Ventricular-arterial decoupling is associated with in-hospital adverse events in normotensive pulmonary embolism

Omid Kiamanesh1,2 · Graeme Prosperi-Porta3,4 · Lea Harper5 · Kevin Solverson6 · Paul Boiteau6 · Doug Helmersen5 · André Ferland6 · Nowell Fine1,2 · Jason Weatherald2,5,7

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Abstract
During acute pulmonary embolism (PE) a compensatory increase in right ventricular (RV) contractility is required to match increased afterload to maintain right ventricular-pulmonary arterial (RV-PA) coupling. The aim of this study was to assess the prognostic utility of RV-PA decoupling in acute PE. We assessed the association between measures of transthoracic echocardiography (TTE)-derived RV-PA coupling including tricuspid annular plane systolic excursion (TAPSE)/right ventricular systolic pressure (RVSP) and right ventricular fractional area change (FAC)/RVSP as well as stroke volume index (SVI)/RVSP (a measure of pulmonary artery capacitance) with adverse PE-related events (in-hospital PE-related mortality or cardiopulmonary decompensation) using logistic regression analysis. In 820 normotensive patients TTE-derived markers of RV-PA coupling were associated with PE-related adverse events. For each 0.1 mm/mmHg decrease in TAPSE/RVSP the odds of an adverse event increased by 2.5-fold [adjusted OR (aOR) 2.49, 95% confidence interval (CI) 1.46–4.24, p = 0.001], for every 0.1%/mmHg decrease in FAC/RVSP the odds of an adverse event increased by 1.4-fold (aOR 1.42, CI 1.09–1.86, p = 0.010), and for every 0.1 mL/mmHg m2 decrease in SVI/RVSP the odds of an event increased by 2.75-fold (aOR 2.78, CI 1.72–4.50, p < 0.001). In multivariable analysis, TAPSE/RVSP and SVI/RVSP were independent of other risk stratification methods including computed tomography-derived right ventricular dysfunction (RVD), the Bova score, and subjective assessment of TTE-derived RVD. In patients with normotensive acute PE, TTE-derived measures of RV-PA coupling are associated with adverse in-hospital PE-related events and provide incremental value in the risk assessment beyond computed tomography-derived RVD, the Bova score, or subjective TTE-derived RVD.

Keywords Pulmonary embolism · Transthoracic echocardiography · Right ventricular dysfunction · Right ventricle-pulmonary artery coupling

Introduction
Acute pulmonary embolism (PE) is a common cardiopulmonary disorder with a high morbidity and mortality [1]. In PE, the primary physiologic abnormality is an acute increase in pulmonary arterial pressure and right ventricular (RV)
afterload, hypoxic vasoconstriction, and neurohormonal activation [1]. A compensatory increase in RV contractility is required to match increased RV afterload and maintain right ventricular-pulmonary arterial (RV-PA) coupling. If the RV is unable to match the increased afterload, RV-PA decoupling occurs with resultant reduction of cardiac output and RV failure [2].

The 2019 European Society of Cardiology (ESC) guidelines recommend stratifying patients into high-risk (defined by the presence of hemodynamic instability), intermediate-risk (normotensive but have a simplified pulmonary embolism severity index (sPESI) of > 0 and/or evidence of RV dysfunction (RVD) and/or positive cardiac biomarkers), and low-risk (sPESI = 0 with the absence of RVD and positive cardiac biomarkers) [3]. While routine systemic thrombolysis [4], surgical embolectomy, or catheter-directed treatment are recommended in high-risk PE, the guidelines recommend against the routine use of systemic thrombolysis in low- and intermediate-risk patients unless there is hemodynamic decompensation [3–5].

Prior meta-analyses have demonstrated that RVD on transthoracic echocardiography (TTE) is associated with an increased odds of short-term mortality in both low- and intermediate-risk patients [6, 7] leading to a recommendation to consider transthoracic echocardiography (TTE) for risk stratification. However, there are no standardized echocardiographic measures to define the presence or absence of RVD and the presence of RVD has previously failed to identify a cohort of normotensive patients that benefit from thrombolysis based on the PEITHO trial [3, 5].

The prognostic importance of TTE-derived RV-PA coupling indices such as tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) and stroke volume/PASP have been recently reported [8–11]. However, questions regarding the role of RV-PA coupling in PE still exist. First, multiple TTE markers of RV-PA coupling exist which have not been directly compared to determine which is most accurate or reliable. Second, for clinical use, RV-PA coupling indices should have incremental value over other common and proven methods of risk stratification such as cardiac biomarkers [12]. RVD determined by computed tomography pulmonary angiography (CTPA) [13], the conventional definition of RVD used in the PEITHO trial [5], the Bova score [14], and an echocardiographer’s subjective evaluation of RVD on TTE.

Therefore, we aimed to evaluate the association between several candidate markers of RV-PA coupling assessed by TTE and adverse outcomes in a large cohort of normotensive patients with PE. We hypothesized that TTE markers of RV-PA decoupling would be associated with PE-related outcomes and would have incremental value when added to conventional tools used in guideline-based risk stratification in a population of normotensive patients.

