ORIGINAL RESEARCH

Early Use of Echocardiography in Patients With Acute Pulmonary Embolism: Findings From the RIETE Registry

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***Background*—**Transthoracic echocardiography (TTE) is often considered for risk stratification of patients with acute pulmonary embolism (PE). We sought to determine the contemporary utilization of early TTE (within 72 hours of PE diagnosis) and explored the association between TTE findings and PE-related mortality.

***Methods and Results*—**Data from the RIETE (Registro Informatizado Enfermedad TromboEmbolica) registry, a multicenter registry of consecutive patients with acute PE, were used (2001–July 2017). We used a generalized linear mixed model to determine predictors of early TTE performance. Moreover, the association between 3 TTE variables (right atrial enlargement, right ventricular hypokinesis, and presence of right heart thrombi) and 30-day PE-related mortality was assessed in generalized linear mixed models adjusted for PE severity index, and other comorbidities. Among 35 935 enrollees with acute PE, 15 375 (42.8%) underwent early TTE. There was an increase in early TTE utilization rate over time ($P<0.001$ for trend). Younger age, female sex, enrollment in countries other than Spain, history of coronary disease, heart failure, atrial fibrillation, tachycardia, and hypotension were the main predictors of early TTE ($P<0.01$ for all). In multivariable analyses, right atrial enlargement (adjusted odds ratio: 3.74; 95% confidence interval, 2.10–6.66), right ventricular hypokinesis (adjusted odds ratio: 3.11, 95% confidence interval: 1.85–5.21) and right heart thrombi (adjusted odds ratio: 4.39, 95% confidence interval, 1.99–9.71) were associated with increased odds for PE-related mortality.

***Conclusions*—**Early TTE is commonly performed for acute PE and utilization rates have increased over time. Right atrial enlargement, right ventricular hypokinesis, and right heart thrombi are predictive of worse outcomes.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02832245. **(*J Am Heart Assoc*. 2018;7: e009042. DOI: 10.1161/JAHA.118.009042.)**

Key Words: echocardiography • pulmonary embolism • trends

Acute pulmonary embolism (PE) is a serious thromboembolic condition accounting for thousands of hospitalizations and associated with high short-term mortality rates.[1,2] Some studies suggest that transthoracic echocardiography (TTE) could help in early risk stratification of patients with acute PE. Yet, the results have been inconsistent and the use of TTE in real life and its prognostic value have not been consistently studied.[3–6] We used the data from the RIETE

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Clinical Perspective

What Is New?

- Use of transthoracic echocardiography has increased in the early care of patients with pulmonary embolism.
- Presence of right atrial enlargement, right ventricular hypokinesis, and right heart thrombi are predictive of pulmonary embolism–related mortality in unadjusted and adjusted analyses.

What Are the Clinical Implications?

- Echocardiography could help with better prognostication in the early care of patients with pulmonary embolism.
- Future studies should identify the optimal management strategies for high-risk subgroups identified by early echocardiography.

(Registro Informatizado Enfermedad TromboEmbolica) registry to report the real-world use and predictors of early TTE (within the first 72 hours from diagnosis) in patients with PE, and to explore the association between some of the main TTE findings and 30-day PE-related mortality in unadjusted and adjusted analyses.

Methods

RIETE is an ongoing multicenter registry of patients with venous thromboembolism, with 179 collaborating centers in the Americas, Asia, and Europe. The methodology of the registry has been described elsewhere.[7] All enrollees provided written or oral informed consent. The protocol for patient enrollment in RIETE was approved by local ethics committees at each enrolling site. For this study, we included patients with acute symptomatic PE from March 2001 to July 2017. We compared the demographics, comorbidities (such as underlying coronary disease, heart failure, and atrial fibrillation) as well as the baseline simplified PE severity index (sPESI)[8] and PESI[9] in PE patients with versus those without early TTE. We used a generalized linear mixed model, with random effect for enrolling centers, to determine significant predictors of early TTE.

