

Prognostic implication of noninvasive right ventricle-to-pulmonary artery coupling in chronic thromboembolic pulmonary hypertension

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Abstract

Aims: Impairment of right ventricle-to-pulmonary artery coupling (RV-PA coupling) is a major determinant of poor prognosis in patients with pulmonary hypertension. This study sought to evaluate the ability of an echo-derived metric of RV-PA coupling, the ratio between tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery systolic pressure (PASP) and to predict adverse clinical outcomes in chronic thromboembolic pulmonary hypertension (CTEPH).

Methods and results: A total of 205 consecutive patients with confirmed CTEPH were retrospectively recruited from Fuwai Hospital between February 2016 and November 2020. Baseline echocardiography, right heart catheterization, and cardiopulmonary exercise testing were analyzed. Patients with lower TAPSE/PASP had a significantly compromised echocardiographic and hemodynamic status and exercise capacity at baseline. The TAPSE/PASP ratio correlated significantly with hemodynamic parameters, including pulmonary vascular resistance ($r = -0.48$, $p < 0.001$) and pulmonary arterial compliance ($r = 0.45$, $p < 0.001$). During a median period of 1-year follow-up, 63 (30.7%) patients experienced clinical worsening. The relationship between TAPSE/PASP and clinical worsening was assessed using different multivariate Cox regression models. After adjustment for a series of previously screened independent predictors, TAPSE/PASP remained significantly associated with outcomes, and the hazard ratio (per standard deviation increase) of the final model was 0.402.

Conclusion: In patients with CTEPH, baseline RV-PA coupling measured as the TAPSE/PASP ratio is associated with disease severity and adverse outcomes. A low TAPSE/PASP identifies patients with a high risk of clinical deterioration, and this novel metric could be applicable for risk stratification in CTEPH.

Keywords: chronic thromboembolic pulmonary hypertension, right ventricular dysfunction, echocardiology, right ventricle-to-pulmonary artery coupling

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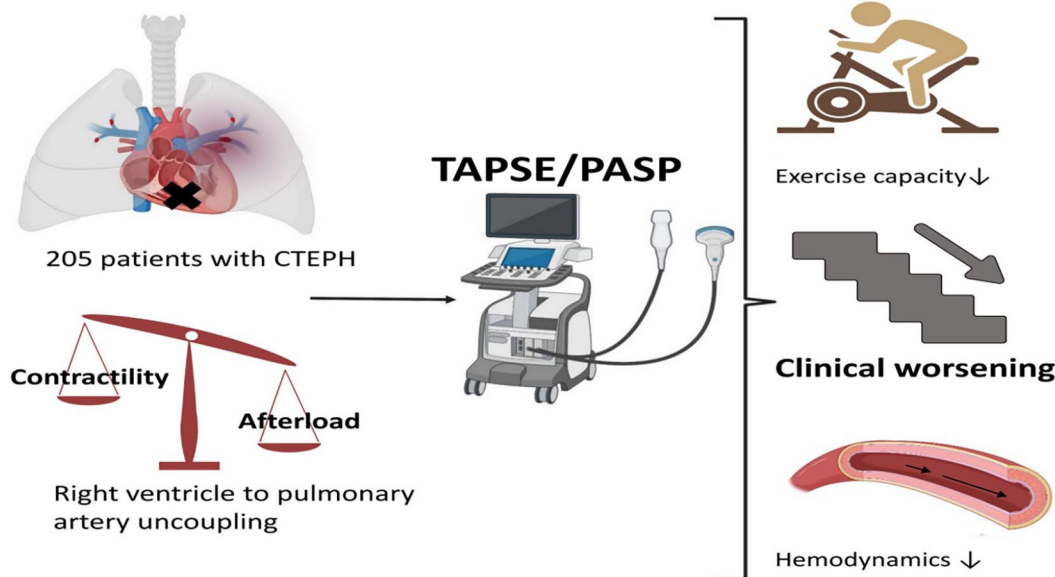
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Graphical abstract

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening but potentially curable subtype of pulmonary hypertension (PH) that occurs in approximately 3.4% of patients after acute pulmonary embolism (PE).¹ CTEPH is characterized by mismatched perfusion defects, persistent fibrothrombotic obstruction, and elevated mean pulmonary arterial pressure (mPAP).² In the early stage of CTEPH, mild elevation in afterload leads to adaptive hypertrophy in the right ventricle (RV), allowing for temporary preservation of cardiac output (CO; homeometric adaptation). However, the prolonged overloaded RV fails to increase contractility proportionally to the further elevated afterload and eventually uncouples from the pulmonary circulation. Prognosis of PH largely depends on RV function, especially its contractility, to compensate for the afterload. It has been appreciated in recent years that RV-pulmonary artery (PA) uncoupling, which refers to a mismatch between RV contractility and its afterload, may serve as an early marker of right ventricular dysfunction.³ Thus, assessment of RV-PA coupling is of pathophysiological importance in PH.

