Prognostic Value of Transthoracic Echocardiography in Hemodynamically Stable Patients With Acute Symptomatic Pulmonary Embolism

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OBJECTIVE: To determine the prognostic value of transthoracic echocardiography in hemodynamically stable patients diagnosed with acute symptomatic pulmonary embolism.
PATIENTS AND METHODS: Hemodynamically stable outpatients diagnosed with acute symptomatic pulmonary embolism at a tertiary university hospital were prospectively included in the study. All patients underwent transthoracic echocardiography within 48 hours of diagnosis. The primary endpoint was all-cause mortality at 1 month.
RESULTS: Right ventricular dysfunction was documented by echocardiography in 86 of the 214 patients (40%) in our series. In the first month of follow-up, 7 patients died—4 with positive echocardiographic findings and 3 with negative findings (odds ratio, 2.0; 95% confidence interval, 0.4-9.3; *P*=.41). For the primary endpoint, the negative predictive value of transthoracic echocardiography was 98%, the positive predictive value was 5%, and the negative likelihood ratio was 0.7. The negative predictive value was 100% and the positive predictive value was 3% when we analyzed death due to pulmonary embolism only.
CONCLUSIONS: In our setting, transthoracic echocardiography is not useful for prognostic stratification of hemodynamically stable patients with pulmonary embolism.

Key words: *Pulmonary embolism. Prognosis. Echocardiography.*

Valor pronóstico de la ecocardiografía transtorácica en pacientes estables hemodinámicamente con tromboembolia de pulmón aguda sintomática

OBJETIVO: El objetivo de este estudio ha sido evaluar el valor pronóstico de la ecocardiografía transtorácica en pacientes estables hemodinámicamente con diagnóstico de tromboembolia pulmonar (TEP) aguda sintomática.
PACIENTES Y MÉTODOS: Se incluyó prospectivamente en el estudio a todos los pacientes ambulatorios, estables hemodinámicamente, diagnosticados de TEP aguda sintomática en un hospital universitario terciario. Se realizó a todos ellos una ecocardiografía transtorácica en las 48 h posteriores al diagnóstico. El criterio de evaluación principal fue la muerte por todas las causas a un mes.
RESULTADOS: La prevalencia de criterios ecocardiográficos de disfunción del ventrículo derecho fue de un 40% en nuestra serie (86/214). Durante el primer mes de seguimiento se produjeron 7 fallecimientos, 4 en el grupo con ecocardiografía positiva y 3 en el grupo con ecocardiografía negativa (*odds ratio* = 2,0; intervalo de confianza del 95%, 0,4-9,3; p = 0,41). La ecocardiografía transtorácica demostró un valor predictivo negativo del 98%, un valor predictivo positivo del 5% y un cociente de probabilidad negativo de 0,7 respecto al parámetro de valoración principal. Cuando sólo se consideró la muerte por TEP, el valor predictivo negativo fue del 100% y el valor predictivo positivo, del 3%.
CONCLUSIONES: En nuestro medio la ecocardiografía transtorácica carece de utilidad en la estratificación pronóstica de los pacientes estables hemodinámicamente con TEP.

Palabras clave: *Tromboembolia pulmonar. Pronóstico. Ecocardiografía.*

Introduction

Pulmonary embolism has many different clinical manifestations, with differing prognoses and treatments.[1] Approximately 10% of the patients with pulmonary embolism present initially with cardiogenic shock.[2] The treatment of choice in this group of patients is systemic

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fibrinolysis.[3] At the other extreme, there are patients with pulmonary embolism who have few initial symptoms. In these cases, treatment consists of using low molecular weight heparin or unfractionated heparin as a bridge to oral anticoagulation therapy. Although these patients normally remain in hospital during the initial treatment phase, some may be considered for early discharge or even treatment in an outpatient setting.[4] However, early mortality in hemodynamically stable patients diagnosed with pulmonary thromboembolism ranges from 1.5% to 7%.[5-8] It is essential to identify subgroups of patients with worse prognosis for 2 reasons: *a)* these patients may benefit from more aggressive treatments[9,10] and *b)* higher-risk patients are candidates for intensive hospital surveillance, whereas lower-risk patients could be treated as outpatients.

Several studies have reported a correlation between right ventricular dysfunction, documented by transthoracic echocardiography, and prognosis (measured in terms of mortality and/or more intensive treatment) in patients with pulmonary embolism.[11-15] However, each of these studies used different inclusion criteria, diagnostic techniques, and definitions of right ventricular dysfunction.

The aim of the present study was to prospectively assess the prognostic value of transthoracic echocardiography in a consecutive series of hemodynamically stable patients diagnosed with acute symptomatic pulmonary embolism.