RIETE collects several data elements related to TTE. However, the 3 most widely available parameters across all TTEs were the following: visualization of thrombus in either the right atrium (RA) or right ventricle (RV) (available in 89.6% of participants), RA enlargement (available in 87.1%), and RV hypokinesis (available in 86.1%). In this article, we chose to focus on these 3 findings and determined the association between these TTE findings and 30-day PE-related mortality in bivariate analyses. Subsequently, for each exposure (ie, each of the 3 above TTE variables) we built generalized linear mixed models, with random effect for enrolling centers, sequentially adjusting for demographics, sPESI, PESI, and other comorbidities to see whether the association between TTE findings and 30-day PE-related mortality persisted after multivariable adjustment.

For multivariable analyses, several of the variables in RIETE are among the mandatory fields (including demographics, history of heart failure, history of venous thromboembolism, and others) and were available in all patients.[7] Further, for the current study, we only focused on all patients who had valid information for the studied echocardiographic parameters (the main exposure variable[s]). As such, variables such as use of TTE (yes/no) and the 3 studied echocardiographic findings were also available in all the patients included in this article. If the a priori selected covariates had missing values, we used multiple imputations to estimate the missing values for such covariates. We used an automatic method of imputation. This option automatically selects an imputation method based on a checking of the data. According to the SPSS tutorial, the automatic method explores the data and selects the monotonic method if they have a monotonic pattern for missing values. If not, it uses conditional specification. For each variable in the monotone order, the monotone method fits a univariate (single dependent variable) model using all preceding variables in the model as predictors, then imputes missing values for the variable being fit. These imputed values are saved to the imputed data set. To assure the robustness of the models, we conducted the multilevel multivariable analyses for patients enrolled from centers with >1 PE-related mortality. A $P<0.05$ was considered significant. The data related to the analyses presented in this article will be available to interested investigators after submission of a formal request and signing the RIETE confidentiality and data use agreement. The analyses were performed using the IBM SPSS Statistics program (Version 22; IBM Corp, Armonk, NY).

Results

The study included 35 935 patients presenting with acute symptomatic PE, of whom 15 375 (42.8%) had a TTE during the first 72 hours after PE diagnosis. Over time, there was an increase in the proportion of patients with PE who underwent early TTE ($P<0.001$ for linear trend).

Table 1 summarizes the demographics and comorbidities in patients with and without TTE. In multivariable analysis, history of diabetes mellitus, coronary disease, heart failure, atrial fibrillation, hypertension, and markers of clinical severity at presentation (including tachycardia, hypoxemia, and systolic hypotension) were the significant positive predictors of

Table 1. Basic Cohort Characteristics and Main TTE Findings

	Early TTE (N=15 375)	No Early TTE (N=20 560)
Demographics		
Male (%)	7128 (46%)	9637 (47%)
Age, y±SD	65.9±17.2	68.3±16.7
Prior history		
Diabetes mellitus	16%	16%
Hypertension	52%	50%
Coronary artery disease	8.1%	8.4%
Heart failure	10%	8.4%
Ischemic stroke	7.4%	8.1%
Atrial fibrillation (prior history or at baseline)	6.8%	7.3%
VTE	14%	15%
Chronic lung disease	15%	14%
Active cancer	17%	26%
Clinical factors		
Systolic blood pressure <90 mm Hg	4.2%	3%
sPESI Score <1	35%	32%
Select laboratory tests		
Anemia	29%	36%
Creatinine clearance levels, mL/min	79.2±46.5	72.8±36.9
Key echocardiographic findings		
Pulmonary artery systolic pressure, mm Hg	43 (34–55)	N/A
Thrombus in the right atrium or right ventricular or pulmonary artery	2.5%	N/A
Right atrial enlargement (yes/no)	29%	N/A
Right ventricular hypokinesis (yes/no)	23%	N/A

N/A indicates not applicable; SD, standard deviation; sPESI, simplified pulmonary embolism severity index; TTE, transthoracic echocardiogram; VTE, venous thromboembolism.

early TTE. Conversely, enrollment from Spanish centers, older age, male sex, chronic lung disease, and active cancer were associated with lower odds of performing early TTE (Table 2). RA enlargement was reported in 3831 (29%) patients, and 3109 (23%) had RV hypokinesis. Thrombi were visualized in the RA or RV in 350 (2.5%) patients.

