Prognostic Role of Echocardiography Among Patients With Acute Pulmonary Embolism and a Systolic Arterial Pressure of 90 mm Hg or Higher

Nils Kucher, MD; Elisa Rossi, BS; Marisa De Rosa, PhD; Samuel Z. Goldhaber, MD

Background: The prognostic role of echocardiographic right ventricular (RV) dysfunction for predicting mortality in patients with acute pulmonary embolism and a preserved systemic arterial pressure remains controversial.

Methods: We evaluated 1035 patients with pulmonary embolism from the International Cooperative Pulmonary Embolism Registry who (1) presented with systolic systemic arterial pressure of 90 mm Hg or higher and (2) who underwent echocardiography within 24 hours of a diagnosis of pulmonary embolism, showing presence (n=405) or absence (n=630) of RV hypokinesis. The main outcome measure was the cumulative survival rate through 30 days in patients with and without RV hypokinesis.

Results: In patients with RV hypokinesis, the initial systolic systemic pressure was lower (125±22 mm Hg vs 131±22 mm Hg; $P<.001$), and the initial heart rate was higher (104±21 beats per minute vs 99±22 beats per minute; $P<.001$) than in patients without RV hypokinesis. Cancer was less often present (14.1% vs 22.5%, $P=.001$). The 30-day survival rates in patients with and without RV hypokinesis were 83.7% (95% confidence interval [CI], 79.3%-87.0%) and 90.6% (95% CI, 88.0%-92.6%), respectively (log-rank P value $<.001$). The univariate hazard ratio of RV hypokinesis for predicting 30-day mortality was 2.11 (95% CI, 1.41-3.16; $P<.001$). Right ventricular hypokinesis remained an independent predictor of 30-day mortality (hazard ratio, 1.94; 95% CI, 1.23-3.06) after adjusting for univariately significant predictors, including cancer, congestive heart failure, chronic lung disease, age older than 70 years, systolic arterial pressure of 100 mm Hg or lower, administration of thrombolytic therapy, and heart rate greater than 100 beats per minutes.

Conclusion: Among patients with pulmonary embolism who present with a systolic arterial pressure greater than or equal to 90 mm Hg, echocardiographic RV hypokinesis is an independent predictor of early death.

Arch Intern Med. 2005;165:1777-1781

ACUTE PULMONARY EMBOLISM (PE) spans a wide spectrum of clinical outcomes, with an overall mortality rate that exceeds 10% at 30 days.[1] The most common cause of death within 30 days is right ventricular (RV) failure. Beyond 30 days, chronic underlying comorbidities such as cancer, congestive heart failure, or lung disease cause most PE deaths.[1,2]

CME course available at www.archinternmed.com

The role of echocardiography for predicting mortality among patients with PE who present with a preserved systemic arterial pressure remains unclear. According to a recent meta-analysis,[3] only 2 small cohort studies[4,5] have investigated the accuracy of echocardiographically diagnosed RV dysfunction for PE-related death. The low positive predictive values of 4%[4] and 5%[5] for PE-related in-hospital death raised the concern that echocardiography may not be helpful for prognostication. Therefore, we investigated whether echocardiographic RV hypokinesis helps predict early death in the large group of patients enrolled in the International Cooperative Pulmonary Embolism Registry (ICOPER) who presented with a preserved systemic arterial pressure.

METHODS

The ICOPER enrolled 2454 consecutive patients with acute PE from 52 hospitals in 7 countries, from January 1995 through November 1996.[1] Inclusion criteria were acute PE, diagnosed by the attending physician within 31 days of symptom onset, and major PE first discovered by necropsy. The ICOPER accepted without independent review the diagnoses and interpretation of imaging tests provided by the participating institution. There were no exclusionary criteria.

Author Affiliations: Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (Drs Kucher and Goldhaber); and CINECA, Bologna, Italy (Ms Rossi and Dr De Rosa).
Financial Disclosure: None.

