

Right Heart Thrombi in Pulmonary Embolism

Results From the International Cooperative Pulmonary Embolism Registry

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OBJECTIVES	This study was designed to investigate the prevalence and prognostic significance of right heart thrombi (RHTh) in pulmonary embolism.
BACKGROUND	Most reports about patients with RHTh are small case series. We analyzed data referring to RHTh among 2,454 consecutive pulmonary embolism patients enrolled in the International Cooperative Pulmonary Embolism Registry.
METHODS	Of the 2,454 patients, 1,113 had results available from baseline echocardiography. We compared the 42 patients with RHTh versus 1,071 without RHTh.
RESULTS	Patients with RHTh had shorter duration of symptoms (2.2 ± 2.9 days vs. 4.3 ± 6.0 days, $p = 0.013$), lower systolic blood pressure (BP) (116.0 ± 28.8 vs. 125.7 ± 25.0 mm Hg, $p = 0.008$), and more frequent right ventricular hypokinesia (64% vs. 40%, $p = 0.002$) and congestive heart failure (26% vs. 13%, $p = 0.024$); but they had similar age (62.9 vs. 62.5 years), arterial oxygen pressure (71.3 ± 26.0 vs. 69.5 ± 30.5 mm Hg), and prevalence of cancer (14% vs. 19%). The overall mortality rate at 14 days and at three months was higher in patients with RHTh (21% vs. 11%, $p = 0.032$, and 29% vs. 16%, $p = 0.036$). The difference in early mortality was observed almost entirely within the subgroup of patients treated with heparin alone (23.5% vs. 8%, $p = 0.02$), despite similar clinical severity at presentation (systolic BP 122.2 ± 24.2 vs. 127.8 ± 24.1 mm Hg, hypotension in 5.9% vs. 3.4% patients).
CONCLUSIONS	Among patients with acute pulmonary embolism, RHTh is usually found in those more hemodynamically compromised but is also a marker of worse prognosis in initially apparently stable patients treated with heparin alone. (J Am Coll Cardiol 2003;41:2245–51) © 2003 by the American College of Cardiology Foundation

Small case series have described the prevalence, natural history, and prognostic significance of right heart thrombi (RHTh) in pulmonary embolism (1–6). The International Cooperative Pulmonary Embolism Registry (ICOPER) of 2,454 prospectively enrolled patients from 52 hospitals in seven countries provided a unique opportunity to study further this clinical problem. Almost half of the patients underwent baseline echocardiography. We achieved three months' follow-up of vital status in 98% of patients. We correlated findings on baseline echocardiography with clinical management and outcome (7).

METHODS

The International Cooperative Pulmonary Embolism Registry enrolled consecutive patients with acute pulmonary embolism (PE) between January 1995 and November 1996. The principal inclusion criterion was acute PE diagnosed according to clinical routine of the reporting center within 31 days of the onset of symptoms. No recommendations were made regarding the use of echocardiography, general diagnostic strategy, or therapeutic approach. A detailed electronic case report form was filled out for each patient by participating institutions, using an online system devised by CINECA, an interuniversity consortium of 15 Italian uni-

versities. This report included information on the history and clinical presentation at the time of PE diagnosis as well as on the presence of echocardiographic signs of right ventricular (RV) dysfunction and the presence of intracardiac thrombi. No other echocardiographic variables were requested. We analyzed patients with (+) and without (–) RHTh with respect to clinical characteristics and therapy. We compared the differences by chi-square test (for categorical variables) and Mann-Whitney *U* test (for continuous variables). We assessed the absence of normal distribution of quantitative variables using the Kolmogorov-Smirnov test. Cumulative probabilities of surviving and their 95% confidence intervals were evaluated by the Kaplan-Meier method. Survival rates for the groups with and those without RHTh were compared using the log-rank test. The mortality rate was also evaluated according to treatment received. We also performed a subgroup analysis excluding patients with right heart (RH) catheters and pacemaker electrodes. Multivariate analysis was performed using Cox proportional-hazards regression analysis.