Overall, 1889 patients (5.3%) died within the first 30 days. Of these, 561 (29.7%) died of PE. In bivariate analyses, RA enlargement (odds ratio: 6.69; 95% confidence interval, 4.22–10.62), RV hypokinesis (odds ratio: 5.59, 95% confidence interval, 3.67–8.50), and presence of right heart thrombi (odds ratio: 8.51, 95% confidence interval, 5.06–14.32), were significantly associated with higher odds of 30-day PE-related mortality (P<0.001 for all). In separate multivariable models, sequentially adjusted for demographics, sPESI, PESI, and other comorbidities, the significant association among each of the 3 variables and 30-day PE-related mortality persisted (Figure).

Discussion

In our study of 35 935 patients with acute symptomatic PE, early TTE was performed in over one third of patients, and the proportion increased over time. History of prior cardiovascular disease (coronary disease, heart failure, and atrial fibrillation) and clinical markers of PE severity were among the main predictors of early TTE and we noted regional variations, with patients from Spanish centers less commonly undergoing early TTE. RA enlargement, RV dysfunction, and right heart thrombi were predictive of 30-day PE-related mortality. Findings were fundamentally similar in multivariable adjusted analyses, confirming the robustness of the associations. The observed utilization rate of TTE in our study (42.8%) is consistent with 2 recent studies from Australia and the United States,[6,10] and is attributable to many potential factors. Some patients may have had low-risk PE. In others, TTE may have not been ordered because of less widespread availability of

Table 2. Predictors of Early TTE in Bivariate and Multilevel Multivariable Analysis

	Bivariate Multilevel (Center)		Multivariable Multilevel (Center)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Variables level 1				
Center volume (>50 patients)	1.18 (0.84–1.65)	0.339	…	…
Hospital size (>250 beds)	1.22 (0.83–1.78)	0.309	…	…
Country (Spain)	0.52 (0.37–0.74)	<0.001	0.53 (0.37–0.74)	0.000
Variables level 2				
Age (every 5-y increments)	0.96 (0.95–0.97)	<0.001	0.97 (0.96–0.98)	0.000
Sex (male)	0.95 (0.90–0.99)	0.029	0.93 (0.88–0.98)	0.006
Diabetes mellitus	1.11 (1.02–1.19)	0.009	1.15 (1.07–1.25)	0.000
History of coronary disease	1.15 (1.04–1.28)	0.007	1.21 (1.08–1.35)	0.001
History of heart failure	1.12 (1.03–1.22)	0.011	1.14 (1.04–1.25)	0.005
Atrial fibrillation	1.22 (1.10–1.35)	0.000	1.22 (1.10–1.36)	0.000
Prior history of VTE	0.95 (0.88–1.01)	0.113	…	…
History of chronic lung disease	0.91 (0.85–0.98)	0.012	…	…
Active cancer	0.51 (0.48–0.55)	0.000	0.54 (0.50–0.58)	0.000
Anemia	0.75 (0.71–0.79)	0.000	0.82 (0.78–0.87)	0.000
History of hypertension	1.03 (0.98–1.08)	0.214	…	…
Creatinine clearance (10 points)	1.03 (1.02–1.04)	0.000	1.02 (1.01–1.03)	0.000
Systolic hypotension (<90 mm Hg)	1.59 (1.39–1.81)	0.000	1.56 (1.36–1.79)	0.000
O_2 sat (<90%)	1.11 (1.05–1.17)	0.000	1.10 (1.04–1.16)	0.000
Tachycardia (>110 bpm)	1.30 (1.22–1.38)	0.000	1.24 (1.16–1.32)	0.000
sPESI score	0.96 (0.93–0.98)	0.000	…	…
PESI score (10 points)	0.97 (0.96–0.98)	0.000	…	…

bpm indicates beats per minute; CI, confidence interval; OR, odds ratio; sPESI, simplified pulmonary embolism severity index; TTE, transthoracic echocardiogram; VTE, venous thromboembolism.

the technology in certain centers, or less availability (or incentives) for echocardiographers to perform TTE.

