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ORIGINAL RESEARCH

Simultaneous Pulmonary Artery Pressure and Left Ventricle Stroke Volume Assessment Predicts Adverse Events in Patients With Pulmonary Embolism

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BACKGROUND: Certain echocardiographic parameters may serve as early predictors of adverse events in patients with hemodynamically compromising pulmonary embolism (PE).

METHODS AND RESULTS: An observational analysis was conducted for patients with acute pulmonary embolism evaluated by a Pulmonary Embolism Response Team (PERT) between 2014 and 2020. The performance of clinical prediction algorithms including the Pulmonary Embolism Severity Index and Carl Bova score were compared using a ratio of right ventricle and left ventricle hemodynamics by dividing the pulmonary artery systolic pressure by the left ventricle stroke volume. The primary outcome of in-hospital mortality, cardiac arrest, and the need for advanced therapies was evaluated by univariate and multivariable analyses. Of the 343 patients meeting the inclusion criteria, 215 had complete data. Pulmonary artery systolic pressure/left ventricle stroke volume was a clear predictor of the primary end point (odds ratio [OR], 2.31; P=0.005), performing as well or better than the Pulmonary Embolism Severity Index (OR, 1.43; P=0.06) or the Bova score (OR, 1.28; P=0.01).

CONCLUSIONS: This study is the first study to demonstrate the utility of early pulmonary artery systolic pressure/left ventricle stroke volume in predicting adverse clinical events in patients with acute pulmonary embolism. Pulmonary artery systolic pressure/left ventricle stroke volume may be a surrogate marker of ventricular asynchrony in high-risk pulmonary embolism and should be prognostically evaluated.

Key Words: pulmonary artery pressure ■ pulmonary embolism ■ right ventricle ■ stroke volume

Pulmonary embolism (PE) is a heterogenous, life threatening condition associated with poor clinical outcomes ranging from persistent dyspnea to death. In the United States, over 100 000 annual deaths are attributed to PE. Of those deaths, 10% to 30% occur within the first month of presentation.[1] Effective risk stratification could influence therapeutic management decisions and reduce PE-related morbidity and mortality.

The European Society of Cardiology and the American College of Chest Physicians recommend the routine use of risk stratification scores to predict adverse outcomes in patients with acute PE.[2,3] Risk stratification algorithms including Pulmonary Embolism Severeity Index (PESI) and Bova, although helpful, depend partly on fluctuating subjective data and can underestimate patient acuity.[4] PESI is a validated score encompassing baseline patient

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CLINICAL PERSPECTIVE

What Is New?

- In patients with hemodynamically challenging acute pulmonary embolism (PE), echocardiography provides rapid and important data on how right heart pressure affects left heart pressure and effective circulating blood volume.
- Obstructive shock from acute PE raises pulmonary artery and right ventricular pressure, which decreases blood flow across the pulmonary capillary bed to the left heart resulting in underfilling and promotes right-to-left septal bowing with a net effect of decreased left ventricle stroke volume (LVSV).
- Simultaneously assessing the pulmonary artery systolic pressure and LVSV as a ratio (pulmonary artery systolic pressure/LVSV) accurately predicts adverse clinical events including death, cardiogenic shock, and the need for advanced interventional procedures.

What Are the Clinical Implications?

- Patients with acute PE are often risk-stratified using complicated algorithms like Pulmonary Embolism Severity Index and Bova that require multiple clinical variables, some of which are not immediately available.
- An elevated pulmonary artery systolic pressure/LVSV ratio performs better than Bova and Pulmonary Embolism Severity Index in predicting adverse events, notably in patients with submassive PE who display marked heterogeneity and are challenging to determine the best treatment for.
- A pulmonary artery systolic pressure/LVSV ratio >1.0 mm Hg/mL can assist in decision making for treatments beyond anticoagulation alone for patients with acute submassive PE.

Nonstandard Abbreviations and Acronyms

LVSV	left ventricle stroke volume
PASP	pulmonary artery systolic pressure
PESI	Pulmonary Embolism Severity Index
RVOT	right ventricular outflow tract

comorbidities, as well as information on respiratory and hemodynamic function to predict 30-day all-cause mortality in patients with acute PE.[5] PESI, however, is mostly effective for identifying low-risk PE where rapid decision making is less important.[6] Bova incorporates right ventricle (RV) dysfunction into clinical and laboratory data and predicts PE-related complications and mortality at 30 days. Bova was, however, validated only for patients with a normal blood pressure.[7] Our group previously demonstrated that detecting early RV dysfunction by imaging performs better than PESI and Bova in predicting adverse outcomes for patients presenting with intermediate- (submassive) and high-risk (massive) PE. In fact, we observed that Bova and PESI can underestimate the true short-term mortality risk for intermediate- and high-risk PE.[8]

