Peak systolic velocity of tricuspid annulus is inferior to tricuspid annular plane systolic excursion for 30 days prediction of adverse outcome in acute pulmonary embolism

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Abstract
Background: Tricuspid annular plane systolic excursion (TAPSE) is an established index of right ventricular (RV) systolic function and a significant predictor in normotensive patients with pulmonary embolism (PE). Recently, Doppler tissue imaging-derived tricuspid annular systolic velocity (TV S’), a modern parameter of RV function was reported to be useful in the diagnosis and prognosis of a broad spectrum of heart diseases. Therefore, herein, is an analysis of the prognostic value of both parameters in normotensive PE patients.

Methods: One hundred and thirty nine consecutive PE patients (76 female, age 56.4 ± 19.5 years) were included in this study. All patients were initially anticoagulated. Transthoracic echocardiography was performed on admission. The study endpoint (SE) was defined as PE-related 30-day mortality and/or need for rescue thrombolysis.

Results. Seven (5%) patients who met the criteria for SE presented more severe RV dysfunction at echocardiography. Univariable Cox regression analysis showed that RV/LV ratio predicted SE with hazard risk (HR) 10.6 (1.4–80.0; p = 0.02); TAPSE and TV S’ showed HR 0.77 (0.67–0.89), p < 0.001, and 0.71 (0.52–0.97), p = 0.03, respectively. Area under the curve for TAPSE in the prediction of SE was 0.881; 95% CI 0.812–0.932, p = 0.0001, for TV S’ was 0.751; 95% CI 0.670–0.820, p = 0.001. Multivariable analysis showed that the optimal prediction model included TAPSE and systolic blood pressure (SBP showed HR 0.89 95% CI 0.83–0.95, p < 0.001 and TAPSE HR 0.67, 95% CI 0.52–0.87, p<0.03). Kaplan-Meier analysis showed that initially PE patients with TAPSE ≥ 18 mm had a much more favorable prognosis that patients with TAPSE < 18 mm (p < 0.01), while analysis of S’ was only of borderline statistical significance.

Conclusions: It seems that TV S’ is inferior to TAPSE for 30 day prediction of adverse outcome in acute pulmonary embolism. (Cardiol J XXXX; XX, X: xx–xx)

Key words: transthoracic echocardiography, right ventricular function, tricuspid valve, Doppler tissue imaging, prognosis, pulmonary embolism
Introduction

Normotensive patients with acute pulmonary embolism (PE) include not only subjects with a benign clinical course, but also patients with an increased risk of PE-related mortality. Intermediate-high-risk PE patients require close monitoring to detect hemodynamic decompensation and to consider rescue reperfusion therapy [1].

Right ventricular dysfunction (RVD) detected at computed tomography or in transthoracic echocardiography (TTE) indicates an increased risk of a complicated clinical course, including early mortality. The assessment of right ventricle (RV) function is recommended in the current 2014 guidelines of the European Society of Cardiology (ESC) for risk stratification of normotensive PE patients [1, 2]. However, despite accumulating evidence there is generally no accepted echocardiographic definition of RVD proposed for risk stratification in normotensive PE patients. The criteria used to define RVD vary between studies and have included RV dilatation, an increased RV/LV diameter ratio, hypokinesis of the free RV wall, an increased velocity of the tricuspid regurgitation jet [1–4]. As shown previously, that in initially normotensive PE patients tricuspid annular plane systolic excursion (TAPSE), the only independent echocardiographic outcome predictor among a wide set of echocardiographic indices [5], and others subsequently reported similar results [6].

Doppler tissue imaging (DTI) has become a widely available technique, which plays an important role in the diagnosis and prognosis of a broad spectrum of heart diseases [7–9]. It is a simple, reproducible diagnostic method with a good ability to detect RV dysfunction [10]. DTI-derived tricuspid lateral annular systolic velocity (TV S') correlates well with other parameters of global RV systolic function [11, 12]. It was reported that the assessment of RV myocardial S' velocity by DTI may be adequate to confirm RVD in patients with PE [13, 14]. DTI can be also used to monitor RV function and filling pressure in PE patients [15].

Although there are some reports suggesting a prognostic value of TV S' in patients with acute PE [16, 17], no direct comparison between TAPSE and tricuspid annular systolic velocity (TV S') is available. Therefore, the prognostic value of both parameters in normotensive PE patients was analyzed.

