Right Atrial Size and 30-Day Mortality in Normotensive Patients with Pulmonary Embolism

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Abstract

Background: The role of right atrial (RA) dilatation for predicting mortality in normotensive patients with pulmonary embolism (PE) has not been thoroughly studied.

Methods: We used the Riete Registry data to evaluate the prognostic value of RA dilatation (visual estimate) on transthoracic echocardiography (ETT) in patients with acute PE presenting with systolic blood pressure levels ≥ 90 mm Hg.

Results: As of April 2013, 7,677 normotensive patients with acute PE underwent ETT within the first 48 hours. Of these, 2,268 (29.5%) had RA dilatation. At 30 days, 212 patients (2.76%) died, of whom 59 (0.77%) died of confirmed PE. Patients with RA dilatation had a 6-fold higher rate of fatal PE (1.85% vs. 0.31%; odds ratio [OR]: 5.98; 95% CI: 3.44-10.8) and a 2-fold higher all-cause mortality (4.32% vs. 2.11%; OR: 2.10; 95% CI: 1.59-2.76) compared with those without RA dilatation. On multivariable analysis, RA dilatation independently predicted fatal PE (relative risk [RR]: 3.71; 95% CI: 1.68-8.17), while right ventricle hypokinesis did not (RR: 1.36; 95% CI: 0.66-2.80).

Conclusions: Among normotensive patients with acute PE, RA dilatation on ETT independently predicted fatal PE at 30 days.

Keywords: Echocardiography; Right atrial dilatation; Pulmonary embolism; Mortality; Prognosis

Introduction

In patients with pulmonary embolism (PE), early mortality rates range from over 50% in those initially presenting with cardiogenic shock to less than 5% in those with systolic blood pressure (SBP) levels over 90 mm Hg [1-6]. Based on risk profiles, some patients with acute PE may require hospitalization or even immediate recanalization of the occluded pulmonary arteries with thrombolytic therapy or surgery, while others may safely undergo treatment at home and avoid hospital admission [7-10]. One area of controversy focuses on the extension of the indication for thrombolytic therapy to a subgroup of patients who appear stable at presentation but have impending right ventricular failure and a high risk of PE-related death. Thus, a major challenge is the identification of potential candidates for thrombolytic therapy by a simple, rapid, and non-invasive method.

Transthoracic echocardiography (TTE) may detect changes occurring in the right ventricle (RV) anatomy and function as a result of PE-associated acute pressure overload, and some of these abnormalities have been associated with outcome in patients with acute PE [11-13]. However, the complex anatomy of the RV and the subjective nature of routinely obtained standard measurements often limit its usefulness in clinical practice, since reliable and reproducible indices of RV dysfunction are difficult to obtain [13-15]. On the contrary, the right atrium (RA) can be clearly seen in the apical view, and its dimensions easily assessed, thus reducing measurement variability [16,17]. In patients with idiopathic pulmonary hypertension, RA dilatation has been associated with outcome [18], and recent studies in patients with acute PE have correlated the RA size with the severity of PE assessed with scintigraphy or CT-scan [16,19]. However, no studies have thoroughly evaluated the relationship between RA dilatation on TTE and outcome in patients with acute PE.

The Riete (Registro Informatizado de Enfermedad TromboEmbolica) Registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Germany, Switzerland, Czech Republic, Macedonia, Portugal and Ireland), observational registry of consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism (VTE). It started in Spain in 2001, and 6 years later the database was translated into English aimed to expand the Registry to other countries. Data from this registry have been used to evaluate outcomes after acute PE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [20-23]. In the current study, we used the Riete database to compare the 30-day mortality of patients with acute PE presenting with SBP levels ≥ 90 mm Hg, according to the presence or absence of RA dilatation on TTE at baseline.