The 2019 European Society of Cardiology guidelines recommend using echocardiography for risk stratification even in patients with low-risk PE.[3] Increased right ventricle afterload and decreased RV stroke volume are associated with worse clinical outcomes in patients with intermediate-risk PE, as demonstrated by the predictive power of measuring right ventricular outflow tract (RVOT) velocity time integral (VTI) at the time of acute PE.[9,10] Similalrly, decreased left ventricle (LV) stroke volume was recently demonstrated to predict poor outcomes in acute PE.[11] Pulmonary artery vasoconstriction secondary to hypoxemia, along with increased thrombus burden both increase pulmonary artery systolic pressure (PASP).[12,13] Elevated PASP and RV pressure promote leftward bowing of the intraventricular septum, and acute RV afterload at the time of PE may limit blood flow across the pulmonary capillary bed and lead to underfilling of the LV. Both LV underfilling and bowing of the intraventricular septum decrease LV stroke volume (LVSV), which in turn creates systemic hypotension from a decrease in effective circulating blood volume.[14,15] Recently, low left ventricular outflow tract (LVOT) VTI, a marker of LV stroke volume, predicted adverse outcomes in patients with acute PE.[11] Our goal was to use a very simple clinical tool with limited variables compared with PESI and Bova to accurately predict outcomes in patients with intermediate- and high-risk PE treated by a Pulmonary Embolism Response Team (PERT). To test the hypothesis that early simultaneous measurement of PASP and LVSV predicts adverse clinical sequelae, surface echocardiography was used and the performance of the PASP/LVSV ratio was compared with traditional PE risk stratification algorithms such as Bova and PESI.

METHODS

Study Design

In order to minimize the possibility of unintentionally sharing information that can be used to reidentify private information, a subset of the data generated for this study are available by the communicating author upon reasonable request, and the code used for statistical modeling is available. We conducted a retrospective

analysis of patients evaluated by our multidisciplinary PERT for acute PE management between July 2014 to March 2020. The study protocol was approved by Cleveland Clinic Institutional Review Board. Patients without confirmed PE by imaging and without Doppler assessment of PASP or LVSV evaluated by PERT were excluded from analysis. The requirement for informed consent was waived given the retrospective nature of this study.

Baseline Characteristics and Clinical Variables

Demographic and clinical variables and comorbidities were obtained by manual chart extraction. Plasma biomarkers of RV strain including NT-proBNP (N-terminal pro-B-type natriuretic peptide) and TnT (troponin T) were recorded. NT-proBNP was recorded as a continuous variable whereas cardiac TnT >0.029 ng/mL with an acceptable assay coefficient of variation was considered positive at our institution. These data were used to calculate risk stratification scores including PESI and Bova. Patients presenting with acute PE were also classified according to European Society of Cardiology criteria for PE severity.[3]

Echocardiography

Echocardiographic parameters were recorded for patients who presented with acute PE. PASP was determined by the Bernoulli method.[16] Stroke volume was calculated using the LVOT cross-sectional area in the parasternal long axis and LVOT VTI by pulsed wave Doppler below the aortic valve.[17] PASP/LVSV (mm Hg/mL) was calculated as the ratio of PASP (mm Hg) to LVSV (mL).[18] For the purposes of this study, echocardiographic evidence of RV dysfunction include RV dysfunction by visual estimation; decreased RVOT VTI; decreased RVOT acceleration time; the presence of an RV systolic notch, decreased tricuspid annular systolic excursion, and decreased RV free wall tissue Doppler velocity.[10,19,20] Echocardiographic data were adjudicated by 2 board-certified cardiologists not involved in statistical execution.

Outcomes

The need for advanced respiratory support via noninvasive and mechanical ventilation was evaluated. Cardiogenic shock was defined as sustained systolic blood pressure <90 mm Hg or requiring pressor support to maintain systolic blood pressure >90 mm Hg. Sustained hypotension was defined as 2 consecutive systolic blood pressure recordings <100 mm Hg over 30 minutes in the first 72 hours of presentation. The need for advanced reperfusion therapies including systemic thrombolytic agents, catheter-guided therapies, extracorporeal membrane oxygenation support, and surgical embolectomy. Outcomes including cardiac arrest, in-hospital mortality and 90-day all-cause mortality were recorded. Cardiac arrest was defined as the need for cardiopulmonary resuscitation. The *primary composite outcome* was defined as in-hospital mortality, the need for advanced interventional therapies, and cardiac arrest. Advanced interventional therapies were defined as the need for systemic thrombolytics, catheter-directed therapies, or thromboendarterectomy. The *secondary composite outcome* was cardiac and respiratory failure defined by the need for pressor therapy and noninvasive positive pressure ventilation or mechanical ventilation.

Statistical Analysis

Continuous variables were reported as the mean with SD for normally distributed variables or median with interquartile range for nonnormally distributed variables. Normality was evaluated by the Shapiro-Wilks test. Categorical variables were evaluated by χ^2, and continuous variables were evaluated by the Student *t* test for mean values or Wilcoxon rank-sum or Mann–Whitney *U* tests to compare medians. PASP/LVSV was not normally distributed and therefore stratified by the median cut-point of 1.0 to generate a dichotomous variable for some of the analysis using PASP/LVSV, with baseline patient characteristics and clinical variables evaluated for each of the 2 groups.

In order to study the association of PASP/LVSV with composite outcomes, we used logistic regression with PASP/LVSV as the outcome predictor. Regression models were built for composite outcomes including PESI and Bova. For the primary composite outcome, adjustments were made for the presence of RV dysfunction and proximal deep vein thrombosis. For the Bova score RV dysfunction is part of the scoring system, so no adjustment was made. For the secondary composite outcome, there was no difference in baseline characteristics between those with or without the outcome, so univariate analyses were conducted for the 3 outcome predictors: PASP/LVSV, PESI, and Bova. Regression diagnostics were performed to evaluate the fit of each model. Each logistic regression model was reported as an odds ratio (OR) and displayed as Forest plots. Receiver operator characteristic curves were used with PASP/LVSV as a continuous variable to evaluate the performance against standard clinical decision tools (PESI, Bova) in predicting the primary end point. All statistical analyses were performed using STATA MP Software for macOS 13 (StatCorp, College Station, TX, version 13.1). A 2-sided *P* value of ≤0.05 was considered statistically significant.

