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Full Length Article

Echocardiography does not predict mortality in hemodynamically stable elderly patients with acute pulmonary embolism

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ABSTRACT

Background: The evidence on the prognostic value of transthoracic echocardiography (TTE) in elderly, hemodynamically stable patients with Pulmonary Embolism (PE) is limited.
Objectives: To evaluate the prevalence of common echocardiographic signs of right ventricular (RV) dysfunction and their prognostic impact in hemodynamically stable patients aged ≥65 years with acute PE in a prospective multicenter cohort.
Methods: TTE was performed by cardiologists. We defined RV dysfunction as a RV/left ventricular ratio >0.9 or RV hypokinesis (primary definition) or the presence of ≥1 or ≥2 of 6 predefined echocardiographic signs (secondary definitions). Outcomes were overall mortality and mortality/non-fatal recurrent venous thromboembolism (VTE) at 30 days, adjusting for the Pulmonary Embolism Severity Index risk score and highly sensitive troponin T values.
Results: Of 400 patients, 36% had RV dysfunction based on our primary definition, and 81% (≥1 sign) and 53% (≥2 signs) based on our secondary definitions, respectively. Using our primary definition, there was no association between RV dysfunction and mortality (adjusted HR 0.90, 95% CI 0.31–2.58) and mortality/non-fatal VTE (adjusted HR 1.09, 95% CI 0.40–2.98). Similarly, there was no statistically significant association between the presence of ≥1 or ≥2 echocardiographic signs (secondary definitions) and clinical outcomes.
Conclusion: The prevalence of echocardiographic RV dysfunction varied widely depending upon the definition used. There was no association between RV dysfunction and clinical outcomes. Thus, TTE may not be suitable as a stand-alone risk assessment tool in elderly patients with acute PE.
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1. Introduction

Evidence suggests that echocardiographic signs of right ventricular (RV) dysfunction or pulmonary hypertension (hereafter called signs of

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RV dysfunction) are associated with a 2-fold increase in short-term overall mortality in hemodynamically stable patients with acute Pulmonary Embolism (PE) [1,2]. Several professional societies have therefore incorporated transthoracic echocardiography (TTE), alone or in combination with cardiac biomarkers, into their risk assessment strategies for hemodynamically stable patients with acute PE [3,4]. According to current recommendations, fibrinolysis may be considered in selected hemodynamically stable patients with RV dysfunction [3,4]. TTE has been widely adopted into clinical practice and despite its costs and the need for a trained physician, currently more than a third of patients diagnosed with acute PE undergo TTE [5,6].

Although elderly patients have more severe venous thromboembolism (VTE) and a higher short-term mortality rate than younger patients [7,8], the prognostic performance of TTE to predict mortality has not been specifically examined in elderly patients with acute PE. The aim of this study was to prospectively evaluate the prevalence of common echocardiographic signs of RV dysfunction and their prognostic impact in elderly patients with acute PE.

2. Methods

2.1. Cohort sample

This study was conducted between September 2009 and June 2012 as part of a prospective, multicenter cohort study to assess long-term medical outcomes and quality of life in patients aged ≥65 years with an acute VTE from all five Swiss university and four high-volume non-university hospitals [9]. Consecutive patients aged ≥65 years with an acute VTE were identified in the inpatient and outpatient services of all participating study sites. Exclusion criteria were catheter-related thrombosis, insufficient German or French-speaking ability, no follow-up possible (i.e., terminal illness), an inability to provide informed consent (i.e., severe dementia), or previous enrollment in the cohort. The study was approved by the Institutional Review Board at each participating center. The detailed study methods were previously published [9]. For the present study, we only considered hemodynamically stable patients with an acute symptomatic, objectively confirmed PE [9]. Hemodynamic stability was defined as a systolic blood pressure of ≥90 mm Hg at the time of PE diagnosis.

2.2. Baseline data collection

Trained study nurses prospectively collected baseline demographic characteristics, comorbid conditions, type of PE (unprovoked vs. provoked), localization of PE, vital signs, routine laboratory findings (hemoglobin, serum creatinine), and anticoagulation-related treatments. In addition, we recorded whether the patient was admitted to the intensive care unit or received intravenous catecholamines, cardiopulmonary resuscitation, vena cava filter, fibrinolysis, or thromboembolectomy in the hospital.