Methods

Study population

This retrospective multi-site cohort study was performed at four academic hospitals in Calgary, Alberta, Canada. The methods of the study are previously reported [15, 16]. Briefly, we included all normotensive patients age ≥ 18 years admitted to hospital with PE between January 1, 2012 and March 31, 2017 who underwent TTE within 48 h of admission. We excluded patients who had: (1) hemodynamic instability on presentation, (2) diagnosis of PE > 24 h after admission, (3) no imaging confirmation of PE, (4) recurrent PE within 6 months, (5) incidental or asymptomatic PE, (6) reperfusion therapy at presentation, or (7) a palliative approach to care. The research study was approved by the health research ethics board at the University of Calgary (REB17-2368) and followed the ethical research principles outlined by the 1964 Declaration of Helsinki.

Demographics and clinical data

We collected demographic and clinical data from the electronic medical records, including age, sex, height, weight, blood pressure, heart rate, and comorbidities. Acute pulmonary embolism was confirmed by CTPA and/or nuclear medicine ventilation-perfusion scan. Laboratory variables completed within 24 h of admission were recorded including high sensitivity troponin T, N-terminal pro B-type natriuretic peptide, D-dimer, and serum lactate. Simplified pulmonary embolism severity index (sPESI) and Bova scores were calculated from hospital admission data [14, 17].

Echocardiographic variables

Comprehensive 2-dimensional and doppler echocardiogram imaging was performed as recommended by the American Society of Echocardiography using commercially available systems with a 1–5 MHz transducer (iE33; Philips Medical Systems) [18–20]. All measurements performed by a single reviewer were confirmed by a second reviewer who were both blinded to baseline patient data and outcomes with any discrepancies resolved by consensus.

RV structure and function

Using 2-D echocardiography, RV fractional area change (FAC) was calculated based on the RV end diastolic area minus the end systolic area divided by the end diastolic area. Tricuspid annular plane systolic excursion was measured using M-mode. Right ventricular systolic pressure (RVSP)
was estimated based on the sum of the right atrial pressure and the maximum systolic pressure gradient across the tricuspid valve in any view. The RVSP was used rather than PASP as pulmonary valve disease was not accounted for in this calculation. Right atrial pressure was defined based on the size and collapsibility of the inferior vena cava [18]. Right to left ventricular diameter ratio (RV/LV) was determined by the ratio of the diameters of the basal RV and left ventricle. The stroke volume was calculated by the product of left ventricular outflow tract area and its corresponding pulsed wave doppler signal trace obtained from either of the standard 3-chamber or 5-chamber views. The overall subjective assessment of RVD (defined as none, mild, moderate, or severe) was made by the interpreting echocardiographer at the time of the clinical study was collected to avoid bias introduced during quantitative measurements. The PEITHO trial definition of RVD was based on criteria outlined in the trial which included any of the following: right ventricular end-diastolic diameter > 30, right-to-left ventricular end-diastolic diameter > 0.9 (apical or subcostal 4-chamber view), hypokinesis of the right ventricular free wall (any view), or tricuspid systolic velocity > 2.6 m/s [5].

**RV-PA coupling**

We evaluated RV-PA coupling using the TAPSE/RVSP ratio, which has been shown to have prognostic value and to correlate with invasive pressure—volume catheter measurements in other conditions of RV overload [21–25]. We also calculated FAC/RVSP as secondary measure of RV-PA coupling. We evaluated pulmonary artery capacitance using the ratio of stroke volume index (SVI)/RVSP, which has been previously validated to correlate with invasive pulmonary artery capacitance during right heart catheterization [26].

**Outcomes**

The primary composite outcome was in-hospital PE-related mortality or cardiopulmonary decompensation, defined as systolic blood pressure < 90 mmHg for > 15 min, administration of catecholamines for hypotension, endotracheal intubation, rescue thrombolysis or cardiopulmonary resuscitation. Secondary outcomes included PE-related mortality and all-cause mortality. All events were independently adjudicated by two authors and disagreements were resolved by consensus.

**Statistical analysis**

Continuous variables are reported as mean ± standard deviation if normally distributed or median (interquartile range (IQR)) if nonnormally distributed. The Shapiro–Wilk test was used to determine normality. Categoric variables are reported as absolute and relative frequencies. Continuous variables were compared using the t-test or Wilcoxon rank-sum test for normally and nonnormally distributed populations, respectively. Categoric variables were compared using the chi-squared test. The relationship between echocardiographic parameters and the primary outcome was evaluated using logistic regression analyses, unadjusted and adjusted for age and sex with a multiple imputation model to account for missing cases using 20 imputations. A multivariable logistic regression analysis was performed on complete cases to assess whether RV-PA coupling parameters had incremental value over other risk stratification methods including RVD determined by CTPA, the Bova score [14], and an echocardiographer’s subjective evaluation of RVD on TTE. The diagnostic performance of TAPSE/RVSP, FAC/RVSP, and SVI/RVSP was examined using a receiver operating characteristic curve analysis. The Youden Index (value yielding the maximum sum of sensitivity and specificity) was determined for each RV-PA variable to calculate the diagnostic performance characteristics for each variable [27]. All statistical analyses were performed with Stata Statistical Software (version 17.0; StataCorp, College Station, TX). A two-tailed probability value of < 0.05 was deemed statistically significant.