RESULTS

Of 2,454 patients, 1,135 were assessed by echocardiography, of whom 42 (4%) had RHTh and 1,071 did not. Twenty-two patients in whom RHTh was neither reported nor unequivocally stated as absent were excluded from further analysis (Fig. 1). The use of objective diagnostic tests for venous thromboembolism was similar in RHTh(+) and

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Abbreviations and Acronyms

CHF	= congestive heart failure
COPD	= chronic obstructive pulmonary disease
HR	= heart rate
ICOPER	= International Cooperative Pulmonary Embolism Registry
PE	= pulmonary embolism
RH	= right heart
RV	= right ventricle/ventricular
RHTh	= right heart thrombi

RHTh(-) patients: lung scintigraphy was performed in 79% vs. 79%, pulmonary angiography in 10% vs. 21%, and lower limbs were objectively assessed for venous thrombosis in 40% vs. 53% of patients (all non-significant).

The RHTh(+) patients were more hemodynamically compromised than the RHTh(-) patients, with lower systolic blood pressure, higher heart rate (HR), and more frequent RV hypokinesis on echocardiography (Table 1). The RHTh(+) patients also had double the frequency of clinical congestive heart failure (CHF) and more often had

right bundle branch block on electrocardiogram. Compared with RHTh(-), RHTh(+) patients had a shorter time from onset of symptoms to diagnosis (2.2 ± 2.9 days vs. 4.3 ± 6.0 days, $p = 0.013$) and from onset of symptoms to initiation of treatment of pulmonary embolism (2.2 ± 3.0 days vs. 4.4 ± 6.2 days, $p = 0.013$).

With respect to similarities, age, prevalence of dyspnea, chest pain, and blood gases were almost identical in RHTh(+) patients and RHTh(-) patients, as was the frequency of chronic obstructive pulmonary disease (COPD) and cancer. However, treatment was strikingly different between the two groups: 57% of RHTh(+) patients received thrombolysis, compared with 20% in the RHTh(-) group and 13% in the overall ICOPER cohort. Embolectomy was performed in four RHTh(+) patients (10%) and only in 14 RHTh(-) patients (1%), most of whom were treated with heparin alone (76%) (Table 1).

The overall mortality rate at 14 days and at three months was twice as high in RHTh(+) patients: 21% versus 11% ($p = 0.032$) and 29% versus 16% ($p = 0.036$), respectively (Fig. 2). The difference in early mortality was more marked

Table 1. Characteristics of Patients With (+) and Without (-) RHTh

	RHTh(+)	RHTh(-)	p*
Number of patients	42	1,071	
Demographics and history			
Age (yrs)	62.9 ± 13.3	62.5 ± 16.4	n.s.
Female gender	52%	56%	n.s.
Cancer	14%	19%	n.s.
Congestive heart failure	26%	13%	0.024
COPD	12%	13%	n.s.
Central venous catheters	7%	8%	n.s.
Pacemaker wires	5%	1%	Not possible
At presentation			
Dyspnea	83%	88%	n.s.
Chest pain	46%	47%	n.s.
Syncope	24%	16%	n.s.
Heart rate (beats/min)	107.2 ± 19.5	101.3 ± 22.0	0.030
Systolic blood pressure (mm Hg)	116.0 ± 28.8	125.7 ± 25.0	0.008
Systolic blood pressure <90 mm Hg	14%	5%	0.012
PaO ₂ (mm Hg)	71.3 ± 26.0	69.5 ± 30.5	n.s.
PaCO ₂ (mm Hg)	32.0 ± 8.3	33.7 ± 8.6	n.s.
Respiratory rate (beats/min)	27.8 ± 8.0	25.3 ± 9.5	0.037
Normal electrocardiogram	12%	24%	n.s.
Atrial fibrillation	12%	12%	n.s.
Right bundle branch block	27%	13%	0.023
RV hypokinesis at echo	64%	40%	0.002
DVT diagnosed	40%	53%	n.s.
Treatment used			
Heparin	40%	76%	< 0.001
Thrombolysis	57%	20%	< 0.001
IVC filter	12%	12%	n.s.
Embolectomy†	10%	1%	< 0.001
Outcome			
Mortality at 14 days	21%	11%	0.032‡
Mortality at 3 months	29%	16%	0.036‡

*p-value refers to chi-square test (with Yates continuity correction) for categorical variables and to Mann-Whitney test for quantitative variables. We used Mann-Whitney test instead of t test because of absence of normality distribution of variables.

