

Prognostic Value of Electrocardiographic Findings in Hemodynamically Stable Patients With Acute Symptomatic Pulmonary Embolism

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Introduction and objectives. The aim of this study was to determine the prognostic value of electrocardiography in hemodynamically stable patients with a diagnosis of acute symptomatic pulmonary embolism (PE).

Methods. This prospective study included all hemodynamically stable outpatients who were diagnosed with PE at a university hospital. The electrocardiographic abnormalities investigated were: a) sinus tachycardia (>100 beats/min); b) ST-segment or T-wave abnormalities; c) right bundle branch block; d) an S1Q3T3 pattern; and e) recent-onset atrial arrhythmia.

Results. The study included 644 patients. Overall, 5% of those with an ECG abnormality died due to PE in the 15 days after diagnosis compared with 2% of those with normal ECG findings (relative risk [RR]=2.4; 95% confidence interval [CI], 1-5.8; $P=.05$). Multivariate analysis showed that sinus tachycardia was associated with a 2.2-fold increased risk of death due to all causes in the month after PE diagnosis. After adjusting for age, a history of cancer, immobility, ECG abnormalities, and sinus tachycardia, the presence of recent-onset atrial arrhythmia was significantly associated with death due to PE in the first 15 days (RR=2.8; 95% CI, 1-8.3; $P=.05$). The negative predictive value of atrial arrhythmia for 15-day PE-related mortality was 97%, while the negative likelihood ratio was 0.79.

Conclusions. In hemodynamically stable patients with acute symptomatic PE, the presence of sinus tachycardia and atrial arrhythmia were independent predictors of a poor prognosis. However, the usefulness of these factors for stratifying risk in PE patients is limited.

Key words: Pulmonary embolism. Prognosis. Electrocardiogram.

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Valor pronóstico de los hallazgos electrocardiográficos en pacientes estables hemodinámicamente con tromboembolia de pulmón aguda sintomática

Introducción y objetivos. El objetivo de este estudio es evaluar el valor pronóstico del electrocardiograma (ECG) en pacientes estables hemodinámicamente con diagnóstico de tromboembolia pulmonar (TEP) aguda sintomática.

Métodos. Se incluyó de forma prospectiva a todos los pacientes ambulatorios estables hemodinámicamente diagnosticados de TEP aguda sintomática en un hospital universitario terciario. Las anomalías electrocardiográficas consideradas fueron: a) taquicardia sinusal (> 100 lat/min); b) alteraciones del segmento ST o de la onda T; c) bloqueo de la rama derecha del haz de His (BRDHH); d) patrón S1Q3T3, y e) arritmias auriculares de reciente comienzo.

Resultados. Se incluyó a 644 pacientes en el estudio. Un 5% de los pacientes con ECG anormal fallecieron por TEP en los 15 días posteriores al diagnóstico, comparado con un 2% de los pacientes con ECG normal (razón de riesgo [RR] = 2,4; intervalo de confianza [IC] del 95%, 1-5,8; $p = 0,05$). En el análisis multivariable, la taquicardia sinusal multiplicó por 2,2 el riesgo de muerte por todas las causas en el mes posterior al diagnóstico de TEP. Tras ajustar por edad, antecedentes de cáncer, inmovilización, un ECG alterado y la presencia de taquicardia sinusal, las arritmias auriculares de reciente diagnóstico se asociaron de forma significativa a la muerte por TEP durante los primeros 15 días (RR = 2,8; IC del 95%, 1-8,3; $p = 0,05$). Las arritmias auriculares mostraron un alto valor predictivo negativo de muerte por TEP a los 15 días (97%), pero la razón de probabilidad negativa fue 0,79.

Conclusiones. En pacientes estables hemodinámicamente con TEP aguda sintomática, la taquicardia sinusal y las arritmias auriculares son predictoras independientes de mal pronóstico. Sin embargo, su utilidad en la estratificación pronóstica de estos pacientes es limitada.