**Results**

**Study cohort**

A total of 2067 patients were diagnosed with normotensive pulmonary embolism during the study period, of which 820 underwent TTE within 48 h of diagnosis and were therefore included in the present analysis (Fig. 1). From the overall PE cohort, patients with an SPESI score > 0 were more likely to undergo TTE (864/1628 vs 199/439, p = 0.004). Patients with RVD on CTPA (defined as an RV/LV ≥ 1.0) were more likely to undergo TTE (728/1188 vs 247/718, p < 0.001). Only 4 patients did not have a CTPA or TTE to assess for RVD. No patients were lost to follow-up. The median age was 62 (50–74) years and 391 (47.7%) were female (Table 1). A total of 26 (3.2%) patients had a primary PE-related adverse event. Of these, 11 (42.3%) had PE-related mortality and 15 had hemodynamic decompensation (57.7%) of which 7 received rescue thrombolysis. An additional 10 (1.2%) patients died from non-PE related etiologies during hospitalization.

There were no differences in the patient age, sex, comorbidities, or symptoms between patients with and without an event. There was no difference in heart rate, blood pressure, or the need for supplemental oxygen between patients with and without an event. Most patients were diagnosed by CTPA. The sPESI score was ≥ 1 in 80.5% of those without...
an event and 100% in those with an event (p = 0.01). The Bova score and stages [14] were higher in patients with an event than those without (p < 0.001).

**Echocardiographic findings**

Echocardiographic findings are shown in Table 2. Echocardiography was performed sooner for those who experienced a primary outcome event (6.3 h, IQR 1.0–15.0 vs. 17 h, IQR 8.1–25.6; p < 0.001). Tricuspid annular plane systolic excursion, SVI, and FAC were all lower in patients with an event compared to those without (all had p < 0.001). Right ventricular systolic pressure (p < 0.001) and RV/LV (p = 0.002) were greater in patients with an event compared to those without. Patients with an event had lower TAPSE/RVSP, FAC/RVSP, and SVI/RVSP compared to those without an event (all had p < 0.001). Patients with an event were more likely to have subjective RVD determined by the initial clinical reading echocardiographer (p < 0.001).

**Ventricular-arterial coupling**

Echocardiography-derived RV-PA coupling parameters were strongly associated with PE-related adverse events, PE-related mortality, and all-cause mortality (Table 3). When accounting for missing data using a multiple imputation model, RV-PA coupling parameters remained associated with PE-related adverse events. Neither the PEITHO trial definition of RVD (OR 1.61, 95% CI 0.55–4.74; p = 0.385; n = 813) nor high sensitivity troponin T (OR 1.00, 95% CI 0.997–1.002; n = 705) were associated with PE-related adverse events. In multivariable analysis with subjective TTE-derived RVD, CTPA RV/LV ratio, and the Bova score, only TAPSE/RVSP (p = 0.044) and SVI/RVSP (p = 0.002) were independently associated with PE-related adverse events while FAC/RVSP was not (p = 0.308) (Table 4).

Receiver operating characteristic analysis was performed to assess the diagnostic performances of TAPSE/RVSP, SVI/RVSP, FAC/RVSP (Fig. 2). The area under curve (AUC) for TAPSE/RVSP was 0.81 (CI 0.68–0.87), SVI/RVSP was 0.89 (CI 0.83–0.96), and FAC/RVSP 0.77 (CI 0.64–0.90). SVI/RVSP had a higher AUC than FAC/RVSP (p < 0.01), RV/LV (p = 0.01), RVFAC (p = 0.03), and RVSP (p < 0.001) while FAC/RVSP and TAPSE/RVSP had a higher AUC than RVSP (both had p < 0.001). There was no difference between FAC/RVSP and TAPSE/RVSP (p = 0.678). The diagnostic performance indices for each RV-PA coupling variable are shown in Table 5. There was no difference in the diagnostic performance indices between each RV-PA variable although confidence intervals were large.

**Discussion**

This study showed that TTE-derived estimates of RV-PA coupling including FAC/RVSP, and TAPSE/RVSP and SVI/RVSP were associated with PE-related adverse events in normotensive patients with PE. The RV-PA coupling parameters TAPSE/RVSP and SVI/RVSP had incremental value to the Bova score, CTPA RV/LV ratio, and subjective assessment of TTE-derived RVD in discriminating PE-related adverse events. These findings provide important insights into the importance of RV-PA coupling in the pathophysiology of hemodynamic decompensation in PE.
Additionally, it underscores the challenges in identifying a universal TTE-derived prognostic marker to risk stratify normotensive patients, who represent a significant proportion of patients with PE. This is the first study to assess the association of multiple parameters of RV-PA coupling with PE-related adverse events in the same cohort of patients and directly compare its utility against other markers RVD and risk stratification tools. Importantly, this study showed that in multivariable