RESULTS

A total of 336 PERT activations had complete data and 215 met the inclusion criteria. We purposefully excluded patients known to have preexisting pulmonary hypertension, chronic PE, a previous RV infarction, or incomplete evaluation by echocardiography. The median PASP/LVSV cut-point for distinguishing between groups was 1.0 mm Hg/mL resulting in 103 patients with PASP/LVSV <1.0 mm Hg/mL and 112 patients with PASP/LVSV ≥1.0 mm Hg/mL.

Study Population

Patients with PASP/LVSV <1.0 mm Hg/mL and ≥1.0 mm Hg/mL had similar baseline characteristics, with 52% women and an average patient age of 59±15.5 years as a patient cohort. About one-half of the patient cohort had a history of cardiopulmonary disease, and one-third had a history of cancer. PE and concurrent proximal lower extremity deep vein thrombosis comprised 67% of the study population. Saddle PE was identified in 53% of patients (Table 1).

Clinical Presentation and Risk Stratification

On presentation, there was no difference in baseline hemodynamics including heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure for patients with PASP/LVSV <1.0 mm Hg/mL and PASP/LVSV ≥1.0 mm Hg/mL (Table S1). PASP/LVSV ≥1.0 mm Hg/mL was associated with evidence of increased myocardial strain with elevated NT pro-BNP (3599 versus 1428 pg/mL, *P*<0.001) and evidence of decreased organ perfusion with elevated lactate (2.9 versus 1.8 mM, *P*=0.003) in the setting of acute PE (Figure 1). Myocardial necrosis evaluated by elevated blood TnT was similar between patients with PASP/LVSV <1.0 mm Hg/mL and PASP/LVSV ≥1.0 mm Hg/mL (67.9% versus 60.2%, *P*=0.24) respectively.

In patients with PASP/LVSV ≥1.0 mm Hg/mL, mean PESI (119.5 versus 108, *P*=0.03) and Bova (3.9 versus 3.2, *P*=0.002) scores were significantly higher. Using the European Society of Cardiology criteria, patients with PASP/LVSV ≥1.0 mm Hg/mL more frequently had intermediate- to high-risk PE (85.7% versus 63.1%, *P* value <0.001) and fewer cases of low-risk PE (0.9% versus 11.7%, *P* value <0.001). The incidence of high-risk PE was similar in patients with PASP/LVSV ≥1.0 mm Hg/mL compared with PASP/LVSV <1.0 mm Hg/mL (8% versus 13.6%, *P* value=0.19). (Table S2).

Table 1. Baseline Patient Characteristics

Baseline Characteristics	PASP/LVSV <1.0 (n=103)	PASP/LVSV ≥1.0 (n=112)	*P* Value
Age, y±SD	56.8±16.2	60.9±14.6	0.05
Male sex, %	47 (45.6%)	58 (51.8%)	0.37
Cardiopulmonary disease	46 (44.7%)	65 (58%)	0.05
History of cancer	29 (28.2%)	37 (33%)	0.44
History of VTE	21 (20.4%)	30 (26.8%)	0.27
Provoked VTE	63 (61.2%)	61 (54.5%)	0.32
Saddle pulmonary embolism	51 (50.5%)	63 (56.2%)	0.40
Proximal deep vein thrombosis	72 (20.6%)	73 (66.4%)	0.51
Syncope	15 (14.6%)	17 (15.3%)	0.88

Demographics and relevant baseline clinical characteristics were similar in the groups with lower and higher PASP/LVSV ratios. Continuous variables are presented as mean±SD and differences between groups were evaluated by the Student's *t* test. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by χ^2. LVSV indicates left ventricle stroke volume; PASP, pulmonary artery systolic pressure; and VTE, venous thromboembolism.

