

Timing and magnitude of regional right ventricular function and their relationship with early hospital mortality in patients with acute pulmonary embolism

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ABSTRACT

Objective: Right ventricular (RV) dysfunction in acute pulmonary embolism (APE) has been associated with increased mortality and morbidity. The aim of the present study was to assess the timing and magnitude of regional RV functions using speckle-tracking echocardiography (STE) and their relationship to early hospital mortality in patients with APE.

Methods: One hundred forty-two patients were prospectively studied at the onset of an acute episode and after a median follow-up period of 30 days. Their clinical and laboratory characteristics were recorded. For all patients, conventional two-dimensional echocardiography and STE were performed within 24 h after the diagnosis of APE.

Results: Twenty-eight (19.7%) patients died during the hospitalization follow-up. Patients who died during hospitalization were older and had higher high sensitivity cardiac troponin T levels, and a higher percentage of patients had simplified Pulmonary Embolism Severity Indexes. In STE analyses, they had lower RV free wall peak longitudinal systolic strain (PLSS) and higher RV peak systolic strain dispersion indexes. The time to PLSS difference between RV free wall and LV lateral was longer in patients who died during hospitalization than in those who survived, and this was an independent predictor of early hospital mortality with 85.7% sensitivity and 75.0% specificity in patients with APE.

Conclusion: APE was associated with RV electromechanical delay and dispersion. Electromechanical delay index might be useful to predict early hospital mortality in patients with APE. (*Anatol J Cardiol* 2019; 22: 26-32)

Keywords: pulmonary embolism, right ventricle, speckle-tracking echocardiography

Introduction

Acute pulmonary embolism (APE) is common in clinical practice, and the mortality of patients with APE is still high despite advances in diagnostic modalities and therapeutic options (1). APE results from venous thromboembolic occlusion in the pulmonary artery and its branches, resulting in increased pressure in the right heart cavities leading to various hemodynamic problems (2). The clinical outcomes of APE vary widely, from mild symptoms and no hemodynamic consequences to cardiovascular collapse and respiratory failure (3). The European Society of Cardiology (ESC) consensus guidelines recommend risk stratification of patients with APE to guide appropriate and timely management and disposition. The risk stratification of APE involves weighing various risk predictors including age, demo-

graphics, comorbidities, and physical examination findings, as well as cardiac biomarkers and advanced cardiac imaging (1). In some patients who are low-risk, APE may be treated at home, but patients who have high-risk APE are required to be treated in intensive care units (ICUs). Patients who have high-risk APE, together with massive pulmonary embolism, need to be treated with thrombolytic therapy (4).

Right ventricular (RV) dysfunction is a well-known predictor of early death, and thus the early identification of RV dysfunction is critical in the risk stratification and management of APE (5). Two-dimensional echocardiography (2DE) is the method of choice to identify patients with RV dysfunction. 2DE is a low-cost, portable, real-time, and non-invasive diagnostic method that is used for diagnosis and follow-up of patients with APE. Recently, myocardial mechanics and strain analyses have begun

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to be used to study for RV dysfunction in different clinical settings (6). Despite the obvious clinical importance of assessing electromechanical delay and dispersion, the evaluation of RV function can be more difficult than that of left ventricle (LV) because of the RV's complex anatomy (7, 8). The recent introduction of peak longitudinal systolic strain (PLSS) and time to PLSS using speckle-tracking echocardiography (STE) has provided an objective means to quantify electromechanical delay between RV and LV with improved accuracy and greater reproducibility than conventional 2DE (9).

A number of studies have used 2DE and STE to evaluate the RV dysfunctions in patients with APE (10), but there is currently no research assessing RV electromechanical delay and dispersion. The aim of the present study was to evaluate RV mechanical functions and dyssynchrony and to consider their relationship with early hospital mortality in patients with APE.