†One of four patients with RHTh and 10 of 14 patients without RHTh underwent catheter embolectomies; the remaining underwent surgical embolectomies. ‡p value refers to Log-rank test from Kaplan-Meier survival analysis.

COPD = chronic obstructive lung disease; DVT = deep vein thrombosis; IVC = inferior vena cava; n.s. = not significant; RHTh = right heart thrombi; RV = right ventricle.

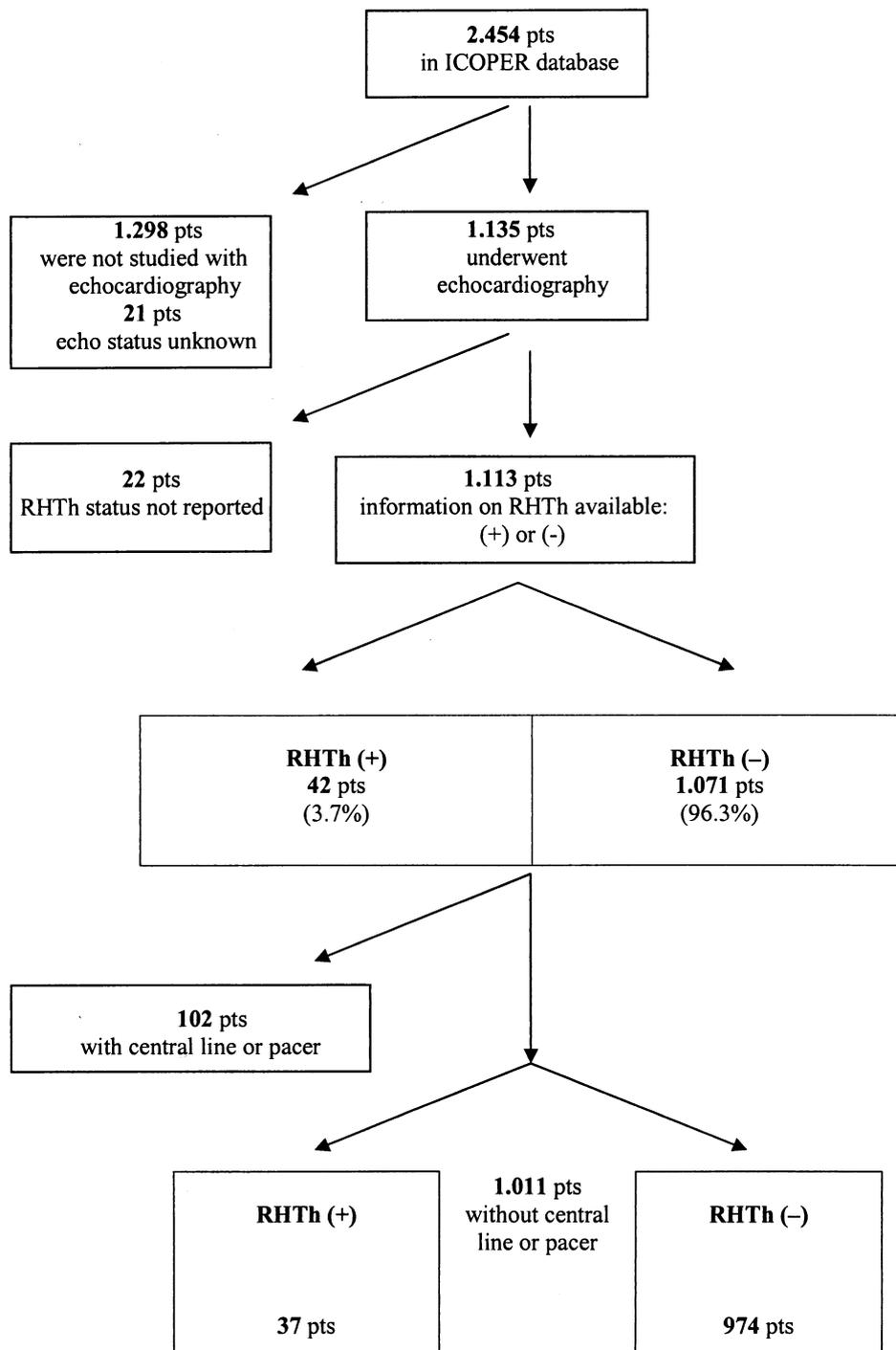


Figure 1. The International Cooperative Pulmonary Embolism Registry (ICOPER) database as a source of information on the presence (+) or absence (-) of right heart thrombi (RHT). pts = patients.