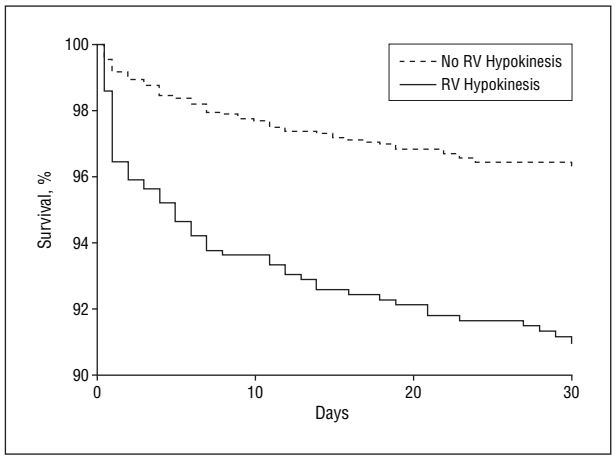

Figure 1. Survival rate through 30 days in 1035 patients with pulmonary embolism with a systolic arterial pressure of 90 mm Hg or higher at presentation, according to the presence or absence of right ventricular (RV) hypokinesis on the baseline echocardiogram, adjusted for cancer, congestive heart failure, chronic lung disease, age, and systolic arterial pressure.

In this analysis, we evaluated 1035 patients who (1) presented with a systolic arterial pressure of 90 mm Hg or higher and (2) who underwent echocardiography within 24 hours of PE diagnosis. Echocardiographic results were analyzed at each center as showing the presence (n=405) or absence (n=630) of RV systolic hypokinesis. Echocardiographic readers were not blinded to patient data. We excluded 1340 patients who did not undergo echocardiography within 24 hours of PE diagnosis, 63 patients who presented with a systolic arterial pressure of less than 90 mm Hg, and 16 patients with unknown systolic arterial pressure at presentation.

Overall, 88% of the 1035 patients had PE confirmed by findings from necropsy, high-probability lung scan, pulmonary angiography, or venous ultrasound of the leg veins in the presence of a high clinical suspicion of PE. The ICOPER accepted without independent review the diagnosis of RV hypokinesis on echocardiography. In addition, the ICOPER did not issue guidelines for treatment of the enrolled patients who had PE. Decisions to use thrombolytic therapy and placement of inferior vena caval filters were made entirely by site physicians; echocardiographic readers may have been involved in clinical decision making. Follow-up in the ICOPER was accomplished by telephone interview with the patient or the patient's primary care physician. Of the 1035 included patients, 19 (1.8%) were lost to 30-day follow-up—10 with and 9 without RV hypokinesis ($P=.24$).

We used the Mann-Whitney test for comparisons of continuous variables between patients with and without RV hypokinesis and the χ^2 test or Fisher exact test for comparisons of nominal variables. We used the Kaplan-Meier estimator and log-rank test to estimate the cumulative probability of 30-day mortality in patients with and without RV hypokinesis. Then, we used the Kaplan estimator to estimate the cumulative probability of 30-day mortality in patients with and without RV hypokinesis while adjusting for univariately significant predictors (**Figure 1**). The Cox proportional hazard regression model was used to calculate the univariate hazard ratio of clinical variables for predicting 30-day mortality. We then performed multivariable analysis to identify independent predictors of 30-day mortality using the proportional hazards model. The primary purpose of the model was to assess the prognostic information of RV hypokinesis on echocardiography while adjusting for univariately significant clinical confounders and stratifying by the participating institutions. We analyzed the association between RV hypokinesis and 30-day survival rates separately for