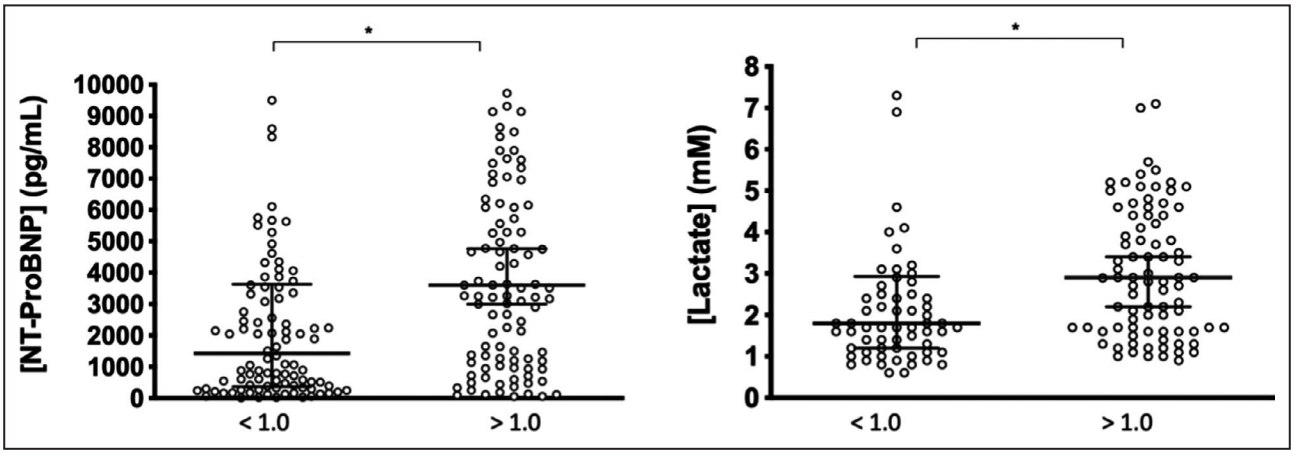

Figure 1. Biomarkers of myocardial strain and reduced end organ perfusion.
Blood NT-proBNP and lactate concentration are shown for the groups with lower and higher PASP/LVSV ratios. Data are represented as median with interquartile range. LVSV indicates left ventricle stroke volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and PASP, pulmonary artery systolic pressure. *P < 0.0001 between groups by Mann-Whitney *U* test, n=103 in the PASP/LVSV ratios < 1.0 group and n=112 in the PASP/LVSV ≥1.0 group.

Echocardiographic Parameters

Table 2 shows the distribution of select echocardiographic parameters between the 2 groups according to the PASP/LVSV ratio. Having a PASP/LVSV ≥1.0 mm Hg/mL was associated with echocardiographic findings of RV dysfunction. (92.9% versus 72.8%, *P* value <0.001), including elevated PASP (57.5 versus 39.8 mm Hg, *P* value <0.001), lower tricuspid annular systolic excursion (1.5 versus 1.7 cm, *P* value=0.003), lower RVOT VTI (9.3 versus 12.8 cm, *P* value <0.001), decreased RVOT acceleration time (58.6 versus 73.9 cm/s, *P*<0.001), decreased RV tissue Doppler velocity (9.08 versus 11.9 cm/s, *P*<0.001), and the presence of an RV systolic notch (62.7% versus 32.2%, *P*<0.001). (Table 2.) Global left ventricular ejection fraction was similar in patients with PASP/LVSV <1.0 mm/Hg and PASP/LVSV ≥1.0 mm Hg/mL, respectively (57.8% versus 59.8%, *P* value=0.22). However, echocardiographic interrogation of the LV in patients with PASP/LVSV ≥1.0 mm Hg/mL suggested compromised function with decreased LVOT VTI (14.7 versus 18.6 cm, *P* value <0.001) and decreased LV stroke volume (41 versus 61 mL, *P* value <0.001). RV afterload from PE impairs blood flow across the pulmomary vascular bed as demonstrated recently by reduced RVOT VTI.[10] We confirmed this recent observation because PASP/LVSV ≥1.0 mm Hg/mL shows a marked reduction in RVOT VTI (9.3 versus 12.8 cm, *P*<0.001), and this may lead to underfilling of the LV.

Outcomes

Baseline patient demographic and clinical variables for patients meeting the primary and secondary outcome criteria are displayed in Tables S3 and S4. There was no significant difference in the distribution of baseline clinical characteristics for patients with and without the primary and secondary outcome. All-cause in-hospital mortality in the entire patient cohort occurred in 16 patients (7.4%). All-cause 90-day mortality with PASP/LVSV ≥1.0 mm Hg/mL and PASP/LVSV <1.0 mm Hg/mL was 12.5 versus 9.7%, *P* value=0.52. Cardiac arrest was similar between groups (6.2 versus 2.9%, *P*=0.25) (Table S5). The use of advanced procedures beyond systemic anticoagulation alone was greater in the group of patients with PASP/LVSV ≥1.0 mm Hg/mL only for surgical embolectomy; however, the use of combined advanced procedures was predictably greater for the patient group with PASP/LVSV ≥1.0 mm Hg/mL (45.5% versus 29.1%, *P* value=0.013) (Table S6). Patients with PASP/LVSV ≥1.0 mm Hg/mL were more likely to require respiratory support using noninvasive positive pressure ventilation (46.4% versus 22.3%, *P* value <0.001) and a nonsignificant trend toward increased mechanical ventilation (19.6% versus 15.5%, *P* value=0.43). Hemodynamic compromise requiring pressors (25.9% versus 15.5%, *P* value=0.062) or sustained hypotension (60.7% versus 40.7%, *P* value=0.053) were numerically higher in the patient group with PASP/LVSV ≥1.0 versus <1.0 mm Hg/mL. Compared with patients with PASP/LVSV <1.0 mm/Hg, patients with PASP/LVSV ≥1.0 mm Hg/mL were more likely to require advanced reperfusion therapies beyond anticoagulation alone (45.5% versus 29.1%, *P* value=0.013).

Table 2. Echocardiographic Characteristics

Echocardiographic Parameters	PASP/LVSV <1.0 (n=103)	PASP/LVSV >1.0 (n=112)	*P* Value
PASP, mm Hg	39.8±9.7	57.5±15.6	<0.001
Tricuspid annular plane systolic excursion, cm	1.7±0.5	1.5±0.4	0.003
RVOT VTI, cm	12.8±3.9	9.3±2.9	<0.001
RVOT acceleration time, cm/s	73.9±22.3	58.6±17.2	<0.001
RV tissue Doppler velocity, cm/s	11.9±4	9.08±2.9	<0.001
RV systolic notch, dimensionless	29 (32.2%)	64 (62.7%)	<0.001
Left ventricular ejection fraction, %	59.6±9.4	57.8±10.7	0.22
Lleft ventricular outflow tract VTI, cm	18.6±4.8	14.7±3.7	<0.001
Stroke volume, mL	60.6±20.7	41±12.1	<0.001

Relevant echocardiographic parameters in groups with lower and higher PASP/LVSV ratios. Continuous variables are presented as mean±SD and differences between groups were evaluated by the Student's *t* test. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by χ^2. LVSV indicates left ventricle stroke volume; PASP, pulmonary artery systolic pressure; RV, right ventricle; RVOT, right ventricular outflow tract; and VTI, velocity time integral.