Palabras clave: Tromboembolia de pulmón. Pronóstico. Electrocardiograma.

ABBREVIATIONS

CI: confidence interval
 COPD: chronic obstructive pulmonary disease
 CT: computed tomography
 DVT: deep vein thrombosis
 ECG: electrocardiogram
 INR: International Normalized Ratio
 LMWH: low molecular weight heparin
 PE: pulmonary embolism
 RBBB: right bundle branch block
 RR: relative risk
 SBP: systolic blood pressure
 VTE: venous thromboembolism

INTRODUCTION

Pulmonary embolism (PE) is a disease with a wide range of clinical manifestations that influences therapeutic strategies.¹ Some 5% of patients present in cardiogenic shock and receive systemic fibrinolysis as the treatment of choice.² In contrast, hemodynamically stable patients are administered low molecular weight heparin (LMWH) or unfractionated heparin as a bridge to oral anticoagulation. Early death in these patients is 2%-10% at ≤ 3 months follow-up.³⁻⁶ Currently, the therapeutic challenge lies in identifying a group of higher-risk, hemodynamically stable patients, for whom a more aggressive treatment may improve prognosis.

Several studies have shown right ventricular dysfunction determined by transthoracic echocardiography or elevated biomarkers (troponin or natriuretic peptide) associates with prognosis in patients with PE.⁷⁻¹⁰ However, not all centers have transthoracic echocardiography facilities and interpretation is operator dependent. Cutoff points for cardiac dysfunction markers have not been standardized¹¹ and echocardiography sometimes needs to be repeated,¹² diminishing its value in clinical practice.

All centers have electrocardiogram (ECG) facilities. The ECG is a fast, low-cost, and possibly simple tool for prognostic stratification of patients with PE.¹³ The objective of the present study is to evaluate the prognostic value of electrocardiographic findings in a consecutive series of hemodynamically stable patients diagnosed with acute symptomatic PE.

METHODS**Design**

We conducted a prospective cohort study at a university hospital from January 2003 thru December 2006.

Patients and Selection Criteria

We included all outpatients consecutively diagnosed with acute symptomatic PE in the emergency room of Hospital Ramón y Cajal, Madrid (Spain). We excluded patients diagnosed as hemodynamically unstable (defined as systolic blood pressure [SBP] < 90 mm Hg, indication for fibrinolytic treatment or inferior vena cava filter, discretionary use of vasoactive drugs, cardiopulmonary reanimation, or orotracheal intubation). Pulmonary embolism was objectively confirmed. Diagnosis of PE using computerized tomography (CT) in angiography showed partial intraluminal defect surrounded by contrast or complete pulmonary artery occlusion in 2 consecutive CT cuts.¹⁴ Diagnosis of PE by ventilation/perfusion scintigraphy was performed in high likelihood patients defined according to PLOPED criteria¹⁵ (at least 1 segment perfusion defect or 2 subsegments with normal ventilation) or in patients with clinical suspicion of PE, inconclusive scintigraphy, and diagnostic echography of lower limbs showing defect of venous lumen compressibility as a sign of deep vein thrombosis (DVT).

Interventions

Weight-adjusted dosage of LMWH was administered every 12 hours for a minimum of 5 days minimum. Administration of vitamin K antagonists together with LMWH was initiated between day 1 and day 3 of treatment and LMWH was interrupted when International Normalized Ratio (INR) was stable and > 2 . Monitoring of INR values was according to local practice at the center.

Electrocardiogram

All patients underwent 12-lead ECG (25 mm/s and 1 mV/cm) at diagnosis. We considered evidence of right ventricular dysfunction and evaluated these electrocardiographic findings as predictors of death: *a*) sinus tachycardia (> 100 beats/min); *b*) ST-segment or T-wave abnormalities; *c*) right bundle branch block (RBBB); *d*) S1Q3T3 pattern; and *e*) recent-onset atrial arrhythmia.