(mortality at 14 days 22% vs. 10%, $p = 0.026$) after 102 patients with RH catheters and electrodes potentially promoting local thrombosis were excluded.

The most evident difference in prognosis was found among patients treated with heparin alone (Tables 2 and 3): mortality at 14 days was 23.5% in RHT(+), versus 8% in RHT(-) ($p < 0.02$) (Table 2) and 25% vs. 7.2% ($p =$

0.007) after excluding patients with central catheters and electrodes. Despite these differences in outcome, markers of clinical severity were not significantly different between RHT(+) and RHT(-) patients treated with heparin alone (Tables 4 and 5).

Mortality was similar in RHT(+) patients treated with heparin alone and in RHT(+) patients treated with

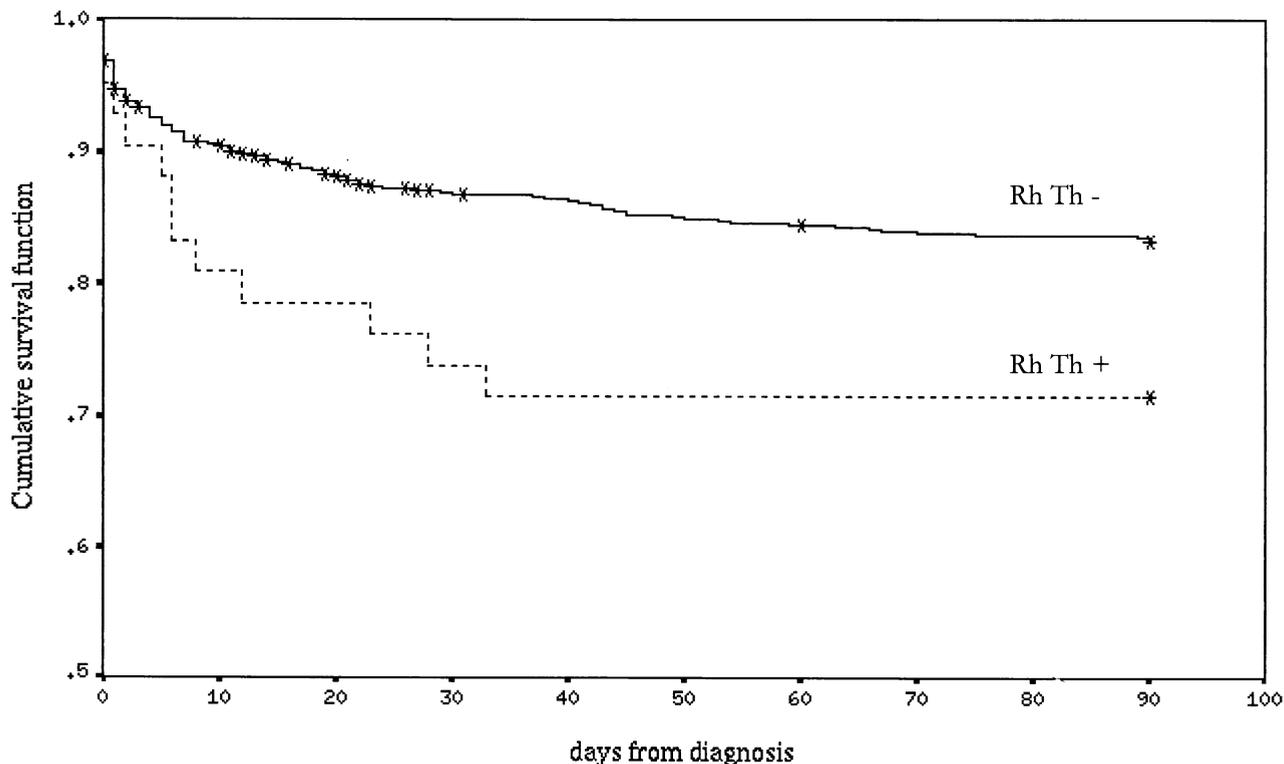


Figure 2. Three months' survival according to the presence (+) or absence (-) of right heart thrombi (RHTh) at echocardiographic examination in a patient with acute pulmonary embolism.