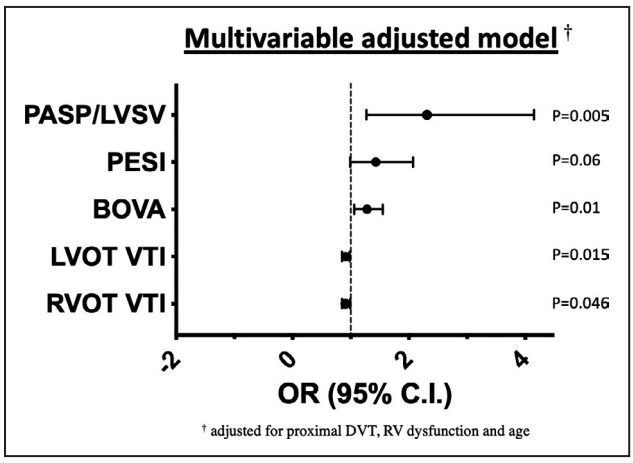

Figure 2. Primary outcome.
Multivariable logistic regression analyses of predictive scoring systems for the the primary outcome (death, cardiac arrest, need for advanced intervention). Data are shown as odds ratio (OR) ±95% CI with *P* values as noted. DVT indicates deep vein thrombosis; LVOT, left ventricular outflow tract; LVSV, left ventricle stroke volume; PASP, pulmonary artery systolic pressure; PESI, Pulmonary Embolism Severity Index; RV, right ventricle; RVOT, right ventricular outflow tract; and VTI, velocity time integral.

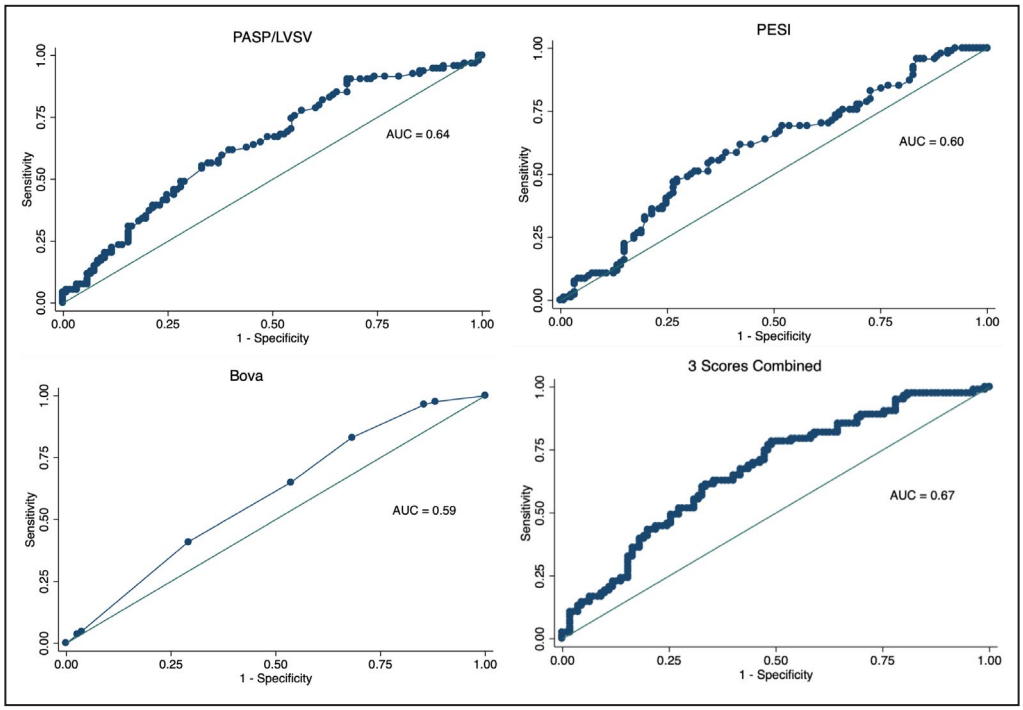

Figure 3. ROC curve analysis for primary outcome.
Receiver operator characteristic (ROC) curve analyses were conducted to show the performance of each scoring system in predicting the primary outcome (death, cardiac arrest, need for advanced intervention) in patients with acute pulmonary embolism. Area under the curve (AUC) for PASP/LVSV=0.64; AUC for PESI=0.60; AUC for Bova=0.59; AUC for PASP/LVSV+PESI+Bova= 0.67. LVSV indicates left ventricle stroke volume; PASP, pulmonary artery systolic pressure; and PESI, Pulmonary Embolism Severity Index.