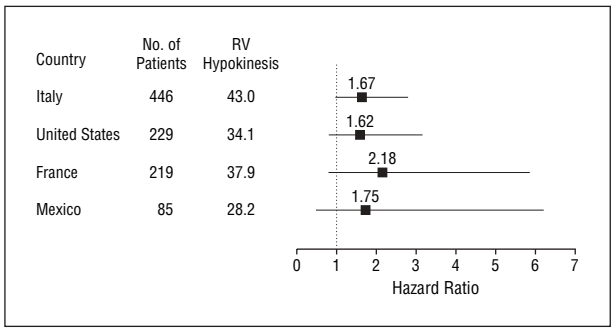

Figure 2. Hazard ratio and 95% confidence intervals of right ventricular (RV) hypokinesis for predicting 30-day mortality in countries with more than 1 participating institution.

institutions with 25 or fewer enrolled patients and for those with more than 25 enrolled patients. We calculated the prevalence of RV hypokinesis and 30-day survival rates for each institution with more than 25 enrolled patients. In addition, we calculated unadjusted hazard ratios of RV hypokinesis for predicting 30-day mortality for each participating country with more than 1 institution (**Figure 2**). All reported *P* values are 2-tailed.

RESULTS

Age and sex were similar in patients with and without RV hypokinesis (**Table 1**). In patients with RV hypokinesis, the initial mean ± SD systolic systemic pressure was lower (125±22 mm Hg vs 131±22 mm Hg; $P<.001$), and the initial heart rate was higher (104±21 beats per minute vs 99±22 beats per minute; $P<.001$). In patients with RV hypokinesis, chest pain was less common and dyspnea more common. Cancer was present less often in patients with than without RV hypokinesis. Patients with RV hypokinesis more often underwent thrombolysis or embolectomy.

The overall survival rate was 87.9% (95% confidence interval [CI], 85.8%-89.8%). Sixty-five patients with and 59 patients without RV hypokinesis died during the 30 days of follow-up; the 30-day survival rates for patients with and without RV hypokinesis were 83.7% (95% CI, 79.3%-87.0%) and 90.6% (95% CI, 88.0%-92.6%), respectively (log-rank *P* value <.001). The 30-day survival rates adjusted for cancer, congestive heart failure, chronic lung disease, age, and systolic arterial pressure at presentation were 91.0% for patients with and 96.4% for patients without RV hypokinesis (Figure 1).

The univariate hazard ratio of RV hypokinesis for 30-day mortality, stratified by institution, was 2.11 (95% CI, 1.41-3.16; $P<.001$). Clinical predictors of 30-day mortality included cancer, congestive heart failure, chronic lung disease, age older than 70 years, a systolic arterial pressure of 100 mm Hg or lower, the administration of thrombolytic therapy, and a heart rate higher than 100 beats per minute; right heart thrombus on echocardiography achieved borderline significance (**Table 2**). Right ventricular hypokinesis remained an independent predictor of 30-day mortality (hazard ratio, 1.94; 95% CI, 1.23-3.06; $P=.004$) after adjusting for univariately significant predictors (**Table 3**).

Negative and positive predictive values of RV hypokinesis for 30-day mortality were 90.6% (95% CI, 88.1%-

Table 1. Characteristics of 1035 Patients With Acute Pulmonary Embolism (PE) and a Systolic Arterial Pressure of 90 mm Hg or Higher According to Presence or Absence of Right Ventricular (RV) Hypokinesis*