thrombolysis. However, thrombolysis-treated patients had a non-significant trend toward more severe hemodynamic compromise, with lower mean systolic blood pressure of 113 ± 31.3 vs. 122.2 ± 24.2 mm Hg, higher mean HR of 111.5 ± 21.6 vs. 102.3 ± 15.0 beats/min, more frequent hypotension (16.7% vs. 5.9%), and more frequent RV hypokinesis on echocardiography.

Multivariate analysis was performed on 799 patients, with information about all risk factors identified as independent contributors to prognosis in the main ICOPER database. When analyzed together with age, CHF, cancer, COPD, systemic arterial hypotension, RV hypokinesis on echocardiogram, and abnormally slow respiratory rate, RHTh did not provide any further contribution to the model.

To assess whether performing echocardiography affected the selection of patients with pulmonary embolism, Table 6 compares baseline characteristics, treatment, and outcome of patients according to whether they underwent echocar-

diography. Thrombolytic treatment was much more frequently used among patients undergoing echocardiography (22% vs. 5%, $p < 0.001$). However, mortality at 14 days and three months was similar for the patients examined and for those not examined with echocardiography.

DISCUSSION

In ICOPER, RHTh was infrequent. Our data demonstrate that patients with RHTh are more hemodynamically compromised at the time of diagnosis than patients without RHTh, as suggested by lower systemic arterial pressure, higher prevalence of hypotension, higher HR, and frequent RV hypokinesis on echocardiography (8). Also, patients with RHTh more often had CHF. Thus, stasis in the dilated RH due either to acute PE or preexisting CHF, or both, seemed to enhance the risk of RHTh, regardless of whether it was due to in situ thrombosis or to entrapment of transiting thrombi.

Table 2. Mortality Rate at 14 days, in Patients With (+) and Without (-) RHTh According to Reported Treatment

Reported Treatment	RHTh(+)		RHTh(-)		Log-Rank Test p value
	n/N	Mortality Rate	n/N	Mortality Rate	
Heparin	4/17	23.5%	65/813	8.0%	<0.02
Thrombolysis	5/24	20.8%	37/217	17.1%	n.s.
Embolectomy	1/4	25.0%	4/14	28.6%	n.a.*

n.a. = not assessed owing to low number of cases; n.s. = not significant; RHTh = right heart thrombi.

Table 3. Mortality Rate at 3 Months, in Patients With (+) and Without (-) RHTh According to Reported Treatment

Reported Treatment	RHTh(+)		RHTh(-)		Log-Rank Test p value
	n/N	Mortality Rate	n/N	Mortality Rate	
Heparin	5/17	29.4%	117/813	14.3%	0.063
Thrombolysis	7/24	29.2%	45/217	20.7%	n.s.
Embolectomy	1/4	25.0%	5/14	35.7%	n.a.*

Abbreviations as in Table 2.

Table 4. Comparison of Clinical Characteristics of Patients Treated With Heparin Only, According to the Presence (+) or Absence (-) of RHTh

	RHTh(+) n = 17	RHTh(-) n = 813	p Value
Age >70 yrs	5 (29.4%)	307 (37.8%)	n.s.
Cancer	3 (17.6%)	170 (21.0%)	n.s.
RV hypokinesia	9 (52.9%)	246 (30.8%)	n.s. (p = 0.051)
Respiratory rate >20/min	9 (60.0%)	398 (65.2%)	n.s.
Respiratory rate	26.3 ± 7.8	25.1 ± 9.9	n.s.
Hypotension (SBP < 90 mm Hg)	1 (5.9%)	27 (3.4%)	n.s.
SBP (mm Hg)	122.2 ± 24.2	127.8 ± 24.1	n.s.
HR (<50 or >100 beats/min)	9 (52.9%)	347 (42.9)	n.s.
HR (beats/min)	102.3 ± 15.0	99.9 ± 21.5	n.s.
PO ₂ (mm Hg)	70.3 ± 10.8	69.6 ± 28.2	n.s.
PCO ₂ (mm Hg)	34.1 ± 8.9	33.8 ± 7.7	n.s.