The primary composite outcome in 94 subjects (43.7%) and secondary outcome occurred in 97 subjects (45.1%). Subjects who experienced the primary outcome were more likely to be older and have provoked venous thromboembolism or documented PE as well as proximal deep vein thrombosis. Patients with PASP/LVSV ≥1.0 mm Hg/mL had the highest adjusted OR of 2.31 (CI, 1.3–4.2; *P* value=0.005) for predicting the primary composite outcome with increased advanced reperfusion therapies, cardiac arrest, and in-hospital mortality (Figure 2). In comparison, only the Bova score came close to the predictive power of PASP/LVSV with an adjusted OR of 1.3 (CI, 1.1–1.6; *P* value=0.01) for the primary composite outcome, and PESI was nonsignificant with an adjusted OR of 1.4 (CI, 0.99–2.1; *P* value=0.06), whereas LVOT VTI had an adjusted OR of 0.93 (CI, 0.87–0.95; *P* value=0.047) and RVOT VTI was 0.96 (CI, 0.89–1.04; *P* value=0.35) for predicting the primary end point. PASP/LVSV ≥1 mm Hg/mm Hg was therefore the strongest predictor of both the primary and the secondary composite outcome using both unadjusted multivariable-adjusted models. (Tables S7 and S8). Comparing the PESI, Bova and PASP/LVSV alone or combining all 3 did not improve the model of discrimination for predicting the primary end point compared with the PASP/LVSV ratio alone when evaluated by receiver operator characteristic curve analysis (Figure 3), though PASP/LVSV alone offers the benefit of using only 2 hemodynamic variables as a simple ratio with more practical value in the context of critically ill patients with intermediate- and high-risk PE.

DISCUSSION

This investigation illustrates the utility of using PASP/LVSV to predict adverse events or the need for employing advanced therapies in patients with acute intermediate-risk PE. This ratio provides simultaneous information on both right and left heart performance, which is important in the context of obstructive shock from acute PE. RV dysfunction in the context of acute hemodynamically compromising PE ultimately can affect left-sided cardiac function as illustrated by the decrease in LVOT VTI recently reported and confirmed using our calculation.[11] PASP/LVSV, therefore, is a simple and logical echocardiographic-derived variable to evaluate interventricular dependence because an increase in the numerator and decrease in the denominator are equally poor prognostic indicators.

In the context of acute PE, PASP/LVSV ≥1.0 mm Hg/mL is associated with a decrease in multiple parameters

of RV performance including tricuspid annular systolic excursion, RVOT VTI, RVOT acceleration time, and RV tissue Doppler velocity. We were pleased to see that both LVOT VTI and RVOT VTI, as recently reported, predicted adverse outcomes in patients with intermediate-risk PE [10,11] and predicted the primary end point in this study. This suggests generalizability of these findings, though LVOT VTI and RVOT VTI predicted the outcome less robustly than PASP/LVSV ≥1.0 mm Hg/mL. A notable difference in our investigation is that we evaluated both intermediate-risk and high-risk PE, which may be more useful for institutions with a PERT. We also used LVOT VTI as a continuous variable in our prediction model compared with Yuriditsky and colleagues who used a <15 cm VTI cut-point in a dichotomous model to define low LV oputput. Nonetheless, we draw the same conclusions as these authors.[11]

In consideration that our primary end point includes death and the need for advanced therapeutic interventions, elevated PASP/LVSV at the time of acute PE diagnosis could be useful in bedside decision-making for instituting treatments beyond anticoagulation if the patient has not yet declared themselves through clinical deterioration. It should be noted that left ventricular ejection fraction, a common parameter asked of the professional echocardiographer, was indistinguishable in both groups with high and low PASP/LVSV ratios and, therefore, not at all predictive of adverse outcomes. Patients with intermediate- to high-risk PE and RV dysfunction present as a heterogenous population and are the most challenging patients for decision-making by a multidisciplinary team such as a PERT. Three-fourths of the patients in our population were found to have intermediate- to high-risk PE and so PASP/LVSV may be a particularly useful risk stratification tool in this group of patients.

PESI and Bova are risk stratification scores associated with adverse outcomes but may underestimate patient acuity in certain clinical contexts of intermediate-risk PE.[21] Compared with PESI and Bova, PASP/LVSV was a better predictor of the primary outcome in this study. Although PESI and Bova require the input of multiple clinical variables that can change multiple times during a patient's initial presentation, PASP/LVSV requires just 2 echocardiographic measurements.

Limitations

Patients with low-risk PE and high-risk (massive) PE were underrepresented in our patient population and so the performance of PASP/LVSV in these patient groups could not be evaluated. The observational nature of this study and the need for a validation patient cohort to allow for algorithm generalizability introduces several biases that will require PASP/LVSV evaluation as a prognostic marker to truly illustrate its clinical utility. Lastly, although using PASP/LVSV as a risk stratification tool in acute PE is very easy and does not require multiple clincal variable input of Bova and PESI, a very important consideration is the method used to assess LVSV. If one manually traces the LVOT VTI and aortic root diameter to obtain stroke volume, interindividual variability may be apparent. As tangible proof of this concept, we asked an expert imaging cardiologist to manually assess LVSV using this method and found the correlation coefficient for aggregability to be 0.71 comparing this manual measurement to the Teichholz method of determining stroke volume for the same patient by a clinician not involved in this study, and the correlation coefficient for aggregability between the expert imaging cardiologist and the investigator in this study using a blinded random sample of patients was 0.68. Echocardiography, therefore, does require a certain degree of expertise and this should be considered by facilities with acute PE teams. We acknowledge the cut-point for maximum sensitivity/specificity by receiver operator characteristic curve analysis of PASP/LVSV in predicting the primary end point is only slightly better than Bova and PESI by area under the curve, but the benefit of using PASP/LVSV is that is relies only on 2 clinical variables rather than a complicated multivariable algorithm. This makes PASP/LVSV more practical in the critical care environment.