Patients and Methods

Patients and Inclusion Criteria

A prospective cohort study was performed in a tertiary university hospital between January 2004 and December 2005. All consecutive patients diagnosed with acute symptomatic pulmonary embolism in the emergency room of the Hospital Ramón y Cajal, Madrid, Spain, were included. Patients were excluded if they were hemodynamically unstable—defined as systolic blood pressure less than 90 mm Hg, indication for fibrinolytic treatment or inferior vena cava filter placement, need for vasoactive medication in the opinion of the treating physician, cardiopulmonary resuscitation, or orotracheal intubation. Diagnosis of pulmonary embolism was confirmed by the finding of partial occlusion indicated by intraluminal filling defect surrounded by contrast medium in computed angiotomography or complete occlusion of a pulmonary artery in 2 consecutive slices of a computed tomography scan.[16] Diagnosis of pulmonary embolism by ventilation–perfusion scintigraphy was done in high-risk patients, defined according to the PIOPED criteria[17] (at least 1 segmental perfusion defect or 2 subsegmental defects with normal ventilation), or in cases of clinical suspicion of pulmonary embolism, inconclusive scintigraphy and, as a sign of deep vein thrombosis, abnormal compressibility of the venous lumen in diagnostic ultrasound of the lower limbs.

Interventions

Patients received treatment with low molecular weight heparin at weight-adjusted doses every 12 hours for at least 5 days. Administration of vitamin K antagonists was initiated along with low molecular weight heparin between the first and third days of treatment, and low molecular weight heparin was discontinued when the international normalized ratio was stable and greater than 2.0. The values of the international normalized ratio were monitored in accordance with the clinical practice of the hospital.

Echocardiography

Transthoracic echocardiography was performed in patients within 48 hours of diagnosis. The echocardiograms were interpreted by cardiologists who were unaware of the clinical characteristics of the patients. The presence of 1 or more of the following signs was used to define right ventricular dysfunction: right ventricular diastolic diameter greater than 30 mm in the parasternal view; right ventricular diameter greater than the left ventricular diameter in the apical or subcostal views, along with the absence of inspiratory collapse of the inferior vena cava; and hypokinesis of the right ventricular free wall.[12]

Episodes Analyzed

The primary outcome measure was defined as all-cause mortality in the month after diagnosis. The secondary outcome measure was mortality due to pulmonary embolism in the month after diagnosis.

Statistical Analysis

Continuous variables, which were expressed as mean (SD), were compared using the Student *t* test for paired and unpaired data. Categorical variables, expressed as a percentage, were compared with the χ^2 test or the Fisher exact test as appropriate. For the multivariate analysis, we used a logistic regression model which included variables selected according to data from published studies and expert opinion. Statistical significance was set at a *P* value less than .05. The statistical analysis was carried out using the SPSS statistics package, version 11.5 (Chicago, Illinois, USA).

On the basis of published data on prognostic indicators for pulmonary thromboembolism,[18] the minimum sample size was calculated to be 100 patients to detect statistically significant differences in the primary event of poor prognosis between patients with and without right ventricular dysfunction.

Results

Between January 2004 and December 2005, 249 patients were diagnosed with acute symptomatic pulmonary embolism in the emergency room of the Hospital Ramón y Cajal. Seventeen of these were excluded from the study because of hemodynamic instability. In 12 patients, transthoracic echocardiography could not be carried out within 48 hours of diagnosis and 6 patients were lost to follow-up. Therefore, the final study population comprised 214 (92%) hemodynamically stable patients diagnosed with acute symptomatic pulmonary embolism.

Of these, 86 (40%) presented with signs of right ventricular dysfunction in the echocardiographic study. The characteristics of the patients with and without echocardiographic signs of right ventricular dysfunction are presented for comparison in Table 1. Signs of right ventricular dysfunction were documented more frequently in women, patients with a history of chronic obstructive pulmonary disease (COPD), and patients with pulmonary embolism whose presenting symptom was dyspnea. The pattern of prominent S in lead I, Q and inverted T in lead III (S1Q3T3) in the electrocardiogram was more common in patients with right ventricular dysfunction and, at the time of admission, these patients had significantly lower PaO_2 values.