Traditionally, RV-PA coupling has been invasively measured through pressure–volume loop (P–V loop) analysis as the ventricular elastance

(Ees) over arterial elastance (Ea) ratio. Recently, the ratio of tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) derived from echocardiography has been validated as a reliable surrogate of invasively measured Ees/Ea in PH.⁴ As a combination of two readily available echocardiographic parameters, TAPSE/PASP integrates changes in RV contractility and afterload and therefore investigates the RV and pulmonary circuit as a unit. Guazzi *et al.*⁵ demonstrated that TAPSE/PASP was able to predict adverse clinical outcomes in heart failure (HF). Subsequently, the functional and prognostic relevance of TAPSE/PASP has also been identified in pulmonary arterial hypertension (PAH),⁶ PAH associated with connective tissue diseases,^{7,8} PH secondary to chronic lung disease,⁹ acute PE,¹⁰ and patients undergoing transcatheter valve procedures.^{11,12} Nevertheless, the prognostic implication of TAPSE/PASP remains unclear in patients with CTEPH.

Therefore, the current retrospective study aimed to evaluate the potential prognostic value of the TAPSE/PASP ratio in patients with CTEPH and its associations with parameters derived from cardiopulmonary exercise testing (CPET) and right heart catheterization (RHC). We hypothesized that patients with a reduced TAPSE/PASP ratio would have an increased risk of clinical worsening.

Methods

Study population

Consecutive patients diagnosed with CTEPH according to the latest guidelines¹³ at Fuwai Hospital in Beijing, China, from February 2016 to November 2020 were retrospectively screened for enrollment. The inclusion criteria were as follows: (1) baseline echocardiographic evaluation with available TAPSE and PASP; (2) RHC within 3 months of baseline echocardiogram; and (3) age between 18 and 80 years. Demographic data, physical examination, 6-min walking distance (6MWD), World Health Organization functional class (WHO FC), and plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) were recorded. Comprehensive clinical evaluation was performed, and data obtained by transthoracic echocardiography, CPET, and RHC were collected. The study was conducted in agreement with the Declaration of Helsinki and approved by the Ethics Committee of Fuwai Hospital (Approval No. 2009-193). Written informed consent was obtained from all participants.

Echocardiography

Standard transthoracic echocardiography was performed by experienced cardiologists. TAPSE was measured in the apical 4-chamber view as the peak excursion of the tricuspid annulus between end-diastole and end-systole. The peak tricuspid regurgitation velocity (TRV) was recorded to calculate the pressure gradient between the right atrium (RA) and the RV using the modified Bernoulli equation. Right atrial pressure (RAP) was estimated based on the diameter and respiratory collapsibility of the inferior vena cava. PASP was calculated as $PASP = 4TRV^2 + RAP$. The left ventricle diameter at end-diastole (LVEDD) was measured in the left ventricular long-axis view; the RV diameter at end-diastole (RVEDD) was measured in the apical 4-chamber view. The ejection fraction (EF) was evaluated using the Simpson's biplane method. All echocardiographic parameters were assessed and averaged over three to five consecutive cardiac cycles.

RHC

RHC was performed for all patients via the femoral or internal jugular vein by experienced

pulmonary vascular physicians. Hemodynamic parameters, including RAP, systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mPAP, and pulmonary arterial wedge pressure (PAWP), were measured. Mixed venous oxygen saturation (S_vO_2) was recorded. CO was obtained using Fick's method. The cardiac index (CI), total pulmonary resistance (TPR), and pulmonary vascular resistance (PVR) were calculated using standard formulas.¹⁴ Pulmonary arterial compliance (PAC) was calculated as $PAC = \text{stroke volume} / \text{pulmonary arterial pulse pressure} = (CO / \text{heart rate}) / (sPAP - dPAP)$.¹⁵

CPET

Symptom-limited CPET was performed as previously described in a subset of 182 patients.¹⁶ The process included 3 min of rest, 3 min of warm-up, and a subsequent exercise test in which the work rate (WR) increased gradually using a ramp protocol until reaching the maximum exercise limitation. The WR raised within each minute was determined according to the estimated exercise tolerance. The following CPET-derived parameters were recorded or calculated using standard methods:¹⁷ WR, minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide output (VCO_2), lowest VE/VCO_2 , VE/VCO_2 slope, end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$), and oxygen pulse.