Methods

Patients and management of acute PE

The study group comprised of consecutive patients with symptomatic PE managed in the documented department. All cases were hemodynamically stable at admission, with systemic systolic blood pressure (SBP) exceeding 90 mmHg, and no signs of peripheral hypoperfusion. Pulmonary embolism was confirmed by contrast-enhanced multi-detector computed tomography when thromboemboli were visualized at least at the level of segmental pulmonary arteries. Acute PE was diagnosed when symptoms of PE had been present for no longer than 14 days before the diagnosis.

All patients were initially anticoagulated with body mass adjusted low molecular weight heparin or activated partial thromboplastin time adjusted unfractionated heparin infusion. In the case of clinical deterioration, urgent rescue thrombolysis (rtPA 0.6 mg/kg body weight, max 50 mg i.v.) was performed. Hemodynamic deterioration was defined by systemic hypotension < 90 mmHg with signs of peripheral hypoperfusion, with tachycardia exceeding 110 bpm. A decision to escalate treatment was facilitated by significant dyspnea. Oral anticoagulation preferably with non-vitamin K antagonist oral anticoagulants or with international normalized ratio adjusted vitamin K antagonists were started according to the decision of the managing physician.

Comorbidities were defined as presence of chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) or active cancer.

Patients not included were those with severe tricuspid regurgitation, a history of RV myocardial infarction, after tricuspid valve replacement, or those with confirmed chronic thromboembolic pulmonary hypertension.

Echocardiography

Standardized transthoracic echocardiography focused on the assessment of RV function was performed using Philips iE33 (Philips Medical Systems, Andover, Massachusetts) and Philips Epiq 7 systems (Philips Medical Systems, Best, the Netherlands) according to the previously described protocol [18], as soon as possible after admission.

Briefly, left ventricle and right ventricle diameters were measured in the apical four chamber view (LV4C, RV4C, respectively) at the level of the mitral and tricuspid valve tips at end-diastole (defined by the ECG R wave). The presence of the McConnell sign was assessed [19]. TAPSE was measured using M-mode presentation in the
apical 4-chamber view, with the cursor exactly aligned along the direction of the tricuspid lateral annulus [11].

Peak systolic velocity of the lateral part of the tricuspid annulus — TV S’ was measured using DTI. Sample volume of pulsed DTI was placed in the tricuspid annulus or in the middle of the basal segment of the RV free wall. To achieve a high quality of recording optimal gain was used. The TV S’ velocity was defined as the highest systolic velocity, without over gaining the Doppler envelope [10, 11]. The isovolumic contraction velocities were excluded from the TV S’ measurement.

In the parasternal short axis view, flattening of the interventricular septum was assessed qualitatively, and the acceleration time (AcT) of pulmonary ejection was measured in the right ventricle outflow tract, proximally to the pulmonary valve (PW Doppler).

Tricuspid regurgitation peak systolic gradient (TRPG) was calculated by the simplified Bernoulli formula using tricuspid regurgitant flow peak velocity (Doppler continuous wave). The examination was completed by the measurement of the inferior vena cava (IVC) at late expiration.

Left ventricular ejection fraction (LVEF) was measured with the modified biplane Simpson method [11]. Doppler measurements reflected an average of three cardiac cycles. The inter- and intra-observer agreement for echocardiographic parameters were previously published [18].

Examinations were digitally recorded and interpreted by experienced sonographers according to a standardized protocol following recommendations of the European Association of Cardiovascular Imaging [11].

In 117 patients TTE was performed within the first 24 h after admission, while in 22 patients, this examination was performed between 24 and 72 h after admission.

Study endpoint
The study endpoint was a combination of 30-day PE-related mortality or need for rescue thrombolysis or both in patients with hemodynamic deterioration.