CONCLUSIONS

PASP/LVSV ≥1.0 mm Hg/mL is associated with an increased risk of adverse short-term outcomes in patients with acute intermediate-risk PE. This is the first study to use a calculation of simultaneous left and right heart hemodynamics to assess patients with acute PE. Further prospective studies are required to better assess utility of this measurement in those with acute PE.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S8

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SUPPLEMENTAL MATERIAL

Clinical Parameter	PASP/LVSV < 1.0 (n = 103)	PASP/LVSV ≥ 1.0 (n = 112)	P value
HR (beats/min ± SD)	107 ± 22.4	111.1 ± 20.1	0.17
SBP (mm Hg ± SD)	124.7 ± 27.3	121.1 ± 22.6	0.30
DBP (mm Hg ± SD)	75.2 ± 17.9	75.6 ± 15.5	0.86
MAP (mmHg ± SD)	90.8 ± 21.6	90.8 ± 15.9	1.00

Table S1. Hemodynamic Parameters: Baseline hemodynamic parameters were similar in the groups with lower and higher PASP/LVSV ratios. Continuous variables are presented as mean ± SD and differences between groups were evaluated by the student's *t*-test. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by *Chi*-square. HR=Heart Rate. SBP=Systolic Blood Pressure. DBP=Diastolic Blood Pressure. MAP=Mean Arterial Pressure.

Clinical profile	PASP/LVSV < 1.0 (n = 103)	PASP/LVSV > 1.0 (n = 112)	P value
Low risk	12 (11.7%)	1 (0.9%)	<0.001
Intermediate- low risk	12 (11.7%)	6 (5.4%)	0.09
Intermediate- high risk	65 (63.1%)	96 (85.7%)	<0.001
High risk	14 (13.6%)	9 (8%)	0.19

Table S2. Pulmonary Embolism Risk Stratification: The European risk stratification system was used to distinguish submassive PE with (intermediate-low risk) and without (intermediate high risk) positive cardiac biomarkers. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by *Chi*-square. PE=Pulmonary Embolism.

	No Primary Outcome (n = 121)	Had Primary Outcome (n = 94)	P value
Baseline characteristic			
Age, years (SD)	57.04 (16.50)	61.47 (13.69)	0.037
Male (%)	56 (46.3%)	49 (52.1%)	0.39
Cardiopulmonary Disease	59 (48.8%)	52 (55.3%)	0.34
History of Cancer	40 (33.1%)	26 (27.7%)	0.39
History of VTE	29 (24.0%)	22 (23.4%)	0.92
Provoked VTE	77 (63.6%)	47 (50.0%)	0.045
Saddle PE	59 (48.8%)	55 (58.5%)	0.19
Proximal DVT	75 (62.0%)	70 (74.5%)	0.035
Syncope	16 (13.2%)	16 (17.0%)	0.45
NTproBNP, median (IQR)	2146.50 (546, 4292)	3322 (1047, 7058)	0.013
Peak lactate, median (IQR)	1.80 (1.30, 3.30)	2.90 (1.70, 4.60)	0.002
Risk Scores			
PESI, mean (SD)	108.87 (39.49)	120.60 (35.74)	0.025
BOVA, mean (SD)	3.31 (1.75)	3.92 (1.40)	0.010
sPESI, mean (SD)	2.01 (1.03)	2.33 (1.10)	0.029
ESC Risk Categories, n (%)			
Low-risk	11 (9.1%)	2 (2.1%)	0.008
Low-intermediate	15 (12.4%)	3 (3.2%)	
High-intermediate	85 (70.2%)	76 (80.9%)	
High-risk	10 (8.3%)	13 (13.8%)	
Echocardiographic Parameters			
PASP/LVSV (mm Hg)	1.00 (0.46)	1.25 (0.63)	<0.001
TAPSE (cm)	1.62 (0.51)	1.49 (0.41)	0.071
RVOT VTI (cm)	11.46 (4.17)	10.27 (3.14)	0.033
LVOT VTI (cm)	17.40 (4.98)	15.53 (4.10)	0.003
RVOT acceleration time (cm/s)	65.40 (21.03)	66.23 (21.36)	0.79
RV tissue Doppler velocity (cm/s)	10.94 (3.91)	10.57 (3.18)	0.53
RV systolic notch (dimensionless)	48 (39.7%)	45 (47.9%)	0.048

Table S3. Distribution of baseline characteristics, risk scores and echocardiographic parameters between subjects who did and did not experience the primary outcome. Continuous variables are presented as mean ± SD and differences between groups were evaluated by the student's t-test. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by Chi-square. VTE = Venous thromboembolism. PE=Pulmonary Embolism.