Characteristic	RV Hypokinesis (n = 405)	No RV Hypokinesis (n = 630)	*P* Value
Age, median (range), y	67 (21-91)	65 (14-95)	.12
Age >70 y	150 (37.2)	223 (35.4)	.55
Men	182 (44.9)	275 (43.7)	.68
Systolic pressure, mean ± SD, mm Hg	125 ± 22	131 ± 22	<.001
90-100	73 (18.0)	58 (9.2)	
101-110	57 (14.1)	82 (13.0)	
111-120	75 (18.5)	114 (18.1)	
121-140	124 (30.6)	221 (35.1)	
141-160	61 (15.1)	112 (17.8)	
>160	15 (3.7)	43 (6.8)	<.001
Heart rate, mean ±SD, beats per minute	104 ± 21	99 ± 22	<.001
Heart rate >100 beats per minute	206 (50.9)	253 (40.2)	.001
Days from symptom onset to diagnosis, median (mean ± SD)	2 (4.2 ± 5.7)	2 (4.6 ± 6.4)	.43
Chest pain	169 (42.1)	320 (51.1)	.005
Dyspnea	376 (93.1)	539 (85.6)	<.001
Cough	89 (22.0)	152 (24.1)	.42
Hemoptysis	21 (5.2)	46 (7.3)	.18
Left ventricular ejection fraction <40%	31 (8.0)	49 (8.6)	.75
Right heart thrombus	26 (6.4)	16 (2.5)	.002
Comorbidities			
Concomitant deep vein thrombosis	219 (54.2)	334 (53.2)	.75
Cancer	57 (14.1)	141 (22.4)	.001
Ongoing cancer chemotherapy	14 (3.5)	41 (6.5)	.03
Prior deep vein thrombosis	95 (24.2)	133 (21.5)	.33
Prior PE	38 (9.6)	51 (8.3)	.47
Chronic lung disease	51 (12.6)	83 (13.2)	.79
Congestive heart failure	60 (14.9)	71 (11.3)	.09
Trauma within 2 mo	45 (11.1)	71 (11.3)	.94
Creatinine >2.0 mg/dL	21 (5.2)	33 (5.2)	.97
Therapy			
Thrombolysis	151 (37.7)	59 (9.4)	<.001
Vena cava filter	53 (13.1)	66 (10.5)	.19
Catheter or surgical embolectomy	14 (3.5)	3 (0.5)	<.001
No anticoagulation†	10 (2.5)	5 (0.8)	.64

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Data are given as number (percentage) of patients unless otherwise specified.

†Unfractionated heparin, low-molecular-weight heparin, or vitamin K antagonist.

Table 2. Univariate Predictors of Mortality at 30 Days in 1035 Patients With Acute Pulmonary Embolism and a Systolic Arterial Pressure of 90 mm Hg or Higher

Variable	Hazard Ratio (95% Confidence Interval)
Congestive heart failure	2.74 (1.84-4.08)
Chronic lung disease	2.38 (1.59-3.58)
Cancer	2.31 (1.59-3.35)
Systolic pressure ≤100 mm Hg	2.16 (1.42-3.29)
Age >70 y	2.03 (1.43-2.88)
Right heart thrombus	1.94 (0.98-3.82)
Thrombolysis	1.77 (1.21-2.60)
Heart rate >100 beats per min	1.66 (1.16-2.37)

Table 3. Multivariable Analysis of Univariately Significant Variables for Predicting Mortality at 30 Days, Stratified by the International Cooperative Pulmonary Embolism Registry Institution

Variable	Adjusted Hazard Ratio (95% Confidence Interval)
Right ventricular hypokinesis	1.94 (1.23-3.06)
Cancer	2.31 (1.52-3.51)
Congestive heart failure	1.92 (1.18-3.11)
Chronic lung disease	1.77 (1.11-2.83)
Age >70 y	1.70 (1.15-2.52)
Systolic arterial pressure ≤100 mm Hg	1.58 (0.98-2.54)
Heart rate >100 beats per min	1.42 (0.95-2.12)
Right heart thrombus	1.11 (0.52-2.33)
Thrombolysis	1.33 (0.81-2.17)

92.7%) and 16.1% (95% CI, 12.8%-19.9%), respectively. Sensitivity and specificity of RV hypokinesis for 30-day mortality were 52.4% (95% CI, 43.7%-61.0%) and 62.7% (95% CI, 59.5%-65.8%), respectively.