Follow-up

The composite endpoint of clinical worsening was defined as any of the following: (a) death, (b) rehospitalization for HF or deterioration of PH, or (c) escalation of targeted therapy. The participants were tracked by in-hospital or outpatient medical charts and were followed by telephone visits until outcome events or the end of the study (August 10, 2021). Information regarding follow-up treatment was also recorded according to medical charts and telephone visits. Follow-up hemodynamic and exercise data of the rehospitalization patients were recorded as much as possible. Time to clinical worsening was defined as the time from the date of baseline echocardiogram to the occurrence of the outcome. Endpoint events were adjudicated by two senior clinicians. All disagreements were resolved through discussion with the supervisors (Q.L. and Z.L.).

Statistical analysis

According to their distribution, continuous variables are presented as means (\pm standard deviation) or medians (interquartile ranges); categorical variables are presented as frequencies (percentages). Student's *t*-test was used to examine the differences in baseline characteristics between the included and excluded participants. The population was divided into three groups according to the tertile value of the baseline TAPSE/PASP ratio. The baseline characteristics of three groups were compared using one-way analysis of variance or the Kruskal–Wallis test (continuous variables) and the Pearson's chi-square test or Fisher's exact test (categorical variables). Spearman correlation analysis was performed to examine the correlations between TAPSE/PASP and hemodynamic variables. Linear regression analysis was conducted to study the relationship between TAPSE/PASP and continuous hemodynamic and exercise parameters.

The association between TAPSE/PASP and prognostic outcome during follow-up was investigated using Cox regression models. Covariate selection was based on univariate Cox regression analysis (variables with a *p* value < 0.05) and clinical relevance reported in previous studies. The selected variables were subsequently screened in multivariate Cox analyses by stepwise regression based on the Akaike information criterion. Considering the limited number of events, five multivariate Cox models were built to prevent overfitting. The TAPSE/PASP ratio was included in each model as a continuous variable. Internal validation of the models was further performed by bootstrapping with 500 repetitions.

Restricted cubic spline with four knots was carried out to identify the dose–response relationship and to assess linearity between TAPSE/PASP and clinical worsening. A receiver operating characteristic (ROC) curve was used to define the optimal cutoff of the TAPSE/PASP ratio for prediction. Kaplan–Meier curves were generated to illustrate the differences in survival among the participants according to TAPSE/PASP tertiles and the cutoff. A *p* value of less than 0.05 was considered statistically significant. All statistical tests were performed using SPSS software (version 22.0; IBM SPSS Statistics, IBM Corp., Armonk, NY, USA) and R (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

From February 2016 to November 2020, 248 consecutive patients with CTEPH were referred for evaluation and RHC. Among them, 37 were excluded due to the lack of echo-derived PASP or TAPSE, 3 were excluded because of a long interval between baseline echocardiogram and RHC, and 3 were excluded because of the age. Ultimately, 205 patients were included in the study (Figure 1). The baseline characteristics of the included ($n=205$) and excluded ($n=43$) patients are summarized in Supplemental Table S1. Of the included patients, the average interval between baseline RHC and echocardiogram was 6.4 days.

The baseline characteristics of the patients are listed in Table 1. The mean age was 55 ± 12 years, and 97 (47.3%) patients were female. The entire group was divided into three groups according to TAPSE/PASP tertiles (<0.154 , $0.154–0.207$, and >0.207). Patients in tertile 1 had a higher WHO FC and lower prevalence of hypertension compared with the other two groups. Echo-derived measurements showed a significantly enlarged RV, impaired TAPSE, and more common pericardial effusion (33.3%) in tertile 1. Lower TAPSE/PASP ratios were also associated with more severe PH, as shown by the significantly higher sPAP, mPAP, PVR, TPR, and NT-proBNP and lower PAC, CI, and S_vO_2 in tertile 1. Regarding CPET parameters, patients with lower TAPSE/PASP presented with significantly decreased WR, $VO_2@Peak$, $P_{ET}CO_2@Peak$, and oxygen pulse@Peak, whereas the VE/VCO_2 slope was significantly increased (Table 2). There was no significant difference in treatment at follow-up among the three groups, and the treatment algorithm of enrolled patients was shown in Supplemental Figure S1.