Methods

Study population

Overall, 142 patients who had a diagnosis of acute PE using personal histories, physical examinations, 2DE, lower limb venous ultrasonography, and laboratory tests were prospectively evaluated. PE diagnosis was confirmed by the presence of thrombi in the pulmonary arteries on thoracic computed tomography, in line with the current ESC guidelines (1). Transthoracic 2DE was performed at the onset of the acute episode. Patients with impairment of LV systolic function (ejection fraction <50%), significant valvular heart disease, cardiomyopathy, and history of coronary artery disease were excluded from the study. In addition, four patients with suboptimal transthoracic echocardiographic images that precluded speckle-tracking analysis were excluded. Therefore, a total of 142 patients with acute PE were included in the final analysis. Simplified Pulmonary Embolism Severity Index (sPESI) scores of all of the patients were calculated according to the clinical data and the ESC guidelines (1). The study was approved by the Local Ethics Committee (protocol no. 70737436-050.06.04) in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Echocardiographic evaluation

Two-dimensional echocardiographic measurements were performed in accordance with the recommendations of the European Association of Cardiovascular imaging using an ultrasound system (IE33; Philips Medical Systems, Andover, MA, USA) (11). Standard echocardiographic views (parasternal long and short axes and apical 4- and 2-chamber) were obtained using a 3.5 MHz transducer in all subjects.

Two independent cardiologists performed STE post-processing analysis using the QLAB Philips off-line software (Philips Healthcare Medical Imaging System, Andover, MA, USA). They recorded three consecutive cardiac cycles in DICOM format for

each view with a frame rate >50/s, which appears to be the best compromise between appropriate temporal resolution and acceptable spatial definition of the LV lateral wall and RV free wall. In post-processing analysis, the region of interest (ROI) was obtained by tracing the RV endocardial borders at the level of the interventricular septum and the free wall in a still frame at end-systole (12). The ROI was adjusted to cover at least 90% of the myocardial wall thickness. If first tracking is thought to be suboptimal, other retracings were manually or semi-automatically performed. Longitudinal strain curves were obtained for six RV segments [the basal, mid, and apical segments of the RV free wall and interventricular septum (IVS)], and the longitudinal strain curves of the LV lateral wall were obtained by repeating the same analysis. RV peak systolic strain dispersion (PSSD) index, which presented RV mechanical dispersion, was derived from the standard deviation of the times from QRS beginning to PLSS of the RV six segments. The extent of myocardial deformation (defined as the PLSS) was expressed as a percentage of the longitudinal shortening in systole compared with diastole for each segment of interest. In the measurement of RV electromechanical delay, the RV apex was excluded due to its interaction with LV global contraction and ventricular interdependence. The temporal pattern of RV mechanical contraction was evaluated as the time needed to reach peak strain (time to PLSS) using the beginning of the QRS complex as a reference point. RV electromechanical delay was defined as the maximum difference in time to PLSS among IVS, LV lateral wall, and free RV wall (9, 13). In the RV PSSD index measurement, the intraobserver and interobserver variabilities were 6.1% and 9.3%, respectively.

Statistical analysis

All statistical tests were performed using a commercially available software program (SPSS 21.0 for Mac; SPSS Inc., Chicago, IL, USA). The variables were investigated using visual (histograms and probability plots) and analytic methods (Kolmogorov–Smirnov and Shapiro–Wilk tests) to determine whether or not they are normally distributed. Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean±standard deviation. Since all continuous variables were normally distributed, statistical comparisons of quantitative data were performed by an unpaired sample t-test. For multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine the independent predictors of early hospitalization of subjects. Hosmer–Lemeshow goodness-of-fit statistics was used to assess model fit. The capacity of time to PLSS difference between RVF–LVL (RV free wall and LV lateral wall) and RV PSSD index values in predicting early hospital mortality was analyzed using receiver operating characteristic (ROC) curve analysis. A p-value of <0.05 was considered statistically significant.