HR = heart rate; RV = right ventricular; SBP = systolic blood pressure. Other abbreviations as in Table 2.

The role of local stasis as a prerequisite for RHTh is supported by the observation that the majority (88%) of patients with RHTh in ICOPER had no other factors promoting local thrombosis such as central catheters or electrode wires. Moreover, cancer, a common and potent factor inducing thrombophilia, was not more frequent among RHTh(+) than RHTh(-) patients. In contrast to hemodynamics, age, prevalence of COPD, and arterial blood gases were similar in RHTh(+) patients and RHTh(-) patients.

Assessment of prognosis is of crucial importance for the therapeutic choices in patients with pulmonary embolism. We found that those with RHTh had a worse 14-day as well as three-month outcome when compared to those without RHTh. Interestingly, mortality was higher in RHTh(+) patients, despite much shorter delay from onset of symptoms to diagnosis and treatment in this group. One explanation may be that the RHTh, especially when in transit from the peripheral veins, usually appears in the early phase of acute venous thromboembolic disease and is usually fatal if undiagnosed and thus left untreated. Another explanation may be that echocardiographic documentation of a RHTh immediately establishes the diagnosis of pulmonary embolism, without the need to recur to other imaging tests

Table 5. Distribution of Clinical Severity Factors According to the Presence or Absence of RHTh in Patients Treated With Heparin Alone

Clinical Severity Factors*	RHTh(+)		RHTh(-)	
	N	%	N	%
≤2 factors	12	70.6%	574	70.6%
>2 factors	5	29.4%	239	29.4%
Total	17	100%	813	100%

*According to the results of the analysis of ICOPER Registry Database Clinical severity factors consist of age > 70 years, cancer, right ventricular hypokinesia, respiratory rate > 20/min, systolic blood pressure < 90 mm Hg, heart rate < 50 or > 100 beats/min.

RHTh = right heart thrombus.

that might delay both diagnosis and treatment. This would imply that earlier diagnosis and initiation of treatment does not outweigh the increased risk of death related to RHTh.

Unfortunately, an independent causative effect of RHTh on mortality could not be unequivocally confirmed, because multivariate analysis involving all prognostic risk factors identified in the main ICOPER database analysis was limited to 799 patients and failed to confirm an independent prognostic value of RHTh. Therefore, owing to coexisting hemodynamic differences between RHTh(+) and RHTh(-) patients, it is unclear whether RHTh is a direct cause or just a marker of adverse outcome.

As was the case with Kinney and Wright (9), we found no major differences in survival between the heparin, thrombolytic, and surgical treatment of RHTh. However, ICOPER provided a unique opportunity to compare the clinical characteristics and outcome of RHTh(+) and of similarly treated RHTh(-) patients.

Interestingly, the high 23.5% mortality at 14 days among RHTh(+) patients treated with heparin alone contrasted markedly with the 8% mortality of RHTh(-) patients treated in the same way. This could not be attributed simply to the slight differences in severity of hemodynamic compromise. Mortality was also high (20.8%) among RHTh(+) patients who received thrombolytic treatment, but this could be explained by a high prevalence of hypotension (16.7%) and RV dysfunction (76.2%) within this subgroup. In contrast to patients who were treated with heparin alone, those who received thrombolysis had similar mortality, regardless of the presence or absence of RHTh.

Taken together, these observations suggest that heparin alone might not be adequate treatment for patients with RHTh, even among those who appear clinically stable. A similar conclusion was reached by Rose et al. Their analysis of outcome of 177 published case reports revealed 28.6% mortality in patients with RHTh treated with heparin alone, compared to 11.3% mortality among patients with thrombolysis (10). Surprisingly few ICOPER patients with RHTh underwent open surgical embolectomy, making statistical analysis of this interesting subgroup impossible (11).