Episodes Analyzed

We defined all-cause death one-month following diagnosis as the principal outcome parameter. Death from PE during the 15 days following diagnosis was the secondary parameter. Two researchers (CEC and DJC) agreed on cause of death without access to patients' clinical characteristic data or electrocardiographic findings.

Statistical Analysis

We analyzed the univariate relation between ECG and other baseline characteristics and the principal outcome

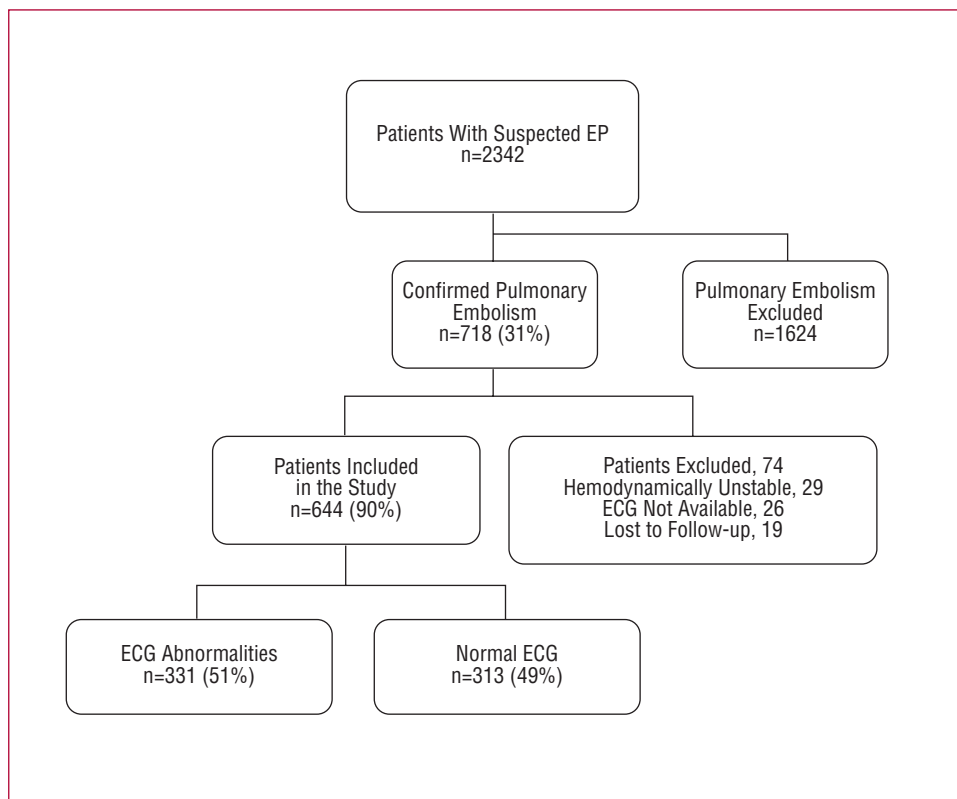


Figure. Flow chart of patients included in the study

parameter with χ^2 for categorical variables and Student *t* test for continuous variables. We used the Fisher exact test when expected values were <5 . A *P* value less than .05 was considered significant. We conducted multivariate logistic regression analysis to identify variables predicting death at the month following diagnosis of PE. In the final analysis, we only included variables with $P < .10$. We calculated risk ratios (RR) with a 95% confidence interval (CI) for each variable in the model. We present sensibility, specificity, positive and negative predictive values, and positive and negative likelihood ratios for prognostic electrocardiographic findings. Statistical analysis was with SPSS 12.0.

RESULTS

From January 2003 thru December 2006, 718 patients were diagnosed with acute symptomatic PE in the Emergency Room of Hospital Ramón and Cajal, Madrid (Spain); 29 (4%) were excluded as hemodynamically unstable; 26 patients could not undergo ECG at the 48 hours following diagnosis; 19 patients were lost to follow-up. The final population consisted of 644 (93%) hemodynamically stable patients diagnosed with acute symptomatic PE (Figure).