Results

Overall patient characteristics

A total of 142 patients were included in the final analysis. The mean age of the patients was 56.9 ± 13.1 years. The study included 82 (57.7%) male patients. Thirty-six patients were initially admitted to the ICU. Patient risk factors for the development of APE include idiopathic ($n=49$), immobilization ($n=41$), cancer ($n=38$), recent major surgery ($n=38$), use of contraception methods ($n=6$), and thrombophilia ($n=7$). Of the 142 patients, 26.1% had at least two risk factors for APE. Among patients with histories of malignancy ($n=38$), 14 were receiving chemotherapy at the diagnosis of PE. The qualifying event was the first episode of PE in 84% of the patients. The other 16% of the patients had prior episodes. PE was located in the central, lobar, and segmental or subsegmental branches of the pulmonary artery in 19%, 43%, and 38% of the patients, respectively. Mechanical ventilation was required in 17.6% of the patients. Fourteen (9.8%) patients were administered intravenous thrombolytic therapy. Twenty-one (14.8%) patients died during the ICU admission, and a total of 28 (19.7%) patients died during hospitalization. The length of an ICU stay was 4.4 ± 1.2 days. The length of a hospital stay was 12.0 ± 3.9 days. Baseline and laboratory characteristics are shown in Table 1. Patients who died during hospitalization had increased age, had higher high sensitivity cardiac troponin T and pro-brain natriuretic peptide levels, and lower mean blood pressure, and a higher percentage of those patients had sPESI.

Based on ECG morphology, right bundle branch block was present in 51 (35.9%) patients. The ECG-QRS width was 102 ± 17 ms in patients who died during hospitalization and 99 ± 14 in those who survived ($p=0.43$).

2DE and STE-derived measurements

A comparison of the 2DE characteristics and STE-derived measurements between hospital survivors and patients who died during hospitalization is shown in Table 2. In the 2DE measurements, there was no statistically significant difference between the two groups, except tricuspid annular plane systolic excursion (TAPSE) ($p=0.001$).

In the STE analyses, patients who died during hospitalization had a lower RV free wall PLSS ($p=0.02$) and a higher RV PSSD index ($p<0.001$). The time to PLSS difference between RVF-LVL (52.5 ± 17.9 vs. 26.8 ± 22.1 , $p<0.001$) and RV free wall and IVS (39.3 ± 19.9 vs. 23.4 ± 18.4 , $p=0.03$) was longer in patients who died during hospitalization than in those who survived.

Prediction of early hospital mortality

Significant univariate correlations with early hospital mortality are shown in Table 3. ROC curve analyses revealed that a time to PLSS difference between RVF-LVL >38 ms predicted early hospital mortality with 85.7% sensitivity and 75.0% specificity (area under curve (AUC) 0.832, 95% confidence interval (CI) 0.720–0.944, $p<0.001$). An RV PSSD index >62 also predicted hospital mortality with 71.4% sensitivity and 90.9% specificity (AUC

Table 1. Comparison of demographic, clinical, and laboratory characteristics between hospital survivors and patients who died during hospitalization

	Hospital survival (n=114)	Hospital death (n=28)	P-value
Age (years)	52.7 ± 11.9	65.0 ± 12.8	0.001
Gender (male)	62 (54.3%)	20 (71.4%)	0.07
Body mass index (kg/m ²)	28.2 ± 6.8	27.9 ± 6.5	0.26
sPESI ≥ 1	13 (30%)	11 (78%)	0.001
Hypertension (n, %)	20 (45%)	6 (43%)	0.53
Diabetes mellitus (n, %)	18 (41%)	5 (36%)	0.34
Hyperlipidemia (n, %)	14 (32%)	4 (29%)	0.42
Smoking (n, %)	14 (32%)	8 (57%)	0.09
Mean blood pressure (mm Hg)	90.8 ± 19.5	71.4 ± 15.5	0.001
Laboratory characteristics			
Pro-BNP (ng/L)	128.1 ± 79.6	206.9 ± 115.4	0.006
D-dimer (mg/L)	9.3 ± 2.3	8.5 ± 1.7	0.20
hs-TNT (μ g/L)	0.26 ± 0.3	0.72 ± 0.6	0.007
Hemoglobin (g/dL)	13.6 ± 2.5	13.1 ± 1.8	0.15
Creatinine (mg/dL)	1.08 ± 1.1	1.19 ± 1.4	0.24