TABLE 1
Baseline Echocardiographic Characteristics of the 214 Patients Studied*

	Echo Positive (n=86)	Echo Negative (n=128)	OR (95% CI)	*P*
Clinical characteristics				
Age >65 years	54 (63%)	78 (61%)	1.1 (0.8-1.3)	.88
Male	33 (38%)	71 (55%)	0.5 (0.3-0.9)	.02
Risk factors for VTD				
Cancer	10 (12%)	7 (5%)	2.3 (0.8-6.2)	.11
Surgery	9 (10%)	10 (8%)	1.4 (0.5-3.5)	.79
Immobility ≥4 days	11 (13%)	20 (16%)	0.8 (0.4-1.7)	.68
Prior VTD	8 (9%)	18 (14%)	0.6 (0.3-1.5)	.38
Comorbidity				
COPD	19 (22%)	9 (7%)	3.7 (1.6-8.7)	<.01
Heart failure	11 (13%)	14 (11%)	1.2 (0.5-2.8)	.82
Clinical presentation				
Syncope	11 (13%)	20 (16%)	0.8 (0.4-1.7)	.68
Dyspnea	70 (81%)	86 (67%)	2.1 (1.1-4.1)	<.0001
Chest pain	46 (53%)	73 (57%)	0.9 (0.5-1.5)	.67
HR>100 beats/min	41 (48%)	44 (34%)	1.7 (1.0-3.0)	.06
PaO_2<60 mm Hg	33 (38%)	80 (62%)	0.4 (0.2-0.7)	<.01
Electrocardiographic findings				
RBBB	17 (20%)	17 (11%)	1.6 (0.8-3.7)	.10
S1Q3T3 pattern	21 (24%)	11 (8%)	3.4 (81.6-7.6)	<.01
Events				
All-cause mortality	4 (5%)	3 (2%)	2.0 (0.4-9.3)	.41
Mortality due to PE	3 (3%)	0 (0%)	–	–

*RBBB indicates right bundle branch block; COPD, chronic obstructive pulmonary disease; VTD, venous thromboembolic disease; HR, heart rate; CI, confidence interval; PE, pulmonary embolism; Echo positive, findings positive for pulmonary embolism; Echo negative; findings negative for pulmonary embolism.

TABLE 2
Sensitivity, Specificity, and Predictive Values of Echocardiographic Signs of Right Ventricular Dysfunction for Predicting All-Cause Mortality*

	%	95% CI
Sensitivity	57	20-94
Specificity	60	54-67
Positive predictive value	5	0-9
Negative predictive value	98	95-100
Positive likelihood ratio	1.44	0.46-2.16
Negative likelihood ratio	0.71	0.49-2.06

*CI indicates confidence interval.

Of the 214 patients studied, 7 (3%) died in the month after diagnosis of pulmonary embolism: 4 in the group with signs of right ventricular dysfunction (3 due to pulmonary embolism and 1 due to major bleeding) and 3 in the group with normal echocardiographic findings (2 due to sepsis and 1 due to left heart failure). Therefore, transthoracic echocardiography had a high negative predictive value for mortality (98%), but the positive predictive value was low (Table 2).

The variables associated with all-cause mortality in the bivariate analysis are presented in Table 3. A history of COPD and active neoplastic disease at the time of diagnosis and immobility for 4 days or more correlated significantly with all-cause mortality in the month after diagnosis. Diagnosis of COPD was the only variable significantly associated with mortality in the logistic regression analysis.

Discussion

Three main findings can be drawn from this study: *a)* echocardiographic signs of right ventricular dysfunction are present in 2 out of every 5 hemodynamically stable patients with acute symptomatic pulmonary embolism; *b)* these echocardiographic findings do not seem to increase the risk of all-cause mortality in stable patients with pulmonary embolism; and *c)* transthoracic echocardiography is not a particularly useful tool for selecting patients with pulmonary embolism and low risk of death in the month after diagnosis or for selecting patients who require more aggressive treatments.

Transthoracic echocardiography has become an increasingly important tool in prognostic stratification of patients with pulmonary embolism.[11-14] Echocardiographic findings of poor prognosis may help select hemodynamically stable patients with pulmonary embolism who would benefit from thrombolytic treatment.[19] Such findings may also identify low-risk patients who are candidates for treatment in outpatient programs.[20] However, the studies done to date have important methodological flaws[15]: the patient selection criteria were not clearly defined, the populations included were heterogeneous in terms of hemodynamic status, and patients were not enrolled consecutively.

In our study, the negative predictive value of the echocardiographic findings was excellent, at 98%, and was even 100% when only mortality due to pulmonary embolism was considered. These results confirm the findings of previous studies.[21,22] However, the small number of events in this series limits the practical use of this predictive value. Furthermore, the negative likelihood ratio