Patients and Methods

Study population

The study population includes all patients with symptomatic acute PE confirmed by objective tests (ventilation/perfusion lung scintigraphy,

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angiography, as appropriate. Each episode of clinically suspected recurrent PE was
or symptoms suggesting recurrent PE or bleeding complications
but a longer follow-up was favored, if possible. At each visit, any signs
After diagnosis, all patients were followed-up for at least one month,
participating hospital (i.e., there was no standardization of treatment).
outcome within the first 30 days.
the type and dose of treatment received upon PE diagnosis; and the
TAPSE of three to five beats.
end-diastole to end-systole, with values representing the average
was assessed in the apical four-chamber view. In addition, the following
transverse diameter on the apical four-chamber view. RA dilatation
were significantly older and more likely had chronic heart failure,
levels, higher RV diameter, or lower TAPSE (Table 1). They presented with lower SBP levels, and more
likely had hypoxemia and/or electrocardiographic features suggesting
acute RV overload (right bundle branch block, S1Q3T3 pattern).
Furthermore, patients with RA dilatation more likely had additional
TTE findings suggesting right heart overload, such as RV hypokinesis,
higher PAP levels, higher RV diameter, or lower TAPSE (Table 1).

Study design

The major outcome was fatal PE at 30 days. The secondary outcome
was all-cause mortality at 30 days. Fatal PE, in the absence of autopsy,
was defined as any death appearing within 10 days after PE diagnosis
(either the initial event or recurrent PE), in the absence of any alternative
cause of death. The causes of death were adjudicated by the attending
physicians. In case of doubt, the cause of death was adjudicated by the
RIETE Adjudication Committee.

Study variables

The following qualitative TTE parameters were evaluated: RA dilatation (visual estimate), RV hypokinesis (visual estimate) and visualization of thrombus. To measure RA we considered its transverse diameter on the apical four-chamber view. RA dilatation was considered when it was larger than the left atrium. RV hypokinesis was assessed in the apical four-chamber view. In addition, the following quantitative TTE parameters were evaluated in only some patients: RV end-diastolic diameter (on M-mode in the parasternal long-axis view), ratio of right vs. left ventricle end-diastolic diameter (in the apical four-chamber view), tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery pressure (PAP) levels. To obtain TAPSE, the apical four-chamber view was used, and an M-mode cursor was placed through the lateral tricuspid annulus in real time. TAPSE was measured as the total displacement of the tricuspid annulus (centimeters) from end-diastole to end-systole, with values representing the average TAPSE of three to five beats.

The following parameters were also recorded in all patients: baseline characteristics; clinical status including any coexisting or underlying conditions such as chronic heart or lung disease; risk factors for PE; the type and dose of treatment received upon PE diagnosis; and the outcome within the first 30 days.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). After diagnosis, all patients were followed-up for at least one month, but a longer follow-up was favored, if possible. At each visit, any signs or symptoms suggesting recurrent PE or bleeding complications were noted. Each episode of clinically suspected recurrent PE was investigated by repeat lung scanning, helical-CT scan or pulmonary angiography, as appropriate.
Most patients in both subgroups received low-molecular-weight heparin as initial therapy, with no differences between subgroups in mean daily doses, but a higher proportion of patients with RA dilatation received unfractionated heparin (23% vs. 11%) or thrombolytic therapy (3.4% vs. 1.0%) (Table 2). Then, most patients in both subgroups switched to vitamin K antagonists as long-term therapy. In all, 212 patients (2.76%) died at 30 days, of whom 59 (0.77%) died of confirmed PE. One in every two patients dying of PE (27 of 59, 46%), and one in every 5 with all-cause death (44 of 212, 21%) died within the first 5 days after PE diagnosis (Figures 1 and 2). PE was the most common cause of death among patients with or without RA dilatation, accounting for 43% (42 of 98) and 15% (17 of 114) of the deaths, respectively (Table 2).

The 30-day rate of fatal PE in patients with vs. without RA dilatation was: 1.85% (95% CI: 1.36-2.47) vs. 0.31% (95% CI: 0.19-0.49), respectively (odds ratio [OR]: 5.98; 95% CI: 3.44-10.8). The 30-day all-cause mortality rate was: 4.32% (95% CI: 3.54-5.22) vs. 2.11% (95% CI: 1.75-2.52), respectively (OR: 2.10; 95% CI: 1.59-2.76). There were no differences between groups for other causes of death (Table 2). On univariable analysis, patients dying of PE more likely had cancer, chronic heart failure or abnormal creatinine levels, and more likely presented with SBP levels <100 mm Hg, tachycardia, tachypnea, atrial fibrillation, hypoxemia, or a right bundle branch block in the electrocardiogram (Table 3). On the TTE exam, patients subsequently dying of PE more likely had RA dilatation, visualization of thrombus, RV hypokinesis, or PAP levels >35 mm Hg (Table 3).