In institutions with 25 or fewer enrolled patients, RV hypokinesis was present in 222 (38.3%) of the 579 patients. Thirty-day survival rates were 82.4% in patients with and 88.8% in patients without RV hypokinesis. In institutions with more than 25 enrolled patients, RV hypokinesis was present in 183 (40.1%) of the 456 patients. Thirty-day survival rates were 85.8% in patients with and 93.0% in patients without RV hypokinesis. There was considerable variability in the percentage of patients with RV hypokinesis and in 30-day survival rates among individual institutions with more than 25 enrolled patients (**Table 4**). The hazard ratio of RV hypokinesis for predicting 30-day mortality was similar in Italy, the United States, France, and Mexico (Figure 2).

COMMENT

Most patients with recognized PE present with preserved systemic arterial pressure. Whether RV dysfunction independently predicts an increased risk of death has been unclear. When we analyzed this patient population enrolled in the ICOPER, we observed that RV hypokinesis on baseline echocardiography independently predicts decreased 30-day survival. This finding is clinically important because it facilitates rapid identification of high-risk patients who present with a preserved systemic arterial pressure and who might deceivingly seem to be stable and at low risk. Such patients had a surprisingly high 30-day mortality rate of almost 17%. The presence of RV hypokinesis, despite initially preserved blood pressure, almost doubled

Table 4. Survival Rates at 30 Days According to Presence or Absence of Right Ventricular (RV) Hypokinesis in International Cooperative Pulmonary Embolism Registry Institutions With More Than 25 Enrolled Patients

Center	No. of Patients	RV Hypokinesis, %	30-Day Survival, %	
			RV Hypokinesis	No RV Hypokinesis
Brigham and Women's Hospital, Boston, Mass	89	41.6	78.4	91.4
Spedali Civili, Brescia, Italy	45	80.0	86.1	100.0
Universitá di Bologna, Bologna, Italy	43	27.9	66.6	91.3
Ospidale Maggiore-Molinette, Torino, Italy	43	41.9	94.4	100.0
Centre Hospitalier Universitaire, Besançon, France	39	12.8	100.0	88.2
Hôpital Notre-Dame de Bon Secours, Metz, France	33	45.4	86.7	100.0
ABC Hospital, Mexico City, Mexico	30	23.3	100.0	95.7
Academy of Medicine, Warsaw, Poland	27	55.6	80.0	91.7
Hôpital Cardiologique, Lille, France	27	44.4	83.3	100.0
Universitá di Perugia, Perugia, Italy	27	3.7	100.0	92.3
Ospedale Maggiore Pizzardi, Bologna	27	33.3	66.6	83.3
Hôpital Trousseau, Tours, France	26	61.5	100.0	100.0

the risk of death. An unfavorable prognosis based on the initial echocardiogram persisted after adjusting for important clinical predictors of death, including cancer, congestive heart failure, chronic lung disease, advanced age, and the use of PE thrombolysis.

Our registry helps validate the trends observed in 3 previous small studies that investigated the prognostic value of echocardiography in patients with hemodynamically stable PE.[4-6] Among 162 normotensive patients from a single cohort center study,[5] the percentage of patients with RV dysfunction (31%) was similar to our study (39%). Five percent of the patients with RV dysfunction died during hospitalization; in contrast, none died in the group with baseline-preserved RV function (Fisher exact *P* value, .009). However, this study did not adjust for other clinical predictors of outcome. In a randomized controlled trial of 101 initially hemodynamically stable patients,[4] RV dysfunction did not emerge as an independent predictor of death. In 126 consecutive patients from a single-center study,[6] RV dysfunction was found in 56% of the patients; all 10 in-hospital deaths occurred in patients with RV dysfunction. Both RV dysfunction and cancer remained independent predictors of mortality at 1 year.

In the present study, right heart thrombi were more often present in patients with vs those without RV hypokinesis. The presence of right heart thrombi itself was associated with an increased risk of death within 30 days. This finding emphasizes the need for echocardiography not only to identify patients with PE with RV dysfunction but to diagnose or exclude right heart thrombi.