### Table 1 Baseline characteristics of patients with normotensive acute pulmonary embolism

|                                | All (n = 820) | Free from PE-related event (n = 794) | PE-related event (n = 26) | p value  |
|--------------------------------|--------------|-------------------------------------|--------------------------|---------|
| **Demographics**               |              |                                     |                          |         |
| Age, years; median (IQR)       | 62 (50–74)   | 62 (50–75)                          | 56 (47–67)               | 0.12    |
| Female sex                     | 391 (47.7%)  | 383 (48.2%)                         | 8 (30.8%)                | 0.08    |
| **Comorbidities**              |              |                                     |                          |         |
| Prior venous thromboembolism   | 158 (19.3%)  | 153 (19.3%)                         | 5 (19.2%)                | 0.99    |
| Lung disease                   | 164 (20.0%)  | 156 (19.7%)                         | 8 (30.8%)                | 0.16    |
| Heart disease                  | 145 (17.7%)  | 140 (17.6%)                         | 5 (19.2%)                | 0.83    |
| Malignancy                     | 97 (11.8%)   | 93 (11.7%)                          | 4 (15.4%)                | 0.57    |
| Diabetes                       | 126 (15.4%)  | 120 (15.1%)                         | 6 (23.1%)                | 0.27    |
| Chronic kidney disease         | 57 (7.0%)    | 55 (6.9%)                           | 2 (7.7%)                 | 0.88    |
| **Symptoms**                   |              |                                     |                          |         |
| Dyspnea                        | 671 (83.8%)  | 647 (83.5%)                         | 24 (92.3%)               | 0.23    |
| Chest pain                     | 393 (47.9%)  | 380 (47.9%)                         | 10 (38.5%)               | 0.83    |
| Syncope                        | 81 (9.9%)    | 79 (10.0%)                          | 2 (7.7%)                 | 0.70    |
| DVT symptoms                   | 10 (1.3%)    | 10 (1.4%)                           | 0 (0.0%)                 | 0.56    |
| **Clinical findings**          |              |                                     |                          |         |
| Heart rate, bpm; median (IQR)  | 96 (83–112)  | 96 (83–112)                         | 94 (78–110)              | 0.48    |
| Systolic blood pressure, mmHg; | 128 (116–143)| 128 (116–143)                       | 120 (113–138)            | 0.08    |
| Diastolic blood pressure, mmHg;| 80 (70–89)   | 80 (70–89)                          | 79 (68–86)               | 0.40    |
| Supplemental oxygen            | 425 (51.8%)  | 411 (51.8%)                         | 14 (53.8%)               | 0.83    |
| Atrial fibrillation            | 49 (6.0%)    | 47 (5.9%)                           | 2 (7.7%)                 | 0.71    |
| BSA, m²; median (IQR)          | 2 (1.8–2.2)  | 2 (1.8–2.2)                         | 2.2 (1.9–2.3)            | 0.10    |
| **Laboratory findings**        |              |                                     |                          |         |
| NT-proBNP, ng/L; median (IQR); | 1734 (407–4396); 187 | 1804 (407–4447); 183 | 739 (345–1774); 4 | 0.34 |
| Troponin, ng/L; median (IQR);  | 36 (12–95); 705 | 36 (12–95); 679 | 37 (8–101); 4 | 0.64 |
| D-dimer, mg/L; median (IQR); n | 4 (1.7–7.3); 475 | 4 (1.7–7.3); 458 | 2.8 (1.5–5.7); 17 | 0.67 |
| Lactate, mmol/L; median (IQR); | 1.7 (1.2–2.4); 299 | 1.7 (1.2–2.3); 288 | 1.5 (0.9–7.2); 11 | 0.96 |
| **Diagnostic method**          |              |                                     |                          |         |
| CTPA                           | 750 (91.5%)  | 724 (91.2%)                         | 26 (100%)                | 0.28    |
| Ventilation-perfusion scan     | 70 (8.5%)    | 70 (8.8%)                           | 0 (0%)                   |         |
| Diagnosis to echo, hours; median (IQR) | 17 (8.1–25.6) | 17 (8.8–26.0) | 6.3 (1.0–15.0) | <0.001 |
| Echo to event, hours; median (IQR) | 23 (6–60) | – | 23 (6–60) | – |
| **Risk stratification**        |              |                                     |                          |         |
| Simplified PESI                |              |                                     |                          |         |
| 0                              | 155 (18.9%)  | 155 (19.5%)                         | 0 (0%)                   | 0.01    |
| ≥ 1                            | 665 (81.1%)  | 639 (80.5%)                         | 26 (100%)                |         |
| Bova score (IQR)               | 4 (2–4)      | 4 (2–4)                             | 5 (4–5)                  | 0.001   |
| Bova stage                     |              |                                     |                          |         |
| 1                              | 272 (41.8%)  | 271 (43.2%)                         | 1 (4.2%)                 | <0.001  |
| 2                              | 236 (36.3%)  | 227 (36.2%)                         | 9 (37.5%)                |         |
| 3                              | 143 (22.0%)  | 129 (20.6%)                         | 14 (58.3%)               |         |