Limitations of the trial. This is a prospective registry and not a randomized trial. In order not to exclude most sick patients, a predefined diagnostic algorithm for pulmonary embolism was not enforced. Therefore, we cannot exclude some influence of diagnostic errors on our results, though the use of objective diagnostic tests was similar in RHTh(+) patients and RHTh(-) patients. As in most registries, neither diagnostic work-up nor therapy was controlled. No detailed information on the morphology and mobility of RHTh was available. Therefore, differentiation between an in situ and an in-transit RHTh could not be established other than by identifying coexisting risk factors for local thrombosis, such as RH catheters and electrode wires. We could not precisely assess the sequence of events as far as echo and initiation of treatment are concerned.

Table 6. Characteristics of Patients in the ICOPER Database According to Whether Echocardiographic Examination Has Been Performed

	ECHO(+)	ECHO(-)	p*
Number of patients	1,135	1,298	
Demographics and history			
Age (yrs)	62.5 ± 16.2	62.0 ± 17.1	n.s.
Female gender	56%	55%	n.s.
Cancer	19%	26%	< 0.001
Congestive heart failure	14%	8%	< 0.001
COPD	13%	12%	n.s.
Central venous catheters	8%	7%	n.s.
Pacemaker wires	2%	1%	n.s.
At presentation			
Dyspnea	88%	76%	< 0.001*
Chest pain	47%	51%	0.041*
Syncope	16%	11%	0.001
Heart rate (bpm)	101.6 ± 22.0	95.8 ± 21.4	< 0.001
Systolic blood pressure (mm Hg)	125.4 ± 25.3	131.5 ± 24.6	< 0.001
Systolic blood pressure <90 mm Hg	6%	3%	0.009
PaO ₂ (mm Hg)	69.5 ± 30.1	69.6 ± 32.4	n.s.
PaCO ₂ (mm Hg)	33.7 ± 8.5	34.5 ± 7.8	< 0.001
Respiratory rate (beats/min)	25.3 ± 9.4	24.0 ± 7.5	< 0.001
Normal electrocardiogram	24%	35%	< 0.001
Atrial fibrillation	12%	7%	< 0.001
Right bundle branch block	14%	9%	0.002
RV hypokinesis at echo	40%	0	n.a.
DVT diagnosed	52%	47%	0.01
Time symptoms-diagnosis (days)	4.2 ± 5.9	3.7 ± 5.5	0.013
Treatment used			
Heparin	76%	91%	< 0.001
Thrombolysis	22%	5%	< 0.001
IVC filter	11%	9%	n.s.
Embolectomy**	2%	1%	n.s.
Outcome			
Mortality at 14 days	12%	11%	n.s.†
Mortality at 3 months	17%	17%	n.s.†

*p value refers to chi-square test (with Yates continuity correction) for categorical variables and to Mann-Whitney test for quantitative variables. We used Mann-Whitney test instead of *t* test because of absence of normality distribution of variables.

†p value refers to log-rank test from Kaplan-Meier survival analysis.

Abbreviations as in Table 1.

Finally, no echocardiographic follow-up assessing the effect of treatment on the morphology and mobility of the RHTH was reported.

Importantly, half of the patients enrolled in the ICOPER were not referred for echocardiography. They were slightly less hemodynamically compromised than those in whom this test was performed. Therefore, the prevalence of RHTH in unselected patients with PE could be even lower than 3.8%. Previous reports suggesting much higher prevalence of RHTH (7% to 18%) came from series collected among patients with PE who were likely to be more hemodynamically compromised, such as those admitted to an intensive care unit (4,6) or presenting with echocardiographic signs of RV overload (3).

Conclusions. In the context of acute pulmonary embolism, the RHTH is infrequent and usually found in more hemodynamically compromised patients with shorter duration of symptoms. The RHTH also indicates higher risk in patients whose clinical condition otherwise seems to permit treat-

ment with heparin alone. Whether more aggressive therapy, such as thrombolysis or embolectomy, would improve prognosis remains to be determined.

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