Our results, based on data from a multinational registry and using multivariable adjustments, build on prior research about the association between TTE findings and PE-related mortality. The significance of prognostication in patients with PE has been recently re-emphasized.[11,12] In our study, each of the 3 studied TTE findings was associated with 30-day PE-related mortality in unadjusted and adjusted models. A study of 529 patients with PE identified separate effects of PESI and TTE findings on 30-day outcomes of patients with PE,[3] while another recent study of 400 patients with PE by Hofmann et al did not find an independent association between TTE findings and outcomes.[5] The association between RA enlargement and PE outcomes has been under recent investigation,[13,14] and may be potentially explained by right heart volume and pressure overload in the setting of acute PE. Similarly, RV hypokinesis is associated with worse hemodynamic effects and thereby worse outcomes. Although in the study by Hofmann et al such association was not observed, their study was limited by having only 5 fatal PEs, severely limiting the statistical power.

Our results confirm prior investigations that suggested the prognostic significance of right heart thrombi.[15] Mobile right heart thrombi may carry an even higher risk.[16] Despite the elevated risk, clinical management of these patients remains controversial, with guidelines being silent or equivocal about optimal management.[11,17,18] Thrombolysis carries the potential risk of further pulmonary emboli as a result of partial dissolution of the thrombi.[19] In a recent propensity-matched investigation, use of reperfusion was associated with a nonsignificant reduction in risk of PE-related mortality.[20] In that study, most patients in the reperfusion therapy group received thrombolysis, with only 12 undergoing surgical thrombectomy. Percutaneous mechanical thrombectomy[21,22] is a potential option, which warrants further investigation.

Our study had some limitations. First, with regard to choice of TTE variables in this study, RIETE captured information on