*BSA* body surface area, *CTPA* computed tomography pulmonary angiography, *DVT* deep vein thrombosis, *IQR* interquartile range, *n* number of patients with measurements, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *PESI* pulmonary embolism severity index
analysis with CTPA-derived RV/LV, the Bova score and subjective TTE assessment of RVD, SVI/RVSP and TAPSE/RVSP were both independently associated with PE-related adverse events. This suggests that RV-PA coupling has additive prognostic value beyond RVD identified by CTPA or clinical risk prediction scores, and it underscores the importance of quantitative assessment of RVD over subjective assessment alone. We also demonstrated that the conventional definition of RVD used in the PEITHO trial was not associated with adverse PE-related events in our population, while quantitative TTE measures including RV-PA coupling indices were strongly associated. Conventional definitions of RVD are highly prevalent in this population, being present in 37% of patients with normotensive PE. This emphasizes the importance of more specific tools for identifying patients at heightened risk of adverse events [6]. This may be one reason that the PEITHO trial was unable to show a net benefit from systemic thrombolysis [5]. It suggests that future trials of thrombolysis or invasive catheter directed therapies may need to use a different definition for TTE-derived RVD that is more strongly associated with adverse events.

Ciurzyński et al. was the first to evaluate an RV-PA coupling parameter in PE using a stepwise approach to risk stratification with TAPSE < 20 mm followed by the

### Table 2  Imaging findings of patients with normotensive acute pulmonary embolism

|                        | All (n = 820) | Free from PE-related event (n = 794) | PE-related event (n = 26) | p value |
|------------------------|--------------|--------------------------------------|--------------------------|---------|
| **Computed tomography pulmonary angiography** |              |                                      |                          |         |
| RV/LV diameter ratio; median (IQR), n              | 1.2 (0.9–1.6); 753 | 1.2 (0.9–1.6); 729 | 1.9 (1.6–2.1); 24 | <0.001  |
| **RV structure** |              |                                      |                          |         |
| RV/LV base diameter ratio; median (IQR), n            | 1.1 (0.9–1.3); 643 | 1.1 (0.9–1.3); 628 | 1.3 (1.1–1.4); 15 | 0.002  |
| RV base diameter, cm; median (IQR), n                 | 4.2 (3.7–4.9); 647 | 4.3 (3.7–4.8); 632 | 4.5 (4.2–5.2); 15 | 0.07   |
| RV diastolic area, cm²; median (IQR), n               | 27.9 (22.5–33.8); 632 | 27.8 (22.4–33.7); 616 | 31.7 (28.0–38.7); 16 | 0.02   |
| RV systolic area, cm²; median (IQR), n                | 18.4 (13.5–24.8); 632 | 18.3 (13.4–24.5); 616 | 26.0 (21.0–31.9); 16 | <0.001  |
| **RV function** |              |                                      |                          |         |
| TAPSE, mm; median (IQR), n                          | 18.7 (14.9–22.6); 763 | 18.8 (15–22.8); 740 | 13 (9.8–18.1); 23 | <0.001  |
| FAC, %; median (IQR), n                            | 33.9 (23.8–42.5); 632 | 34.2 (23.9–42.6); 616 | 26.1 (21.1–31.9); 16 | <0.001  |
| **Subjective right ventricular dysfunction** |              |                                      |                          |         |
| None                                   | 345 (43.8%) | 343 (44.8%) | 2 (8.7%) | <0.001  |
| Mild                                  | 158 (20.1%) | 156 (20.4%) | 2 (8.7%) |         |
| Moderate                               | 213 (27.0%) | 205 (26.8%) | 8 (34.8%) |         |
| Severe                                | 72 (9.1%)   | 61 (8.0%)   | 11 (47.8%) |         |
| **Additional findings**                |              |                                      |                          |         |
| McConnell’s sign                       | 32 (3.9%)   | 29 (3.7%)   | 3 (11.5%) | 0.04    |
| Cardiac thrombus                      | 19 (2.3%)   | 15 (1.9%)   | 4 (15.4%) | <0.01   |
| **PEITHO right ventricular dysfunction** | 636 (77.5%) | 614 (77.3%) | 22 (84.6%) | 0.38    |
| **Pulmonary pressures**               |              |                                      |                          |         |
| RA pressure (mmHg)                     |              |                                      |                          |         |
| 3                                     | 265 (32.7%) | 263 (33.5%) | 2 (8.0%) | 0.03    |
| 8                                     | 266 (32.8%) | 260 (33.0%) | 6 (24.0%) |         |
| 15                                    | 237 (29.2%) | 222 (28.3%) | 15 (60.0%) |         |
| Indeterminate                         | 42 (5.2%)   | 40 (5.1%)   | 2 (8.0%)  |         |
| RVSP, mmHg; median (IQR), n            | 44 (33.8–55.7); 603 | 43.1 (33.7–55.1); 585 | 60.9 (50.2–68.7); 18 | <0.001  |
| **Cardiac output**                    |              |                                      |                          |         |
| Stroke volume, mL; median (IQR), n     | 57.4 (45.4–69.4); 723 | 57.9 (46.3–69.7); 705 | 34.4 (30.1–41.6); 18 | <0.001  |
| SVI, mL/m²; median (IQR), n           | 28.2 (22.8–34.7); 723 | 28.5 (22.9–35.5); 705 | 17.6 (15.5–20.0); 18 | <0.001  |
| **RV-PA coupling**                    |              |                                      |                          |         |
| TAPSE/RVSP, mm/mmHg; median (IQR), n   | 0.40 (0.28–0.59); 572 | 0.41 (0.28–0.59); 556 | 0.21 (0.17–0.31); 16 | <0.001  |
| FAC/RVSP, %/mmHg; median (IQR), n      | 0.67 (0.45–1.09); 493 | 0.68 (0.46–1.10); 480 | 0.34 (0.27–0.65); 13 | <0.001  |
| SVI/RVSP, mL/mmHg; median (IQR), n     | 0.63 (0.43–0.93); 583 | 0.65 (0.44–0.92); 566 | 0.26 (0.23–0.35); 17 | <0.001  |