At 15 days follow-up, 45 (7%) patients died; 24 from PE. Other causes of death were: cancer ($n=8$), hemorrhage ($n=3$), infection ($n=3$), unknown ($n=3$), heart failure ($n=2$), COPD, kidney failure, and epileptic seizure. At

30 days follow-up, 10% (62/644) of patients had died. Cumulative incidence of death from PE at the 30 days follow-up was 5%.

We identified electrocardiographic abnormalities in 51% of patients; sinus tachycardia was the most frequent abnormality (25%). RBBB was identified in 15% of patients; 12% had ST-segment or T-wave abnormalities; 11%, atrial arrhythmias; and 10%, S1Q3T3 pattern. Patient characteristics with or without electrocardiographic abnormalities are compared in Table 1. In patients with abnormal ECG, dyspnea was the most frequent symptom at presentation and they showed significantly lower values of O_2 saturation in arterial blood at admission. At 15 days follow-up, significantly more patients died from PE in the group with abnormal ECG (5% vs 2%; $P=.05$).

Variables associated with all-cause death at one-month following diagnosis in bivariate analysis are in Table 2. After adjusting for predictive clinical variables in bivariate analysis, sinus tachycardia associated significantly with all-cause death at one-month. Variables associated with death from PE at 15 days are in Table 3. Only history of active neoplasia, ≥ 4 days immobility and ECG with atrial arrhythmias not previously diagnosed associate significantly with death in logistic regression analysis.

Atrial arrhythmias not previously diagnosed showed a high negative predictive value for death from PE at 15 days (97%), but the positive predictive value was low (Table 4).

TABLE 1. Baseline Characteristics of the 644 Patients, According to Electrocardiograph Results

	ECG Abnormalities (n=331)	Normal ECG Findings (n=313)	P
Clinical characteristics*			
Age >65 years	233 (70)	224 (68)	.6
Men	149 (45)	128 (41)	.3
VTE risk factors			
Cancer	74 (22)	63 (20)	.6
Surgery	29 (9)	33 (10)	.8
>4 days immobility	72 (22)	58 (18)	.2
Previous VTE	33 (10)	32 (10)	.9
Comorbidity			
COPD	29 (9)	24 (8)	.7
Heart failure	26 (8)	23 (7)	.7
Clinical presentation			
Syncope	51 (15)	46 (15)	.9
Dyspnea	263 (79)	210 (67)	<.001
Chest pain	156 (47)	163 (52)	.2
O ₂ saturation <90%	100 (30)	65 (21)	.01

COPD, indicates chronic obstructive pulmonary disease; ECG, electrocardiogram; PE, pulmonary embolism; VTE, venous thromboembolism.

*In the population studied, 13% of patients received no medication for O₂ saturation in arterial blood. To calculate the percentages, we took the unknown values as normal and included them in the denominator.

The figures express n (%).