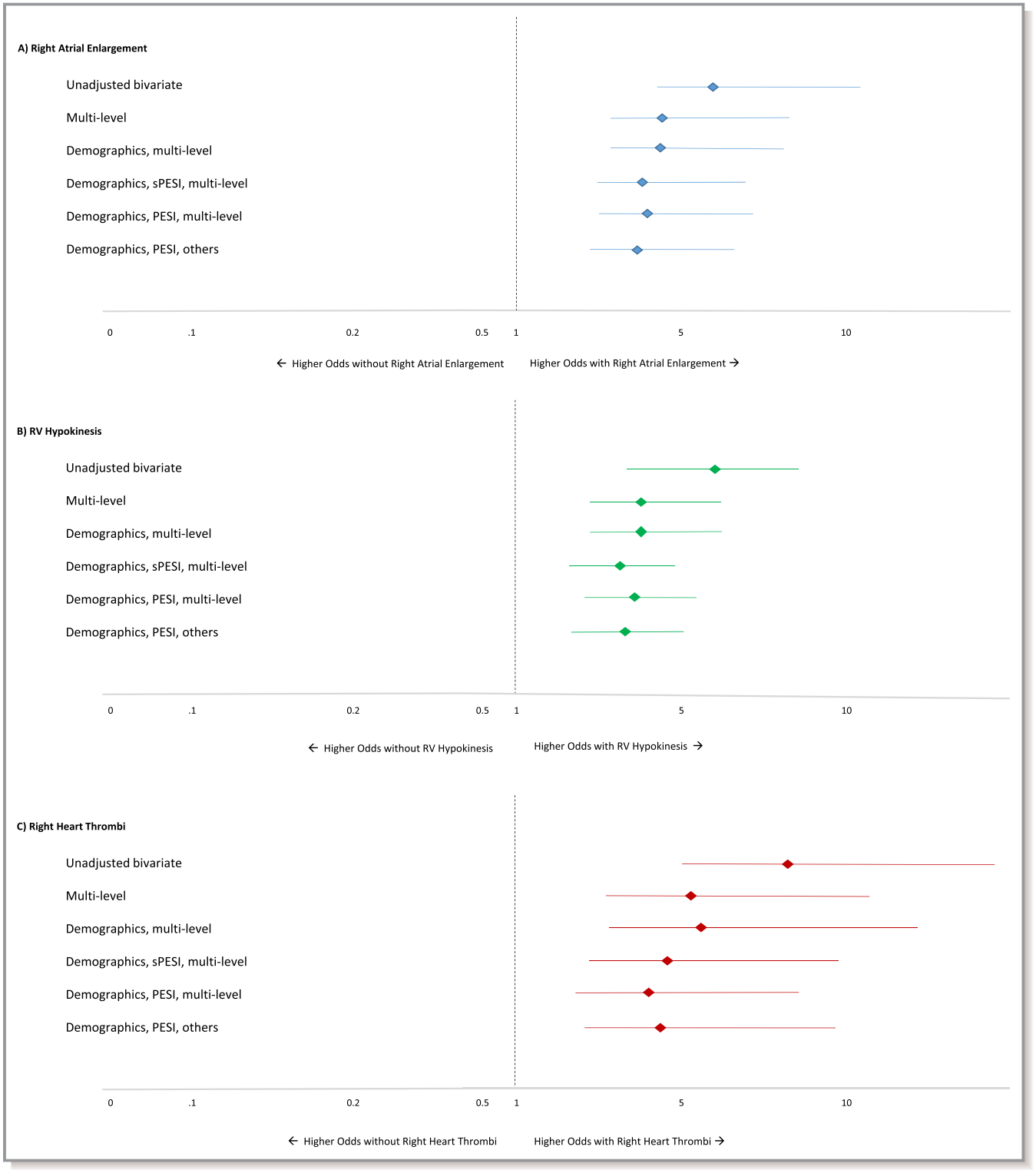

Figure. Association between echocardiographic findings and 30-day PE-related mortality in unadjusted and multivariable adjusted models. The models show unadjusted and multivariable adjusted associations between right atrial enlargement (A), right ventricular hypokinesis (B), and presence of right heart thrombi (C), and 30-day PE-related mortality in patients with acute PE. PE indicates pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricle; sPESI, simplified pulmonary embolism severity index.

several echocardiographic features. However, in this article we focused on data elements that were most widely available. As such, we did not investigate the association between other important TTE variables (such as RV enlargement, or PAP) and outcomes. However, we were able to assess the association between 3 other variables (RA enlargement, RV hypokinesis,

and right heart thrombi) and outcomes, demonstrating a robust association in bivariate and multivariable models. Second, missing values presented a limitation for multivariable analyses. However, several of the covariates (including demographics and many of the comorbidities) were available for all patients, as were the main exposure and outcomes variables. In addition, our analyses based on unadjusted models derived consistent signals compared with those of multivariable models that used multiple imputation. Third, lack of a core laboratory for the TTE evaluations is another shortcoming, and is common among registry studies. However, such a limitation would not impact our real-world results related to TTE utilization rate and predictors of early TTE performance. Further, some recent studies have also suggested fair-to-good interobserver reliability for such TTE data elements.[4]

In conclusion, in a large registry of patients with acute symptomatic PE, early TTE was performed in 42.8% of patients, with prior history of cardiovascular disease and clinical markers of PE severity being among the notable predictors of early TTE. RA enlargement, RV hypokinesis, and right heart thrombi were significantly predictive of 30-day PE-related mortality, highlighting the need for additional studies to identify the optimal management strategies for these high-risk subgroups.

Appendix

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Disclosures

Dr Bikdeli reports that he serves as an expert (on behalf of the plaintiff) for litigation related to inferior vena caval filters. The content of the current article is not directly related to that litigation. The remaining authors have no disclosures to report.

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