We also collected venous blood samples at the time of PE diagnosis. Samples were immediately centrifuged, frozen, and stored at −80 °C and sent for analyses to a core laboratory. Plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) and highly sensitive troponin T (hsTnT) were measured quantitatively using a Cobas e601 automated immunoanalyser (electrochemiluminescence methods, Hoffmann-La Roche, Rotkreuz, Switzerland).

2.3. Echocardiographic examination

Patients underwent TTE at the time of study enrollment to assess RV function. All TTEs were performed by on-site cardiologists according to a standardized protocol. The cardiologists were blinded to patients' baseline characteristics and treatments. The following six signs of RV dysfunction/pulmonary hypertension were recorded: 1) RV/LV end-diastolic diameter ratio >0.9 in the apical four chamber view, 2) RV hypokinesis (defined as a moderately or severely abnormal motion of RV free wall), 3) paradoxical septal motion, 4) decreased or absent inspiratory collapse of the inferior vena cava, 5) shortened pulmonary acceleration time in the parasternal short axis view (≤100 ms), and 6) increase in RV/right atrial gradient in the apical four chamber or parasternal short axis view (≥30 mm Hg) [10–14]. For the present analysis, we considered only patients who had TTE within three days of PE diagnosis [15].

We used the presence of a RV/LV ratio >0.9 or RV hypokinesis as our primary definition of RV dysfunction, as suggested by the American Heart Association [3]. However, because the definition of RV dysfunction varies widely across studies, we also defined RV dysfunction as the presence of at least one and at least two of six echocardiographic signs described above, respectively (secondary definitions).

2.4. Study outcomes

The primary outcome was overall mortality within 30 days of PE diagnosis. The secondary outcome was overall mortality/non-fatal recurrent VTE at 30 days. Recurrent VTE was defined as symptomatic, objectively confirmed recurrent PE or a new symptomatic deep vein thrombosis [9]. Follow-up included a face-to-face patient interview and hospital chart review at 90 days, complemented by proxy interviews and an interview of the patient's primary care physician. A committee of three blinded clinical experts adjudicated all outcomes and classified the cause of all deaths as definitely due to PE, possibly due to PE, or due to another cause [9]. Final classifications were made on the basis of the full consensus of this committee.

2.5. Statistical analysis

We compared baseline characteristics and descriptive outcome data of patients with and without RV dysfunction using the Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous variables as appropriate. In patients treated with vitamin K antagonists, we compared the percentage of time spent in the therapeutic INR range (2.0–3.0) using analysis of variance [16]. We used Kaplan-Meier curves and the log-rank test to compare the cumulative overall mortality and overall mortality/recurrence of non-fatal VTE within 30 days in patients with and without RV dysfunction.

We examined the association between RV dysfunction and clinical outcomes using a Cox-regression model. We adjusted all models for the Pulmonary Embolism Severity Index risk score and hsTnT. The Pulmonary Embolism Severity Index is a validated prognostic score and comprises 11 clinical variables, including demographics (age, gender), comorbid diseases (cancer, heart failure, and chronic lung disease), and vital signs (altered mental status, pulse, systolic blood pressure, respiratory rate, arterial oxygen saturation, and temperature) [17]. Given that NT-proBNP is another marker for RV dysfunction, we did not adjust for this parameter [18]. Because RV dysfunction may be transitory, we also examined the association between RV dysfunction and clinical outcomes in the subgroup of patients who had TTE within one day of PE diagnosis [19]. Missing values in covariates used for adjustment were assumed as normal. We considered P-values < 0.05 to be statistically significant. All analyses were performed using Stata 14.0.

3. Results

3.1. Study sample

Overall, 685 hemodynamically stable patients with PE were initially enrolled in our study. After exclusion of 285 (42%) patients (277 had no TTE within three days and 8 withdrew consent early or did not allow use of their data), our final sample comprised 400 patients. Excluded patients were more likely to be women (53% vs. 44%, $P = 0.02$) and to have hospital-acquired PE (22% vs. 14%, $P = 0.007$) or anemia (43% vs.