Statistical analysis
Data characterized by a normal distribution are expressed as mean followed by standard deviation. Parameters without such a distribution are expressed as median with range. The Student t-test or Mann-Whitney U-test was used for comparisons between the two groups. The chi-square/chi-squared test was used to compare discrete variables (with the Yates correction when needed). Receiver operating characteristics (ROC) analysis was performed and the area under the curve (AUC) was determined to test the performance of selected echocardiographic parameters with regard to the prediction of serious adverse event (SAE). Youden’s index Quantification was used to identify optimal cohort-specific cut-off values. The impact of TAPSE and S’ on study end points was evaluated using univariable Cox proportional-hazards regression. Hazard risk (HR) and corresponding 95% confidence intervals (CI) were calculated. Kaplan-Meier analysis was used to investigate cumulative 30-day event free survival rate. Forward stepwise selection with a 0.1 level for staying in the model was used to identify significant predictors in multivariable analysis. Areas under ROC curves were compared pair-wise. Sensitivity, specificity, negative predictive values (NPV), positive predictive values (PPV), and the corresponding 95% CI were calculated for TAPSE and TV S’. All tests were two-sided. Data were considered significant at p < 0.05. STATISTICA data analysis software system (StatSoft, Inc. 2011, version 10, www.statsoft.com) and MedCalc® software (version 11.0.0.0) were used for statistical calculations. This observational study was approved by the local Ethics Committee.

Results
Patients characteristics and clinical course
The study included 139 consecutive patients with PE (63 males, 76 females, age 56.4 ± 19.5 years), normotensive at admission. The study outcome defined as 30-day PE-related mortality and/or need for rescue thrombolysis in patients with hemodynamic deterioration was observed in 7 (5%) of the patients studied. Despite anticoagulation 6 (4.3%) patients experienced hemodynamic collapse and underwent rescue thrombolysis, 4 of them survived. 30-day PE-related mortality was 2.2% (3 patients), and all-cause mortality was 2.9% (4 patients). The one none-PE related death occurred in a 92-year-old patient with metastatic cancer. Initial systemic SBP was significantly lower in patients who experienced serious adverse events (SAE (+)) than in patients with an uncomplicated clinical course (SAE (−)). There was no difference in age and heart rate between SAE (+) and SAE (−) groups. Clinical characteristics of patients studied are presented in Table 1.
Echocardiography

Echocardiographic data of the group studied are included in Table 2. Patients with a complicated clinical outcome presented more pronounced echocardiographic signs of RVD. Mean values of TAPSE and TV S’ (Figs. 1, 2) and AcT were significantly lower, while TRPG and IVC were significantly higher in the SAE (+) group when compared with the SAE (−) group.

The McConnell sign and flattening of IVS were more frequent in SAE (+) patients, but without statistical significance. There were no differences in RV4C dimensions, RV/LV ratio, and LVEF between SAE (+) and SAE (−) groups.

Echocardiographic predictors of clinical endpoint

Univariable Cox proportional-hazards regression analysis showed that several echocardiographic parameters significantly predicted a complicated clinical outcome. Importantly, TAPSE and TV S’ showed similar HRs, HR 0.77 (0.67–0.89), p < 0.001, and 0.71 (0.52–0.97), p = 0.03, respectively (Table 3).

ROC curve analysis

ROC analysis showed that the AUC for TAPSE in the prediction of a complicated clinical course was 0.881, 95% CI 0.812–0.932, p = 0.0001, mean-
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Figure 1. M-mode presentation of tricuspid annular plane systolic excursion (TAPSE) in two initially normotensive patients with acute pulmonary embolism; A. Patient with a benign clinical course (distance 25 mm — red double-headed arrow); B. Patient with a complicated clinical outcome and decreased annular movement (distance 12.5 mm — red double-headed arrow); RA — right atrium; RV — right ventricle.

Figure 2. Tissue Doppler of the tricuspid annulus in two initially normotensive patients with acute pulmonary embolism; A. Patient with a benign clinical course (TV S’ 14.2 cm/s — yellow arrow); B. Patient with a complicated clinical outcome and decreased annular velocity (TV S’ 8.4 cm/s — yellow arrow); TV S’ — peak systolic velocity of lateral part of tricuspid annulus.
while for TV S’ AUC 0.751; 95% CI 0.670–0.820, p = 0.001; Fig. 3).

Importantly, a direct comparison showed that AUC for TAPSE and for TV S’ did not differ significantly. Using the Youden’s index, a cut-off point for TAPSE at 18 mm and for TV S’ at 12.3 cm/s were identified as optimal values for SAE prediction.