Data are presented as mean \pm standard deviation. Categorical variables were expressed as percentages. Bold values indicate statistical significance at $P<0.05$.
hs-TNT - high sensitivity cardiac troponin T; pro-BNP - pro-brain natriuretic peptide; sPESI - simplified Pulmonary Embolism Severity Index

Table 2. Comparison of echocardiographic characteristics between hospital survivors and patients who died during hospitalization

	Hospital survival (n=114)	Hospital death (n=28)	P-value
Conventional echocardiography measurements			
LV ejection fraction (%)	59.4±8.8	56.5±8.5	0.46
RV end-diastolic basal diameter (mm)	43.4±9.1	45.2±9.6	0.77
RV end-diastolic longitudinal diameter (mm)	74.4±11.2	79.0±12.5	0.46
RV wall thickness, subcostal view (mm)	17.5±1.5	16.1±1.3	0.29
RV fractional area change	40.3±5.6	38.6±5.6	0.37
RV myocardial performance index	0.54±0.2	0.62±0.3	0.12
TAPSE (mm)	18.3±3.4	15.0±2.3	0.001
RV S (cm/s)	11.1±2.1	10.3±1.7	0.21
Estimated PAP (mm Hg)	42.5±19.6	55.6±26.8	0.06
Leftward shifting of the IVS	14 (32%)	8 (57%)	0.09
RV/LV end-diastolic diameter ratio >1.0	12 (27%)	7 (50%)	0.12
Speckle-tracking echocardiography measurements			
RV free wall longitudinal systolic strain (%)	19.6±3.4	16.8±4.4	0.02
LV global longitudinal systolic strain (%)	22.4±4.5	21.8±4.3	0.34
RV peak systolic strain dispersion index	38.4±15.9	70.4±21.4	<0.001
Time to peak longitudinal systolic strain difference (ms)			
RVF-LVL ^a (ms)	26.8±22.1	52.5±17.9	<0.001
RVF-IVS ^b (ms)	23.4±18.4	39.3±19.9	0.03
LVL-IVS ^c (ms)	16.9±11.4	16.0±8.9	0.24
^a Indicate more delay in RV free wall time to peak longitudinal strain compared with LV lateral wall. ^b Indicate more delay in RV free wall time to peak longitudinal strain compared with IVS. ^c Indicate more delay in LV lateral wall time to peak longitudinal strain compared with IVS. Data are presented as mean±standard deviation. Categorical variables were expressed as percentages. Bold values indicate statistical significance at P<0.05. IVS - interventricular septum; LV - left ventricle; PAP - pulmonary artery pressure; RV - right ventricle; RV S - right ventricle systolic excursion; TAPSE - tricuspid annular plane systolic excursion			

0.878, 95% CI 0.775–0.9482, p<0.001) (Fig. 1). Our reported sensitivity and specificity values represent the best-case scenario. Multivariate logistic regression analysis was performed to demonstrate the independent predictors of early hospital mortality in patients with APE (Table 4). The time to PLSS difference between RVF–LVL >38 ms and TAPSE was included in the model. Both of them were found as independent predictors of hospital mortality [odds ratio (OR) 12.39, 95% CI 2.21–69.40, p=0.004 and OR 0.71, 95% CI 0.51–0.96, p=0.029, respectively].

Discussion

The major findings of the present study are as follows: (1) patients with APE who died during hospitalization had a delayed RV free wall activation, a higher RV PSSD index, and a lower RV global longitudinal strain (GLS) compared with survivors; (2) an increase in the RV PSSD index indicates mechanical dispersion in the RV; and (3) the time to PLSS difference

between RVF–LVL was an independent predictor of early hospital mortality.

The present study uses strain imaging to evaluate RV electromechanical delay and dispersion, in addition to investigating the determinants of early hospital mortality in patients with APE. The increase in the RV PSSD index noted in our results is in accordance with a case report that illustrated RV mechanical dispersion using STE in a patient with massive APE and its improvement after effective thrombolytic therapy (7). Sugiura et al. (14) explored the time to PLSS difference between RV free wall and IVS as an RV electromechanical delay, as well as the heterogeneity of six segmental analyses of RV longitudinal strain as RV mechanical dispersion in patients with APE. They also showed RV mechanical dysfunction via a decrease in RV free wall longitudinal strain, all of which is in accordance with our results. Vitarelli et al. (10) and Ramberg et al. (15) in STE-measured studies demonstrated a decrease in RV free wall GLS at admission in patients with APE.