FAC fractional area change, IQR interquartile range, n number of patients with measurement, RVSP right ventricular systolic pressure, RV/LV right to left ventricular diameter ratio, TAPSE tricuspid annular plane systolic excursion, TR tricuspid regurgitation, TTE transthoracic echocardiogram
ratio of tricuspid regurgitation peak gradient divided by TAPSE [8]. More recently, studies by Kamran et al. evaluated PASP divided by left ventricular stroke volume and Lyhne et al. and Falsetti et al. evaluated TAPSE/PASP showing that these markers were associated with adverse outcomes in PE [9–11]. Kamran et al. concluded

| Table 3 | Logistic regression analysis of ventricular-arterial coupling parameters for composite PE-related adverse events, PE-related mortality, and all-cause mortality |
|-------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Number of patients | Crude OR | 95% CI | p value | Adjusted OR | 95% CI | p value |
| **Composite PE-related event** |
| TAPSE/RVSP (per 0.1 mm/mmHg decrease) | 572 | 2.47 | 1.47–4.14 | 0.001 | 2.49 | 1.46–4.24 | 0.001 |
| SVI/RVSP (per 0.1 mL/mmHg m² decrease) | 583 | 2.77 | 1.73–4.43 | <0.001 | 2.78 | 1.72–4.50 | <0.001 |
| FAC/RVSP (per 0.1%/mmHg decrease) | 493 | 1.43 | 1.10–1.87 | 0.008 | 1.42 | 1.09–1.86 | 0.010 |
| **PE-related mortality** |
| TAPSE/RVSP (per 0.1 mm/mmHg decrease) | 572 | 2.97 | 1.18–7.49 | 0.021 | 2.88 | 1.16–7.12 | 0.022 |
| SVI/RVSP (per 0.1 mL/mmHg m² decrease) | 583 | 2.96 | 1.32–6.64 | 0.008 | 2.98 | 1.32–6.70 | 0.008 |
| FAC/RVSP (per 0.1%/mmHg decrease) | 493 | 1.27 | 1.00–1.61 | 0.016 | 1.28 | 1.00–1.64 | 0.052 |
| **All-cause mortality** |
| TAPSE/RVSP (per 0.1 mm/mmHg decrease) | 572 | 1.87 | 1.19–2.92 | 0.007 | 1.84 | 1.18–2.86 | 0.007 |
| SVI/RVSP (per 0.1 mL/mmHg m² decrease) | 583 | 1.44 | 1.11–1.89 | 0.007 | 1.46 | 1.12–1.92 | 0.006 |
| FAC/RVSP (per 0.1%/mmHg decrease) | 493 | 1.31 | 1.01–1.71 | 0.039 | 1.33 | 1.01–1.75 | 0.039 |
| **Multiple imputation model composite PE-related event** |
| TAPSE/RVSP (per 0.1 mm/mmHg decrease) | 820 | 1.70 | 1.23–2.33 | 0.001 | – | – |
| SVI/RVSP (per 0.1 mL/mmHg m² decrease) | 820 | 1.58 | 1.23–2.01 | <0.001 | – | – |
| FAC/RVSP (per 0.1%/mmHg decrease) | 820 | 1.21 | 1.01–1.45 | 0.043 | – | – |

Multiple imputation model using 20 imputations

CI confidence interval, FAC fractional area change, OR odds ratio, PE pulmonary embolism, RVSP right ventricular systolic pressure, SVI stroke volume index, TAPSE tricuspid annular plane systolic excursion