On multivariable analysis, only hypoxemia (risk ratio [RR]: 4.03; 95% CI: 1.87-8.67) and RA dilatation (RR: 3.71; 95% CI: 1.68-8.17) significantly predicted fatal PE at 30 days while RV hypokinesis did not (RR: 1.36; 95% CI: 0.66-2.80), as shown in Table 4. Subsequently, the influence of chronic lung disease or chronic heart disease on this association was analyzed using an interaction analysis, and RA dilatation persisted as an independent predictor for fatal PE.

Then, we compared the inter-individual variability in the measurements of RA and RV in one centre (JLL). The intra-class coefficient of correlation was 0.806 (95% CI: 0.717-0.868), and in only 16% of patients (14 of 88) there was some disagreement for the dilatation of RA (kappa: 0.637). On the contrary, the disagreement for RV dilatation (defined as RVEDD >3.0 cm) appeared in 35% of patients (32 of 92) (kappa: 0.377).

Finally, all RIETE members were recently asked to quantitatively measure the size of RA diameter. It was obtained in 207 patients, and was >5 cm in 32 (15%). Of 3 patients (1.45%) who subsequently died of PE, 2 had a diameter >5 cm and one had ≤5 cm. The hazard ratio of dying of PE in patients with RA diameter >5 cm was 11.1 (95% CI: 1.01-122.7; p=0.049). The area under ROC curve was 0.783 (95% CI: 0.584-0.981).

**Table 2: Treatment strategies and 30-day mortality.**

| Atrial | No atrial | p value |
|--------|-----------|---------|
| Patients, N | 2,268 | 5,409 |
| Initial treatment | | |
| Thrombolytics | 76 (3.4%) | 53 (1.0%) | <0.001 |
| LMWH | 1,630 (72%) | 4,606 (85%) | <0.001 |
| Mean LMWH doses (IU/kg/day) | 183 ± 41 | 183 ± 37 | 0.93 |
| Initial therapy, UFH | 510 (23%) | 586 (11%) | <0.001 |
| Inferior vena cava filter | 83 (3.7%) | 164 (3.0%) | 0.155 |
| Long-term treatment | | |
| Vitamin K antagonists | 1,402 (62%) | 3,285 (61%) | 0.374 |
| LMWH | 721 (32%) | 1,907 (35%) | 0.004 |
| Mean LMWH doses (IU/kg/day) | 173 ± 49 | 189 ± 44 | 0.048 |
| 30-day outcome | | |
| Overall death | 98 (4.32%) | 114 (2.11%) | <0.001 |
| Causes of death | | |
| Pulmonary embolism | 42 (1.85%) | 17 (0.31%) | <0.001 |
| Respiratory insufficiency | 9 (0.40%) | 12 (0.22%) | 0.181 |
| Sudden, unexpected | 4 (0.18%) | 5 (0.09%) | 0.327 |
| Bleeding | 5 (0.22%) | 10 (0.18%) | 0.747 |
| Other | 30 (1.32%) | 66 (1.22%) | 0.712 |
| Unknown | 8 (0.35%) | 4 (0.07%) | 0.005 |

LMWH: low-molecular-weight heparin; IU: international units; UFH: unfractionated heparin.

**Figure 1: Cumulative mortality due to pulmonary embolism, according to the presence or absence of right atrial dilatation at baseline.**

**Figure 2: Cumulative all-cause mortality, according to the presence or absence of right atrial dilatation at baseline.**

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Discussion
Normotensive patients with acute PE represent a challenge to the clinician. Although their 30-day mortality rate is rather low (ranging from 2.8% to 6.5% in recent studies), many of them die of PE, mostly during the first week.2-7 In our series, one in every 36 (2.76%) such patients died within the first 30 days, and one in every 4 (59 of 212) died of confirmed PE. We hypothesize that some of these deaths might have been prevented if a more accurate therapy (i.e., thrombolytic therapy or insertion of a vena cava filter) would have been applied. In our series, one in every 3 (29.5%) normotensive patients with PE had RA dilatation, and these patients had a significantly higher risk of dying.
of PE than those with no RA dilatation. Interestingly, the prognostic value of RA dilatation persisted after multivariate adjustment, while RV hypokinesis did not.