TABLE 3
Prognostic Predictors of Death at 1 Month*

	Death		*P*	
	No (n=207)	Yes (n=7)	Univariate	Multivariate
Clinical characteristics				
Age >65 years	128 (62%)	4 (57%)	.89	-
Male	100 (48%)	4 (57%)	.94	-
Risk factors for VTD				
Cancer	14 (7%)	3 (43%)	<.01	.34
Surgery	19 (9%)	0 (0%)	-	-
Immobility ≥4 days	12 (6%)	4 (57%)	<.001	.72
Prior VTD	26 (13%)	0 (0%)	-	-
Comorbidity				
COPD	24 (12%)	4 (57%)	<.01	.04
Heart failure	24 (12%)	1 (14%)	.67	-
Presenting symptom				
Syncope	31 (15%)	0 (0%)	-	-
Dyspnea	150 (72%)	6 (86%)	.70	-
Chest pain	114 (55%)	5 (72%)	.62	-
HR>100 beats/min	82 (40%)	3 (43%)	.82	-
PaO_2<60 mm Hg	108 (52%)	5 (72%)	.51	-
Electrocardiographic findings				
RBBB	33 (16%)	1 (14%)	.70	-
S1Q3T3 pattern	30 (14%)	2 (29%)	.58	-
Echocardiographic signs of RVD	82 (40%)	4 (57%)	.61	-

*RBBB indicates right bundle branch block; RVD, right ventricular dysfunction; COPD, chronic obstructive pulmonary disease; VTD, venous thromboembolic disease; HR, heart rate; S1Q3T3, prominent S in lead I, Q and inverted T in lead III.

of 0.71 suggests that transthoracic echocardiography adds little value to clinical criteria when selecting patients for early discharge or outpatient treatment. The negative predictive value obtained was comparable with the findings of prognostic scores that have recently been published[23] and validated.[24] Prospective studies should be conducted to evaluate whether transthoracic echocardiography identifies a different subgroup of low-risk patients.

The positive predictive value of the echocardiographic findings for right ventricular dysfunction was low (5%). According to an analysis of the International Cooperative Pulmonary Embolism Registry (ICOPER), the positive predictive value for mortality at 30 days was 16.1% in patients with systolic blood pressure greater than 90 mm Hg.[25] Nevertheless, 20% of the patients (210/635) received thrombolytic therapy and 1340 did not undergo an echocardiographic examination. It could be argued that echocardiography was done in a selected group of patients with indirect evidence of hemodynamic instability other than systolic blood pressure. In the study by Kasper et al,[13] the positive predictive value for mortality due to pulmonary embolism was 13%, probably because hemodynamically unstable patients were included. The 2 studies that included only hemodynamically stable patients reported positive predictive values of 4%[9] and 5%.[12]

Unlike other series published in the literature,[22] we did not find an association between the echocardiographic signs of right ventricular dysfunction and mortality in the logistic regression analysis. Kucher et al[25] studied 1035 patients included in the ICOPER who had a systolic blood pressure equal to or greater than 90 mm Hg and those who had undergone a transthoracic echocardiographic examination within 24 hours of diagnosis of pulmonary embolism. The prevalence of right ventricular dysfunction was 39%, and in the multivariate analysis, right ventricular hypokinesia, was significantly associated with mortality at 30 days. Several factors could explain the discrepancy with our findings. First, the ICOPER is a registry, with all the limitations that analysis of data from such a source implies. Second, it could be argued that transthoracic echocardiography was ordered for selected patients who had some clinical sign of hemodynamic instability. Third, hemodynamic instability is not defined solely by systolic blood pressure less than 90 mm Hg: decreases of 40 mm Hg or more in systolic blood pressure, hypoxemia refractory to supplementary oxygen, and clinical deterioration of the patient regardless of systolic blood pressure are also indications for thrombolytic therapy,[26] and as such could have acted as confounding variables in that registry.

Our study has some advantages over the studies published previously. First, it included consecutive outpatients who were diagnosed with pulmonary embolism using objective methods. Second, only hemodynamically stable patients were included. This is particularly important given that there is no doubt that hemodynamically unstable patients should receive thrombolytic treatment[3] and that these patients should not be included in outpatient treatment programs. Third, the echocardiographic studies were carried out by specialists who had no information on the clinical characteristics of the patients. Finally, a similar treatment protocol was applied to all patients, regardless of the echocardiographic findings.

Nevertheless, our study is subject to some limitations that should be taken into account. First, we did not use properly standardized echocardiographic criteria of right ventricular dysfunction in our study. However, the

prevalence of right ventricular dysfunction in our series (40%) was similar to the rates of most of the studies published to date, and so we do not think that the particular signs we chose were a cause of substantial bias. Second, the number of events in the series studied was small. We used all-cause mortality as the primary outcome measure in the month after diagnosis; the decision to use composite endpoints[10] (death and/or more intensive therapy) is questionable and often subjective.[27-29]

In conclusion, in our setting, transthoracic echocardiography is not useful for prognostic stratification of hemodynamically stable patients with pulmonary embolism. Its usefulness compared to other methods for prognostic stratification, or as a complement to those methods, should be established in appropriately designed prospective studies.

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