| Table 4 | Univariable and multivariable logistic regression analysis for PE-related of RV-PA coupling parameters compared to subjective assessment of RVD, the Bova score, and the CT RV/LV ratio |
|-------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Number of patients | OR | 95% CI | p value |
| **Univariable** |
| Subjective right ventricular dysfunction (per unit increase) | 788 | 3.41 | 2.07–5.60 | <0.001 |
| Bova Score (per unit increase) | 650 | 1.92 | 1.39–2.66 | <0.001 |
| CTPA RV/LV ratio (per unit increase) | 755 | 8.88 | 3.58–22.03 | <0.001 |
| **Multivariable** |
| TAPSE/RVSP (per 0.1 mm/mmHg decrease) | 448 | 1.91 | 1.02–3.58 | 0.044 |
| Subjective right ventricular dysfunction (per unit increase) | 1.70 | 0.72–4.04 | 0.226 |
| Bova Score (per unit increase) | 1.17 | 0.68–4.04 | 0.226 |
| CTPA RV/LV ratio (per unit increase) | 2.18 | 0.41–11.63 | 0.361 |
| SVI/RVSP (per 0.1 mL/mmHg m² decrease) | 457 | 2.21 | 1.35–3.61 | 0.002 |
| Subjective right ventricular dysfunction (per unit increase) | 1.64 | 0.71–3.80 | 0.248 |
| Bova Score (per unit increase) | 1.12 | 0.65–1.93 | 0.673 |
| CTPA RV/LV ratio (per unit increase) | 2.10 | 0.37–12.00 | 0.405 |
| FAC/RVSP (per 0.1%/mmHg decrease) | 386 | 1.17 | 0.87–1.58 | 0.308 |
| Subjective right ventricular dysfunction (per unit increase) | 1.73 | 0.69–4.34 | 0.240 |
| Bova Score (per unit increase) | 1.11 | 0.63–1.94 | 0.717 |
| CTPA RV/LV ratio (per unit increase) | 2.66 | 0.45–15.68 | 0.280 |

CTPA RV/LV computed tomography right to left ventricular diameter ratio, FAC fractional area change, OR odds ratio, PE pulmonary embolism, RVD right ventricular dysfunction, RVSP right ventricular systolic pressure, SVI stroke volume index, TAPSE tricuspid annular plane systolic excursion

Adjusted for age and sex
that PASP/left ventricular stroke volume was superior to the velocity time integral (VTI) although this was done comparing continuous odds ratios with different units [9]. However, Falsetti et al. found no difference in the association with adverse outcomes between TAPSE/PASP and VTI when comparing categorical odds ratios. Similarly, Lyhne et al. showed that TAPSE/PASP was superior to TAPSE in a pulmonary embolism response team (PERT) activation patient population including 105/627 high-risk patients [11]. However, when excluding PERT-related clinical decision making, TAPSE/PASP was no longer independent of TAPSE alone, and a comparison between TAPSE/PASP and TAPSE was not performed in their cohort after excluding high-risk patients. In our study we showed that in normotensive patients RV-PA coupling parameters may have superior diagnostic performance compared to some TTE variables, but no RV-PA coupling parameter was superior to TAPSE. While this analysis was limited in our population due to low event rates leading to wide confidence intervals, it suggests that we may be

![Fig. 2 ROC curves describing the diagnostic performance of FAC/RVSP, TAPSE/RVSP, SVI/RVSP, TAPSE, RV/LV, RVFAC, and RVSP to identify a pulmonary embolism-related mortality or hemodynamic decompensation among patients with normotensive PE. AUC for each variable and the associated p values for each comparison are shown.](image)

### Table 5: Diagnostic performance characteristics for TTE-derived measures of right ventricular dysfunction

| TTE parameter and Youden Index | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | PPV (%) (95% CI) | NPV (%) (95% CI) | Positive LR (95% CI) | Negative LR (95% CI) |
|--------------------------------|--------------------------|--------------------------|-----------------|-----------------|----------------------|---------------------|
| TAPSE/RVSP < 0.29 mm/mmHg      | 75.0 (47.6–92.7)         | 72.1 (68.2–75.8)         | 7.2 (3.8–12.2)  | 99.0 (97.5–99.7) | 2.7 (2.0–3.7)        | 0.3 (0.1–0.8)       |
| SVI/RVSP < 0.36 mL/m²          | 82.4 (56.6–96.2)         | 78.8 (75.4–82.0)         | 9.7 (5.4–15.7)  | 99.4 (98.2–99.9) | 3.9 (3.0–5.1)        | 0.2 (0.1–0.6)       |
| FAC/RVSP < 0.35%/mmHg          | 69.2 (38.6–90.9)         | 86.3 (82.8–89.2)         | 12.0 (5.6–21.6) | 99.0 (97.6–99.7) | 5.0 (3.3–7.7)        | 0.4 (0.2–0.8)       |

**FAC** fractional area change, **LR** likelihood ratio, **NPV** negative predictive value, **PPV** positive predictive value, **RVSP** right ventricular systolic pressure, **SVI** stroke volume index, **TTE** transthoracic echocardiogram
reaching a ceiling effect for using single prognostic TTE variables in normotensive patients.

It is unlikely that identifying an incrementally superior single TTE-derived marker of RVD will dramatically change outcomes of risk stratification. Instead, current guidelines appropriately promote a multimodality approach using clinical, biochemical, and radiologic markers of risk [3]. We did not directly compare markers of RV-PA coupling with other quantitative measures of RVD due to lack of statistical power for meaningful comparisons and because most of the quantitative measures of RVD in this study are components of the RV-PA parameters.