Relationship between TAPSE/PASP and hemodynamics

Correlation analyses showed that the TAPSE/PASP ratio was significantly associated with mPAP ($r=-0.41$, $p<0.001$), sPAP ($r=-0.42$, $p<0.001$), CI ($r=0.33$, $p<0.001$), and S_vO_2 ($r=0.34$, $p<0.001$; Table 3). Of note, TAPSE/PASP was negatively associated with PVR ($r=-0.48$, $p<0.001$) but positively associated with PAC ($r=0.45$, $p<0.001$; Figure 2).

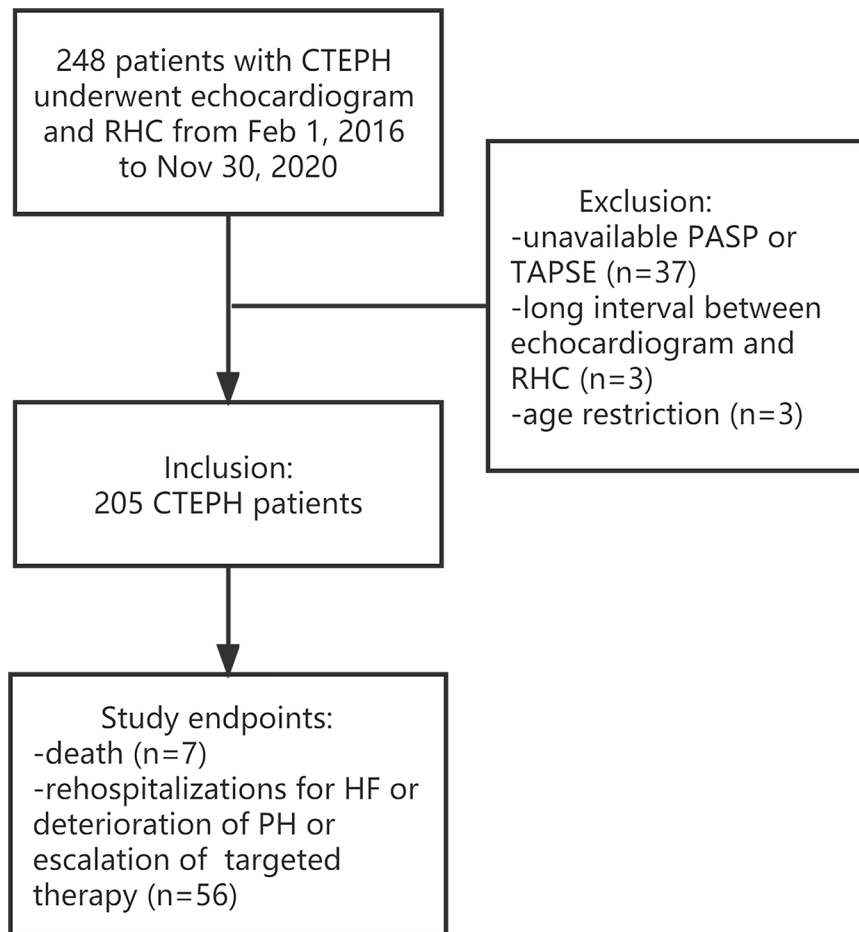


Figure 1. Study flowchart of patient enrollment and exclusion. CTEPH, chronic thromboembolic pulmonary hypertension; HF, heart failure; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization.

Association of TAPSE/PASP with survival outcomes

During a median follow-up of 1.0 (0.2–1.7) years, 63 (30.7%) patients experienced clinical worsening, including 7 (3.4%) deaths and 56 (27.3%) rehospitalizations for HF or deterioration of PH or escalation of PAH therapy. In univariate analysis, sex, WHO FC, 6MWD, LVEDD, RVEDD, TAPSE, TAPSE/PASP, pericardial effusion, RAP, CI, TPR, S_vO_2 , WR, VO_2 @anaerobic threshold (AT), VO_2 @Peak, lowest VE/ VCO_2 , VE/ VCO_2 slope, $P_{ET}CO_2$ @AT, $P_{ET}CO_2$ @Peak, and oxygen pulse@Peak were associated with clinical worsening (all p values < 0.05; Supplemental Table S2).