The increase in the time to PLSS noted in our results is in accordance with the previously reported increased dispersion

Table 3. Univariate logistic regression analysis to determine the hospital mortality

	OD	95% CI	P-value
RVF-LVL time to PLSS difference >38 ms	18.01	3.47-93.27	0.001
RV PSSD index >62 ms	25.02	5.30-117.72	<0.001
RV free wall longitudinal systolic strain (%)	0.81	0.67-0.97	0.02
hs-TNT (µg/L)	1.03	1.009-1.040	0.002
TAPSE (mm)	0.66	0.49-0.87	0.004
Age (years)	1.101	1.04-1.18	0.004
Gender (male)	0.29	0.07-1.22	0.09
Mean arterial blood pressure (mm Hg)	0.92	0.90-0.98	0.004
Pro-BNP (ng/L)	1.09	1.01-1.02	0.01
sPESI ≥1	8.74	2.08-36.59	0.003
Estimated SPAP (mm Hg)	1.03	0.99-1.06	0.07
RV S (cm/s)	0.82	0.60-1.12	0.21
RV fractional area change	0.97	0.87-1.09	0.61
RV/LV end-diastolic diameter >1.0	2.67	0.77-9.22	0.12

Bold values indicate statistical significance at $P < 0.05$.
CI - confidence interval; hs-TNT - high sensitivity cardiac troponin T; LV - left ventricle; LVL - left ventricular lateral wall; OR - odds ratio; PLSS - peak longitudinal systolic strain; pro-BNP - pro-brain natriuretic peptide; PSSD - peak systolic strain dispersion; RV - right ventricle; RVF - right ventricular free wall; RV S - right ventricle systolic excursion; SPAP - systolic pulmonary artery pressure; sPESI - simplified Pulmonary Embolism Severity Index; TAPSE - tricuspid annular plane systolic excursion

Table 4. Multivariate logistic regression analysis to determine the hospital mortality

	OD	95% CI	P-value
RVF-LVL time to PLSS difference >38 ms	12.39	2.21-69.40	0.004
TAPSE	0.71	0.51-0.96	0.029

Bold values indicate statistical significance at $P < 0.05$.
CI - confidence interval; LVL - left ventricular lateral wall; OR - odds ratio; PLSS - peak longitudinal systolic strain; RVF - right ventricular free wall; TAPSE - tricuspid annular plane systolic excursion

with delayed contraction of the RV free wall in patients with pulmonary arterial hypertension (PAH). López-Candales et al. (16) showed that RV significantly delays time to peak strain in patients with chronic thromboembolic pulmonary hypertension compared with healthy subjects. In addition, using STE, Kalogeropoulos et al. (17) observed a delayed time to peak strain in the RV free wall of patients with PAH compared with healthy controls. A previous study with the use of magnetic resonance imaging myocardial tagging in patients with PAH has identified prolonged RV contraction as the cause of interventricular asynchrony (18). Gabrielli et al. (19) showed the improvement of RV mechanical dispersion after iloprost therapy in patients with PAH.

Compared with the previous studies, we have shown that the prominent reduction of RV free wall GLS, electromechanical delay, and dispersion are representative markers of a large regional non-uniformity associated with acute pressure overload and are an important index to predict early hospital mortality. It has also