During acute PE, there is an increase in pulmonary vascular resistance due to the anatomical obstruction caused by the emboli, release of vasoconstricting agents and reflex hypoxemia [16,24]. The resulting overload induces anatomic changes in the RV that may be identified by TTE, but estimating the volume of a complex structure like the RV is often challenging, not allowing any geometrical assumptions, and diameters or areas are used as surrogate measures in 2D echocardiography [24]. In fact, visual estimate of RV dilatation was poor in our study (kappa of 0.377). Estimating PAP levels may be also difficult in the absence of tricuspid insufficiency. In fact, one in every 3 patients in our series (3028 of 7677, 39%) did not have estimated PAP levels.

On the contrary, RA visualization is easier, and its dimensions are reliably obtained on an apical 4-chamber view. However, only a few studies have focused on the prognostic role of RA changes in acute PE to date. The RA assists in filling the RV by acting as a reservoir for systemic venous return when the tricuspid valve is closed, acting as a passive conduit in early diastole when the tricuspid valve is open, and as an active conduit in late diastole during atrial contraction [25]. Thus, it should not be unexpected that RA dilatation reliably predicted outcome.

TTE assessment of the right heart has been largely qualitative until very recently, primarily because of the above mentioned difficulties to assess RV size because of its unusual shape [26,27]. Hence, there are few quantitative data so far for the assessment of RV size and function in patients with acute PE. Current guidelines for the TTE assessment of the right heart, issued in 2010 by the American Society of Echocardiography [12], recommend a gradual shift to more quantitative approaches for the assessment of RV size and function. However, since RIETE started in 2001, most patients had information only on PAP levels and visual estimates on RV hypokinesis or RA dilatation. Only recently we started to gather information on quantitative TTE measurements, such as the TAPSE (which is now available for over 1500 patients) or RA diameter. In future studies we will be able to compare the prognostic value of these new measurements, but our current data suggest that images adequate for RA size estimation should be obtained in patients undergoing evaluation for acute PE.

Our study has important limitations. First, only one in every 3 patients with acute PE in RIETE underwent TTE, and this might have biased our findings thus selecting those perceived to be at a higher risk for complications. However, we compared the 30-day mortality rate in patients with and without TTE and found that those not undergoing TTE had a slightly higher mortality: 3.3% vs. 2.9%. The higher mortality rate in patients with no echocardiogram may likely be due to the higher proportion of patients with advanced cancer, but this would need further analyses. Second, we cannot rule out that some comorbidities leading to increased mortality and RA dilatation (such as chronic lung disease, chronic heart failure or atrial fibrillation) might have influenced the association between RA dilatation and fatal PE. However, the negative interaction analysis suggests that its impact was, if any, minor. Third, the absence of quantitative TTE data is another major limitation, though this has been usual until the recent guidelines from the American Society of Echocardiography [27].

Moreover, visual estimate of RA size (by comparison with LA size) is counterbalanced by the reality that this relation is not uniquely determined by RA size. Patients with LA enlargement might result in a normal RA: LA ratio even though RA size was, in absolute terms, abnormally large. This is the reason why we recently added RA diameter as a new variable into the database: it was measured in 207 patients and those with >5 cm diameter had a significantly higher rate of fatal PE. Thus, we think that correlating RA dilatation with outcome in patients with acute PE could serve as an easy non-invasive way of triaging and better treating patients presenting with this condition. Fourth, given the characteristics of RIETE (over 200 hospitals from 12 countries, recruiting patients for 12 years) it was impossible to coordinate the submission of ETT reports to an independent investigator. We had to rely on the local interpretations at contributing centres. Finally, some patients with PE may have died before obtaining TTE, and this may have also biased our results. Strengths of the current analysis include that a large number of patients were enrolled, and that fatal PE and all-cause death are by far the most important outcomes during the treatment of VTE.

In summary, our findings reveal that one in every 3 patients with acute PE and SBP levels ≥90 mm Hg may have RA dilatation, and that these patients have a significantly higher risk to die of PE within the first 30 days. In our study, the prognostic value of RA dilatation was superior to that of RV hypokinesis, a more often used but less reproducible measurement.

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