As pulmonary vascular resistance increases, there is an inverse nonlinear decrease in pulmonary arterial compliance [28]. In turn, this results in an exaggerated RV pulsatile load, RV ejection pressure, and increased RV stroke work, all of which contribute to RV failure [29, 30]. The cardiovascular system operates in a dynamic state whereby ventricular contractility is coupled with arterial afterload, otherwise known as ventricular-arterial coupling. Accordingly, in response to increased pulmonary artery pressures, the RV undergoes adaptive changes to increase contractility and preserve RV-PA coupling. RV-PA decoupling occurs when the RV contractility fails to match arterial afterload resulting in RV failure and hemodynamic decompensation thereafter. In the case of PE, this may result from excessive arterial elastance, direct impairment of RV contractility by cardiac ischemia, and the harmful RV-LV interaction whereby abnormal septal motion impairs left ventricular filling and left sided stroke volume [15]. The fact that TAPSE/RVSP, FAC/RVSP, and SVI/RVSP were all strongly associated with PE-related adverse events strengthens the finding that RV-PA decoupling is implicated in the pathophysiology of hemodynamic decompensation. SVI uniquely measures the most downstream hemodynamic effect of a PE, which not only decreases during RV-PA decoupling but also when left ventricular filling is impaired due to abnormal septal movement towards the left ventricle.

Indices of RV-PA coupling including SVI/RVSP, FAC/RVSP, and TAPSE/RVSP were strongly associated with adverse in-hospital PE-related events in patients with normotensive PE. TAPSE, RV/LV and RVSP are simple measurements that are easily obtainable during standard TTE. While FAC/RVSP was associated with adverse PE-related events, FAC requires accurate RV endocardial contouring in both systole and diastole which may be difficult to perform reliably in clinical practice. The RV can be particularly challenging to accurately image due to its asymmetric shape and is prone to off axis imaging which may falsely estimate its function. The utility of direct assessment of RV size and function may be more limited due to these factors. Another challenge can be in obtaining a complete doppler signal to calculate the RVSP. In this study, RVSP could be determined in only 603 patients, FAC was only possible in 632 patients compared to TAPSE that was measurable in 763 patients and SVI that was measurable in 795 patients. These RV-PA coupling parameters represent multiple potential measurements that can be obtained during a standard TTE to identify normotensive patients at higher risk of PE-related mortality or hemodynamic decompensation. These parameters could have the potential to enrich future clinical trials of invasive therapies (i.e. thrombolytic therapy or catheter directed therapies) with truly intermediate-high risk patients. Future prospective prognostic studies are required to determine the feasibility of performing these measurements and validate these retrospective findings.

This study has several limitations. Our cohort had only 26 adverse PE-related events (3.2%). This is in part due to the more stringent definition of PE-related mortality rather than all-cause mortality. In our study, markers of RV-PA coupling were less associated with all-cause mortality than PE-related mortality. This is because all-cause mortality is less related to the underlying pathophysiologic mechanism of mortality in PE and is therefore likely of less suitable outcome than PE-related mortality when evaluating echocardiographic measurements. However, our event rates are similar to other unselected PE populations of normotensive patients assessing RV-PA coupling such as Ciurzyński et al. where 8/400 (2%) PE-related death or hemodynamic decompensation [8] and Falsetti et al. where 10/256 (3.9%) had in-hospital mortality [10]. Data collection was retrospective and some TTE parameters were unavailable as they were not recorded routinely but at the discretion of the echocardiography technologist. At least one of FAC/RVSP, TAPSE/RVSP, or SVI/RVSP was only possible in 599/820 (73%) of patients. This means that in 27% of patients another simpler marker of TTE-derived RVD must be used. This seems consistent with Kamran et al. who reported that only 215/343 (63%) patients that met inclusion had complete data [9, 10]. Although we found that RV-PA coupling parameters were independent of Bova score, CTPA RV/LV and subjective RVD, incomplete data limited the strength of these analyses and it was not possible to perform a statistically robust multiple imputation model for multivariable analyses[31]. Because performing a TTE was at the discretion of the attending physician, only 1163/2067 patients with a PE underwent TTE. We did find evidence of selection bias where patients were more likely to undergo TTE if they had an SPESI score > 0 and if they had RVD on CTPA. This selection bias is unfortunately unavoidable in retrospective studies assessing the prognostic value of RVD on TTE. While this selection bias may increase the severity of disease in our cohort, we saw relatively low event rates in comparison to other cohorts of normotensive PE.
Additionally, only 4/2067 patients did not undergo assessment of RVD (TTE or CTPA) which represents a cohort where risk stratification followed current guideline recommendations [3].

Conclusion

In patients with normotensive acute pulmonary embolism, TTE-derived RV-PA coupling parameters including TAPSE/RVSP and FAC/RVSP and SVI/RVSP were associated with adverse in-hospital PE-related events with TAPSE/RVSP and SVI/RVSP being independent of CTPA RV/LV, the Bova score, and subjective TTE assessment of RVD. Future prospective studies evaluating TTE-derived RVD including markers of RV-PA coupling are required to validate these findings and identify whether a single or multivariable approach is most valuable for prognostication of PE-related adverse events using TTE.

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