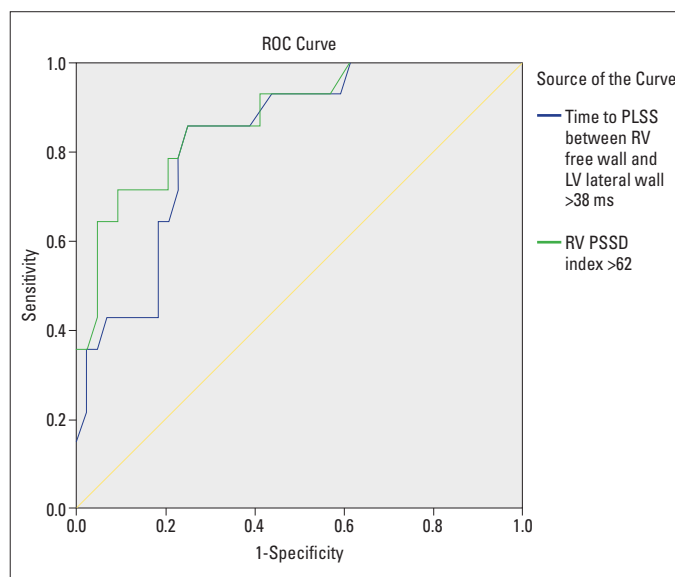


Figure 1. Receiver operating characteristic analyses revealed that the time to peak longitudinal systolic strain difference between right ventricle (RV) free wall and left ventricle lateral wall >38 ms predicted early hospital mortality with 85.7% sensitivity and 75.0% specificity, and the RV peak systolic strain dyssynchrony index >62 predicted with 71.4% sensitivity and 90.9% specificity in patients with acute pulmonary embolism

been speculated that RV acute pressure overload induces heterogeneous mechanical stretch in the myocardium, leading to regional ischemia and altering interventricular pressure interactions (14). Moreover, RV pressure overload affects LV performance via ventricular interdependence, and it has a potential

to contribute to further deterioration of LV performance (20). Patients who died during hospitalization had lower LV GLS than surviving patients in our study; however, this difference failed to reach statistical significance. Nevertheless, LV GLS values of both groups were close to the lower limit of normal range. These conclusions will require confirmation in larger patient populations with APE. It is important to emphasize that in the present study, RV electromechanical delay and dispersion were present even with a normal electrocardiographic QRS interval duration. A finding that is in agreement with previous data states that an abnormal electrical conduction is not necessarily needed to produce RV electromechanical delay and dispersion because it has been identified in the failing myocardium with a normal QRS duration (14, 21). Therefore, it appears that not all contributing mechanisms resulting in mechanical dispersion have been identified, and these mechanisms are probably complex.

Based on the ESC consensus guideline (1), RV dysfunction is an important determinant of early mortality in patients with APE. In the evaluation of conventional 2DE-derived studies, Khemasuwan et al. (22) showed that the decrease in TAPSE values in patients with APE who died during hospitalization compares with the values in survivors. Ciuzyński et al. (23) explained that the tricuspid regurgitation peak gradient/TAPSE ratio has a correlation with poor prognosis in patients with APE. The increase in tricuspid regurgitation peak gradient and decrease in TAPSE demonstrated in those clinical studies are in accordance with our results.

In recent studies, high-risk patients are described using a PESI score with the components (24, 25). Our results correlate with these studies and show that hospital mortality has a close relationship with PESI scores combined with increased age and decreased blood pressure.

Study limitations

Our study has limitations. First, the size of the study population was small. Further studies with larger patient numbers are needed to verify our findings. The validation of electromechanical delay and dispersion by cardiac magnetic resonance imaging and correlation with STE measures might strengthen our results. Owing to the complex morphology of the RV, no single view or imaging plane will provide enough information to adequately evaluate RV structure and function (26). However, in the present study, the longitudinal RV strain was measured from a single 4-chamber view instead of multiple views as in previous studies, because this view provided better visualization of the contracting myocardium (26, 27). The low number of patients who died in-hospital did not allow for precision. Larger prospective multicentered clinical studies are needed to confirm our results.

Conclusion

The results of the present study suggest that APE is associated with RV electromechanical delay and dispersion. Patients

who died during hospitalization had worse RV mechanical functions using both 2DE and STE than survivors. Electromechanical delay index might be used in predicting early hospital mortality in patients with APE. The clinical implications of the present study may guide physicians to have more information about the follow-up care of patients with APE and to make better decisions for reperfusion therapy, intensive care, and monitoring.

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Peer-review: Internally peer-reviewed.

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