Five multivariate Cox regression models were constructed with significant variables indicated in univariate analysis (Table 4). After performing

stepwise selection of demographic and clinical parameters, female sex, NT-proBNP, and TAPSE/PASP were retained as independent predictors (Model 1). Among echocardiographic variables, pericardial effusion and TAPSE/PASP were screened as significant independent predictors for clinical worsening (Model 2). Model 3 and Model 4 included hemodynamic and CPET variables, respectively, and only $P_{ET}CO_2$ @AT emerged as an independent predictor in addition to TAPSE/PASP. In the final model constructed with all the significant predictors above (Model 5), the TAPSE/PASP ratio remained independently associated with clinical worsening (hazard ratio [HR] 0.402, 95% CI 0.239–0.676, p < 0.001; per standard deviation increase). Internal validation confirmed the prognostic value of TAPSE/PASP (C index 0.80, 95% CI 0.744–0.858, bias-corrected C index 0.781).

Table 1. Demographic, clinical, echocardiographic, and hemodynamic characteristics of study population.

| Variables | Total | Tertile 1 (n=69) | Tertile 2 (n=68) | Tertile 3 (n=68) | p value |
|---|------------------|-------------------|----------------------|------------------|----------------|
| TAPSE/PASP | | Low (<0.154) | Middle (0.154–0.207) | High (>0.207) | |
| Age, years | 55 ± 12 | 56 ± 11 | 54 ± 12 | 56 ± 12 | 0.121 |
| Female, n (%) | 97 (47.3) | 32 (46.4) | 34 (50.0) | 31 (45.6) | 0.860 |
| WHO FC | | | | | 0.022 |
| I or II | 102 (49.8) | 25 (36.3) | 38 (55.9) | 39 (57.4) | |
| III or IV | 103 (50.2) | 44 (63.7) | 30 (44.1) | 29 (42.6) | |
| 6MWD, m | 382 ± 103 | 335 ± 110 | 393 ± 91 | 409 ± 97 | 0.001 |
| Hypertension, n (%) | 49 (24) | 9 (13.0) | 20 (29.4) | 20 (29.4) | 0.034 |
| Diabetes mellitus, n (%) | 15 (7.4) | 8 (11.6) | 4 (5.9) | 3 (4.4) | 0.236 |
| Dyslipidemia, n (%) | 38 (18.6) | 12 (17.4) | 9 (13.2) | 17 (25) | 0.203 |
| Echocardiographic parameters | | | | | |
| LA, mm | 33.2 ± 6.0 | 33.0 ± 6.7 | 32.6 ± 5.6 | 34.2 ± 5.0 | 0.107 |
| LVEDD, mm | 39.9 ± 6.3 | 36.6 ± 5.5 | 39.9 ± 5.7 | 43.1 ± 6.0 | < 0.001 |
| RVEDD, mm | 34 ± 7 | 36 ± 7 | 34.2 ± 7.0 | 31.1 ± 6.1 | < 0.001 |
| LVEF, % | 63.8 ± 5.7 | 63.8 ± 6.8 | 64.2 ± 5.3 | 63.6 ± 4.7 | 0.578 |
| PASP, mmHg | 89 ± 23 | 106 ± 20 | 92 ± 16 | 69 ± 15 | < 0.001 |
| TAPSE, mm | 16.0 ± 3.6 | 13.0 ± 3.0 | 16.2 ± 2.7 | 18.8 ± 2.3 | < 0.001 |
| TAPSE/PASP, mm/mmHg | 0.19 ± 0.08 | 0.123 ± 0.023 | 0.176 ± 0.015 | 0.285 ± 0.066 | < 0.001 |
| Pericardial effusion, n (%) | 40 (19.5) | 23 (33.3) | 8 (11.8) | 9 (13.2) | 0.002 |
| Hemodynamic parameters | | | | | |
| S _v O ₂ , % | 67.6 ± 6.9 | 64.8 ± 6.5 | 68.5 ± 5.9 | 69 ± 7 | < 0.001 |
| RAP, mmHg | 6.6 ± 4.2 | 7.3 ± 4.9 | 6.2 ± 3.8 | 6.2 ± 3.7 | 0.317 |
| mPAP, mmHg | 50 ± 12 | 54 ± 11 | 53 ± 11 | 43 ± 10 | < 0.001 |
| PAWP, mmHg | 9.0 ± 3.7 | 8.9 ± 4.2 | 8.4 ± 3.3 | 9.6 ± 3.4 | 0.131 |
| CI, L/min/m ² | 2.9 ± 0.8 | 2.7 ± 0.8 | 2.9 ± 0.7 | 3.1 ± 0.8 | 0.001 |
| PVR, Wood units | 10.0 ± 4.6 | 11.7 ± 4.0 | 11.0 ± 5.0 | 7.6 ± 3.8 | < 0.001 |
| TPR, Wood units | 12.4 ± 4.9 | 14.1 ± 4.3 | 13.0 ± 5.0 | 9.9 ± 4.4 | < 0.001 |
| PAC, ml/mmHg | 1.2 ± 0.8 | 0.93 ± 0.44 | 1.16 ± 0.60 | 1.8 ± 1.2 | < 0.001 |
| Laboratory test | | | | | |
| NT-proBNP, pg/ml | 1162 (284, 2317) | 1923 (1180, 2982) | 1325 (460, 2438) | 216 (106, 1091) | < 0.001 |
| Follow-up treatment | | | | | |
| PEA, n (%) | 29 (14.1) | 11 (15.9) | 12 (17.6) | 6 (8.8) | |
| BPA, n (%) | 97 (47.3) | 27 (39.1) | 28 (41.2) | 42 (61.8) | |
| PAH-specific therapy ^a , n (%) | 72 (35.1) | 30 (43.5) | 24 (35.3) | 18 (26.5) | |
| None, n (%) | 7 (3.4) | 1 (1.4) | 4 (5.9) | 2 (2.9) | |