TABLE 2. Prognostic Predictors of All-Cause Death at 1 Month

	Survival (n=582)	Death (n=62)	Univariate		Multivariate	
			RR (95% CI)	P	RR (95% CI)	P
Clinical characteristics						
Age >65 years	406 (70)	51 (82)	2.0 (1.0-3.9)	.04	2.3 (1.1-4.7)	.03
Men	251 (43)	26 (42)	0.9 (0.5-1.6)	.85	–	
VTE risk factors						
Cancer	111 (19)	26 (42)	3.1 (1.8-5.3)	<.001	4.0 (2.2-7.3)	<.001
Surgery	58 (10)	4 (6)	0.6 (0.2-1.8)	.38	–	
>4 days immobility	110 (19)	20 (32)	1.9 (1.1-3.2)	.02	2.0 (1.1-3.5)	.02
Previous VTE	60 (10)	5 (8)	0.8 (0.3-1.9)	.64	–	
Comorbidity						
COPD	46 (8)	7 (11)	1.5 (0.6-3.4)	.36	–	
Heart failure	40 (7)	9 (14)	2.3 (1.1-5)	.03	2.6 (1.1-5.9)	.02
Clinical presentation						
Syncope	90 (15)	7 (11)	0.7 (0.3-1.6)	.38	–	
Dyspnea	424 (73)	49 (79)	1.4 (0.7-2.6)	.30	–	
Chest pain	293 (50)	26 (42)	0.7 (0.4-1.2)	.21	–	
O ₂ saturation <90%	150 (26)	15 (24)	0.6 (0.4-1.1)	.09	0.7 (0.4-1.2)	.19
Electrocardiographic findings						
Abnormalities of any kind	296 (51)	35 (56)	1.2 (0.7-2.1)	.40	–	
Heart rate >100 bpm	134 (23)	25 (40)	2.2 (1.3-3.9)	.003	2.4 (1.3-4.2)	.003
ST-segment or T-wave abnormalities	71 (12)	6 (10)	0.8 (0.3-1.8)	.56	–	
RBBB	92 (16)	7 (11)	0.7 (0.3-1.5)	.35	–	
S1Q3T3 pattern	62 (11)	4 (6)	0.6 (0.2-1.6)	.30	–	
Atrial arrhythmias	61 (10)	9 (14)	1.4 (0.7-3.1)	.33	–	

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; RBBB, right bundle branch block; RR, relative risk; VTE, venous thromboembolism.

The figures express n (%).

DISCUSSION

In this study, we have analyzed the prognostic capacity of electrocardiographic findings in a consecutive series of stable patients diagnosed with acute symptomatic PE. Essentially, 2 findings derive from our study. Firstly,

sinus tachycardia is the only ECG abnormality that increases risk of all-cause death in stable patients with PE at the 30 days following diagnosis. Secondly, atrial arrhythmias led to a 2.8-fold increase in risk of death from PE at 15 days.

TABLE 3. Prognostic Predictors of Death From Pulmonary Embolism at 15 Days

	Survival (n=620)	Death (n=24)	Univariate		Multivariate	
			RR (95% CI)	P	RR (95% CI)	P
Clinical characteristics						
Age >65 years	436 (70)	21 (87)	2.9 (0.9-10)	.08	3.0 (0.8-11)	.09
Men	267 (43)	10 (42)	0.9 (0.4-2.1)	.89	–	
VTE risk factors						
Cancer	126 (20)	11 (46)	3.3 (1.4-7.6)	.004	4.5 (1.9-11)	.001
Surgery	60 (10)	2 (8)	0.8 (0.2-3.7)	.83	–	
>4 days immobility	121 (19)	9 (37)	2.2 (1-4.8)	.05	2.3 (1-5.3)	.05
Previous VTE	72 (12)	2 (8)	0.7 (0.1-3)	.62	–	
Comorbidity						
COPD	51 (8)	2 (8)	1.0 (0.2-4.4)	.98	–	
Heart failure	46 (7)	3 (12)	1.8 (0.5-6.2)	.36	–	
Clinical presentation						
Syncope	94 (15)	3 (12)	0.8 (0.2-2.7)	.72	–	
Dyspnea	454 (73)	19 (79)	1.4 (0.5-3.8)	.52	–	
Chest pain	309 (50)	10 (42)	0.7 (0.3-1.6)	.43	–	
O ₂ saturation <90%	384 (62)	12 (50)	0.6 (0.3-1.4)	.24	–	
Electrocardiographic findings						
Abnormalities of any kind	314 (51)	17 (71)	2.4 (1-5.8)	.06	1.2 (0.4-4)	.73
Heart rate >100 bpm	149 (24)	10 (42)	2.2 (1-5.2)	.05	1.8 (0.6-5.1)	.26
ST-segment or T-wave abnormalities	73 (12)	4 (17)	1.5 (0.5-4.5)	.47	–	
RBBB	95 (15)	4 (17)	1.1 (0.4-3.3)	.86	–	
S1Q3T3 pattern	65 (10)	1 (4)	0.4 (0-2.8)	.34	–	
Atrial arrhythmias	63 (10)	7 (29)	3.6 (1.4-9.1)	.006	2.8 (1-8.3)	.05

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; RBBB, right bundle branch block; RR, relative risk; VTE, venous thromboembolism. The figures express n (%).