	No Secondary Outcome (n = 118)	Had Secondary Outcome (n = 97)	P value
Baseline characteristic			
Age, years (SD)	57.92 (15.14)	60.26 (15.82)	0.27
Male (%)	54 (45.8%)	51 (52.6%)	0.32
Cardiopulmonary Disease	61 (51.7%)	50 (51.5%)	0.98
History of Cancer	39 (33.1%)	27 (27.8%)	0.41
History of VTE	27 (22.9%)	24 (24.7%)	0.75
Provoked VTE	64 (54.2%)	60 (61.9%)	0.26
Saddle PE	62 (52.5%)	52 (53.6%)	0.86
Proximal DVT	84 (71.2%)	61 (62.9%)	0.24
Syncope	18 (15.3%)	14 (14.4%)	0.89
NTproBNP, median (IQR)	2053 (508, 4748)	3256 (1136, 7058)	0.013
Peak lactate, median (IQR)	1.99 (1.50, 2.90)	2.80 (1.60, 4.60)	0.023
Risk Scores			
PESI, mean (SD)	104.28 (35.24)	125.81 (38.62)	<0.001
BOVA, mean (SD)	3.39 (1.64)	3.80 (1.60)	0.089
sPESI, mean (SD)	1.86 (1.07)	2.51 (0.96)	<0.001
ESC Risk Categories, n (%)			
Low-risk	9 (7.6%)	4 (4.1%)	0.007
Low-intermediate	11 (9.3%)	7 (7.2%)	
High-intermediate	93 (78.8%)	68 (70.1%)	
High-risk	5 (4.2%)	18 (18.6%)	
Echocardiographic Parameters			
PASP/LVSV (mm Hg)	1.03 (0.56)	1.20 (0.54)	0.020
TAPSE (cm)	1.63 (0.53)	1.48 (0.38)	0.035
RVOT VTI (cm)	11.19 (4.02)	10.68 (3.53)	0.37
LVOT VTI (cm)	17.22 (4.32)	15.82 (5.04)	0.029
RVOT acceleration time (cm/s)	66.68 (21.47)	64.52 (20.70)	0.48
RV tissue Doppler velocity (cm/s)	10.65 (3.74)	10.96 (3.45)	0.59
RV systolic notch (dimensionless)	53 (44.9%)	40 (41.2%)	0.95

Table S4. Distribution of baseline characteristics, risk scores and echocardiographic parameters between subjects who did and did not experience the secondary outcome. Continuous variables are presented as mean ± SD and differences between groups were evaluated by the student's t-test. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by Chi-square. VTE = Venous thromboembolism. PE=Pulmonary Embolism.

Mortality	PASP/LVSV < 1.0 (n = 103)	PASP/LVSV ≥ 1.0 (n = 112)	P value
Cardiac arrest	3 (2.9%)	7 (6.2%)	0.25
In hospital all cause mortality	5 (4.9%)	11 (9.8%)	0.17
Cumulative 90 day all cause mortality	10 (9.7%)	14 (12.5%)	0.52

Table S5. Patient Outcomes: Patient outcomes according to PASP/LVSV ratios. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by *Chi*-square.

Treatment	PASP/LVSV < 1.0 (n = 103)	PASP/LVSV > 1.0 (n = 112)	P value
Anticoagulation only	73 (70.9%)	61 (54.5%)	0.19
50 mg tPA	10 (9.7%)	11 (9.8%)	0.98
100 mg tPA	6 (5.8%)	12 (10.7%)	0.18
Aspiration Thrombectomy	6 (5.8%)	6 (5.4%)	0.88
Catheter Directed Thrombolysis	7 (6.8%)	13 (11.6%)	0.23
Surgical Embolectomy	1 (1%)	9 (8 %)	0.014

Table S6. Therapies Delivered: All patients were given therapeutic anticoagulation. Advanced therapies constituted: intravenous tPA administration, catheter directed therapies, and surgical embolectomy. tPA=tissue plasminogen activator. Dichotomous variables are presented as frequencies (% of population) and differences between groups were evaluated by *Chi*-square. ANOVA was used to compare all advanced therapies with PEa ≥ 1.0 with PEa < 1.0 (45.5% vs 29.1%, p value = 0.013).

Variable	Unadjusted		Multivariable-adjusted Model †	
	OR (95% CI)	P-value	OR (95% CI)	P-value
PASP/LVSV	2.46 (1.40, 4.33)	0.002	2.31 (1.27, 4.15)	0.005
RVOT VTI	0.91 (0.84, 0.99)	0.035	0.91 (0.85, 0.99)	0.046
LVOT VTI	0.91 (0.85, 0.97)	0.004	0.91 (0.85, 0.98)	0.015
PESI score (per 50 units)	1.50 (1.04, 2.16)	0.027	1.43 (0.99, 2.07)	0.055
BOVA score	1.27 (1.05, 1.53)	0.012	1.28 (1.06, 1.55)	0.010

† adjusted for proximal DVT and RV dysfunction and age (except for BOVA score and RVOT VTI)

Table S7. Primary Outcome. Univariate and adjusted multivariable logistic regression analyses of predictive scoring systems for the the secondary outcome (death, cardiac arrest, need for advanced intervention). Data are shown as Odds Ratio ± 95% C.I. with P values as noted.

Variable	Unadjusted		Multivariable-adjusted Model †	
	OR (95% CI)	P-value	OR (95% CI)	P-value
PASP/LVSV	1.82 (1.08, 3.07)	0.024	2.31 (1.05, 3.14)	0.034
RVOT VTI	0.96 (0.89, 1.04)	0.37	0.96 (0.89, 1.04)	0.35
LVOT VTI	0.93 (0.87, 0.99)	0.032	0.93 (0.87, 0.99)	0.047
PESI score (per 50 units)	2.21 (1.49, 3.27)	<0.001	2.23 (1.49, 3.33)	0.055
BOVA score	1.16 (0.97, 1.39)	0.090	1.17 (0.97, 1.40)	0.090

† adjusted for proximal DVT and RV dysfunction and age (except for BOVA score and RVOT VTI)

Table S8. Secondary Outcome: Univariate and adjusted multivariable logistic regression analyses of predictive scoring systems for the the secondary outcome (cardiac and respiratory failure)). Data are shown as Odds Ratio ± 95% C.I. with P values as noted.