When cut off values of TAPSE and TVS’ defined according to ROC analysis were used in hazard risk analysis TAPSE < 18 showed HR for study end point of 16.3 (2.0–135.3, p = 0.01), while TV’S < 12.3 cm/s was only of borderline significance HR 4.3 (0.8–22.2, p = 0.08).

Table 4 shows the sensitivity and specificity of ROC-derived cut-offs for TAPSE and TV S’ in SAE prediction.

Multivariable analysis testing all clinical and echocardiographic parameters which were found to be significant in the univariable analysis were performed. Multivariable analysis showed that the optimal prediction model included TAPSE and systemic SBP only, while other clinical and echocardiographic parameters, with TV S’ were not included. SBP showed HR 0.89 95% CI 0.83–0.95, p < 0.001 and TAPSE HR 0.67, 95% CI 0.52–0.87, p < 0.03. Kaplan-Meier analysis showed that initially PE patients with TAPSE ≥ 18 mm had much more favorable prognosis that patients with TAPSE < 18 mm (p < 0.01), while Kaplan-Meier analysis of S’ was only of borderline statistical significance (Fig. 4).

**Discussion**

Normotensive patients with acute PE include subjects with a benign clinical course, as well as patients with an increased risk of PE-related mortality, who can deteriorate despite anticoagulation. Although short-term prognosis in acute PE predominantly depends on the hemodynamic status, RVD detected at echocardiography has significant prognostic value, especially in initially hemodynamically stable PE patients [5]. Several echocardiographic parameters for quantitative assessment of RV systolic function have been intensively studied, however echocardiographic assessment...
of RV function remains challenging because of the complex RV anatomy. Various echocardiographic criteria have been proposed as prognostic parameters, however decreased TAPSE was recently reported to be superior to other indices including RV/LV ratio or TRPG [5, 6].

There is accumulating evidence that tricuspid valve systolic velocity assessed with tissue Doppler is a significant prognostic parameter in various diseases affecting RV [20]. Moreover, the assessment of RVD with tissue Doppler was reported to be related to pulmonary artery thromboembolic burden. Mid-right ventricular myocardial longitudinal dysfunction quantified by tissue Doppler was related to the degree of pulmonary vascular obstruction [21]. Since tissue Doppler has become widely available and the measurement of peak systolic velocity of tricuspid annulus can be performed easily, which were compared herein, the two parameters of RV systolic function, TAPSE or TV S’, was more useful in the prognosis assessment in initially hemodynamically stable patients with acute PE. A univariable analysis revealed that both indices significantly predicted a complicated clinical outcome, defined by hemodynamic collapse and need for rescue thrombolysis or PE-related 30-day mortality or both. Additionally, TAPSE and TV S’ were characterized by a high AUC in ROC analysis (AUC 0.881; 95% CI 0.812–0.932 p = 0.0001; and AUC 0.751; 95% CI 0.670–0.820, p = 0.001, respectively). Furthermore, Youden’s index was used to determine optimal predictive values for both parameters. In the group of 139 consecutive PE patients there were 7 SAE cases including 3 PE related deaths. TV S’ < 12.3 cm/s was characterized by HR of 4.3, 95% CI 0.8–22.3, p = 0.08 for complicated clinical course and showed 86% sensitivity and 60% specificity in SAE prediction. However, when all significant clinical and echocardiographic parameters were included in the multivariable analysis only systemic SBP and TAPSE were found to be of predictive value. Thus, it seems that TV S’ is not superior to TAPSE in early risk stratification in normotensive patients with acute PE. The present data corresponds with a recent observation that TAPSE is a reliable predictor of RV systolic dysfunction, and that TAPSE can be recommended for clinical use [22]. Interestingly, no significant differences were found in the initial values of TAPSE or TV S’ between patients who died 1 year after discharge and patients who are still alive.

limitations of the study

The main limitation of the current study is its single center character with a relatively small number of patients studied and a low number of clinical end points. Therefore, the results of the current study should be interpreted with caution.

Additionally, the DTI measurement is angle-dependent and both TAPSE and TV S’ measurements are influenced by movement of the whole heart.
Conclusions

Although TV S’ predicts short term outcome in normotensive patients with acute symptomatic PE, it seems to be inferior to TAPSE for 30 day prediction of adverse outcome and therefore TAPSE should be recommended as part of the echocardiographic assessment in this group of patients.

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References