We isolated electrocardiographic abnormalities in 51% of the 644 patients studied. This prevalence was significantly below that reported elsewhere.¹⁶⁻¹⁹ Stein et al¹⁶ identified ECG abnormalities in 77% of patients with submassive PE and in 94% of patients with massive PE. Ferrari et al¹⁷ described electrocardiographic abnormalities in 91% of patients, although the majority (74%) presented massive PE. The discrepancy with our results is probably due to the different hemodynamic profiles of the populations studied. The electrocardiographic pattern of subepicardial ischemia (negative T-waves in precordial leads) has been considered the most common electrocardiographic abnormality^{20,21} and is described in <85% of patients with massive PE. However, prevalence falls to 18% in patients with submassive PE.¹⁷ Again, the low-risk profile of our patients could explain the low prevalence of this pattern in the series analyzed.

In logistic regression analysis, we found no association between the electrocardiographic abnormalities previously described as indicators of severe PE^{16,17} and prognosis. Only sinus tachycardia associated with all-cause death at the first month following diagnosis of PE. This had already been reported.²² Recent-onset atrial arrhythmias, together

TABLE 4. Sensibility, Specificity, and Predictive Values of Atrial Arrhythmias to Predict Death From Pulmonary Embolism at 15 Days

	95% CI	
Sensibility, %	29	11-47
Specificity, %	90	87-92
Positive predictive value, %	10	3-17
Negative predictive value, %	97	96-98
Positive likelihood ratio	2.87	1.47-5.59
Negative likelihood ratio	0.79	0.61-1.02

CI indicates confidence interval.

with history of neoplasia and immobility, associated with death from PE at 15 days follow-up. In patients with PE, these arrhythmias create secondary atrial distension increasing pressure overload²³ or could be a marker of preexisting cardiac disease.

In our experience, the negative predictive value of atrial arrhythmias for death from PE is excellent (97%). However, the number of events in the series analyzed was small and, in practical terms, limits this predictive value. In this context, negative (0.79) and positive (2.87) likelihood ratios indicate atrial arrhythmias contribute

little added value to clinical considerations in selecting patients at low- (candidates for early discharge) or high-risk (candidates for thrombolytic treatment).

The relation between electrocardiographic findings of right ventricular overload and hemodynamic abnormalities in PE is well-documented.^{5,17,24} In 151 patients with confirmed diagnosis of PE, presence of a QR pattern in V₁ and negative T in V₂ associated with moderate or severe right ventricular dysfunction.⁵ In a study of 80 patients with PE, presence of negative T-wave in V₂ associates with mean pulmonary artery pressure elevation (37 [8] mm Hg).¹⁷ However, this association seems more complex than initially suspected. Although it is attractive to assume that electrocardiographic abnormalities in patients with PE are the result of myocardial ischemia or of right ventricular wall distension, some studies have been unable to show this association.²⁵

By comparison with previously published studies, ours has a number of advantages. Firstly, we included outpatients consecutively diagnosed with PE by using objective methods. Secondly, only hemodynamically stable patients participated in the study. This is especially important given that there is no doubt that hemodynamically unstable patients should receive thrombolytic treatment³ and cannot be included in outpatient treatment programs. Thirdly, instead of analyzing the correlation between electrocardiographic abnormalities and angiographic, or hemodynamic findings,^{16,17,24} we directly evaluated the prognostic capacity of the ECG in relation with all-cause death and death from PE. Finally, all patients were managed according to a similar treatment protocol, independently of the electrocardiographic findings.

CONCLUSIONS

Although atrial arrhythmias increase the risk of death from PE in the population studied, electrocardiographic abnormalities are of limited use in the prognostic stratification of these patients.

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