arterial pressure, decreased systemic arterial pressure, increased sympathetic tone and neuroadrenal hormones to maintain pressure, increased RV workload and wall tension of the RV due to pulmonary arterial pressure and finally, right heart failure [21-25]. It is critical to diagnose RV compromise in embolism, because it changes the therapeutic approach. Plain anticoagulation is almost enough for patients with low or intermediate risk, however; thrombolytic agents are advised for patients with cardiogenic shock (26). Guidelines advise

clinicians to check the RV status with echocardiography in patients who are not in shock but whose clinical status is concordant with heart failure [27]. Computerized tomography is another option to determine RV failure [28]. Furthermore, natriuretic peptides are also known as surrogates for right heart failure in PE. The severity of hemodynamic compromise and RV dysfunction in acute PE were demonstrated through plasma levels of natriuretic peptides [29].

At this point, we suggest an index, which is a combination of three parameters, to predict preserved RV functions. As discussed above, when all three parameters (age and heart rate and oxygen saturation values) are within determined cut-off limits, the indicator has a positive predictive value of 100 percent and a negative predictive value of 85.6%, according to research. These three parameters are obtained very easily and most importantly, in a noninvasive way.

Limitations

The current study has some limitations. Because of its monocentric nature, our research was constrained. As a result, the findings cannot be generalized to the full population of PE patients. The sample size, which is relatively small, was the most significant constraint. It should be noted that a limited sample size may have an impact on the wide percent 95 CI. It's possible that a combination of natriuretic peptides and other indicators like troponins might be utilized to monitor blood pressure. However, because we have echocardiography, natriuretic peptides are rarely used in our center.

Conclusion

Right ventricular function can be evaluated by many non-invasive methods that are not expensive, routinely available, and bedside procedures, such as computed tomography, radionuclide methods, and magnetic resonance imaging. Using the AHO index, we found that physicians can rule out RV dysfunction in acute PE with very high precision. Our findings need to be confirmed by randomized prospective studies with larger patient populations.

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