Our findings regarding echocardiographic RV hypokinesis may be generalizable and may also apply to RV enlargement visualized on chest computed tomography.[7] Among 431 consecutive patients with PE at Brigham and Women's Hospital (Boston, Mass), RV enlargement on multidetector row computed tomography, defined as a right-to-left ventricular diameter ratio greater than 0.9, was an independent predictor of 30-day mortality (hazard ratio, 5.2; 95% CI, 1.6-16.4).

The present study population may not be representative of the entire ICOPER population because echocardiography was obtained possibly more often in patients with more severe PE, and those with minor PE symptoms or signs may not have undergone echocardiographic evaluation. This may also explain the low overall 30-day survival rate of 87.9%. Patients without RV hypokinesis had a 30-day survival rate of 91.6%. Although we did not track the causes of death, it is likely that most of these patients died from underlying disease and not from PE-related complications. After adjusting for important clinical confounders, the 30-day survival rate increased to 96.4% in patients without RV dysfunction.

Right ventricular function was assessed by qualitative interpretation of systolic RV free wall motion, and data on the degree of RV hypokinesis were not obtained. Right ventricular wall motion was not centrally adjudicated. Variability in the interpretation of findings among echocardiography technicians and institutions may potentially have affected our results, and substantial variation in the prevalence of RV hypokinesis was observed among individual institutions. All regression analyses were therefore stratified by the participating ICOPER institutions. In addition, we found similar rates of patients with RV hypokinesis and similar 30-day survival rates in Italy, the United States, France, and Mexico. Another study limitation is that additional echocardiographic findings for evaluating RV dysfunction were not obtained, such as RV dilation, paradoxical motion of the interventricular septum, an increased tricuspid regurgitant jet velocity, or a dilated inferior vena cava without respiratory variation.[8,9] The finding of RV hypokinesis was probably used to guide the use of thrombolysis in many ICOPER patients, although a substantial number of patients without RV hypokinesis also received thrombolysis. The adjustment for thrombolysis in our multivariable analysis can only partly eliminate this confounding effect.

Nevertheless, the ICOPER is the largest prospective international registry of patients with acute PE, and echocardiography was performed within 24 hours of PE diagnosis in more than 1000 patients who presented with a preserved systemic arterial pressure. There were no exclusion criteria, which led to enrollment of a broad clinical spectrum of consecutive patients. Only 1.8% were lost to follow-up.

In conclusion, our study shows that echocardiographic RV hypokinesis independently predicts early death among patients with PE who present with a systemic arterial pressure of 90 mm Hg or higher. The prognostic information obtained from echocardiography in these patients may be increased by cardiac biomarker test results, including cardiac troponins[10] and natriuretic peptides.[11] Our findings are useful both for clinical triage and management of patients with newly diagnosed PE and for planning future trials on reperfusion therapy among high-risk PE patients.

Accepted for Publication: March 27, 2005.
Correspondence: Samuel Z. Goldhaber, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (sgoldhaber@partners.org).

REFERENCES

1. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353:1386-1389.
2. Goldhaber SZ, Elliott CG. Acute pulmonary embolism, part II: risk stratification, treatment, and prevention. *Circulation*. 2003;108:2834-2838.
3. ten Wolde M, Sohne M, Quak E, Mac Gillavry MR, Buller HR. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. *Arch Intern Med*. 2004;164:1685-1689.
4. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet*. 1993;341:507-511.
5. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation*. 2000;101:2817-2822.
6. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. *Am Heart J*. 1997;134:479-487.
7. Schoepf UJ, Kucher N, Kipfmueller F, Quiroz R, Costello P, Goldhaber SZ. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. *Circulation*. 2004;110:3276-3280.
8. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. *Ann Intern Med*. 2002;136:691-700.
9. Task Force on Pulmonary Embolism, European Society of Cardiology. Guidelines on diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2000;21:1301-1336.
10. Kucher N, Wallmann D, Windecker S, Meier B, Hess OM. Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism. *Eur Heart J*. 2003;24:1651-1656.
11. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. *Circulation*. 2003;108:2191-2194.