BPA, balloon pulmonary angioplasty; CI, cardiac index; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEDD, right ventricular end-diastolic diameter; S_vO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TPR, total pulmonary resistance; WHO FC, World Health Organization functional class; 6MWD, 6-min walking distance.

Values in bold are significant (*p* < 0.05).

^aPAH-specific therapy included endothelin receptor antagonists, nitric oxide-cGMP enhancers, and prostacyclin pathway agonists.

Table 2. CPET parameters according to tertiles of TAPSE/PASP at baseline.

| Variables | Total | Tertile 1 (n=56) | Tertile 2 (n=63) | Tertile 3 (n=63) | p value |
|---|------------|---------------------|---------------------|---------------------|------------------|
| WR, watts | 69 ± 31 | 57 ± 25 | 70 ± 28 | 77 ± 36 | 0.001 |
| VO ₂ @AT, ml/min/kg | 9.5 ± 2.6 | 8.8 ± 2.4 | 9.6 ± 2.4 | 9.9 ± 2.8 | 0.038 |
| VO ₂ @Peak, ml/min/kg | 12.3 ± 3.5 | 11.0 ± 3.1 | 12.2 ± 2.7 | 13.4 ± 4.2 | <0.001 |
| VE@Peak, l/min | 44 ± 15 | 41 ± 14 | 44 ± 15 | 45 ± 14 | 0.181 |
| Lowest VE/VCO ₂ | 45 ± 9 | 48 ± 10 | 45 ± 7 | 42 ± 8 | 0.012 |
| VE/VCO ₂ slope | 49 ± 15 | 57 ± 19 | 49 ± 12 | 42 ± 11 | <0.001 |
| P _{ET} CO ₂ @AT, mmHg | 25.5 ± 5.0 | 23.4 ± 4.0 | 25.0 ± 3.9 | 27.9 ± 5.5 | <0.001 |
| P _{ET} CO ₂ @Peak, mmHg | 23.3 ± 5.5 | 20.5 ± 4.0 | 22.8 ± 4.4 | 26.4 ± 6.1 | <0.001 |
| Oxygen pulse@Peak, ml/min/beat | 6.5 ± 2.1 | 5.6 ± 1.3 | 6.3 ± 1.8 | 7.5 ± 2.6 | <0.001 |

AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; PASP, pulmonary arterial systolic pressure; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide; TAPSE, tricuspid annular plane systolic excursion; VCO₂, carbon dioxide output; VE, minute ventilation; VO₂, oxygen uptake; WR, work rate.
Values in bold are significant (*p* < 0.05).

Table 3. Correlation between the TAPSE/PASP ratio and RHC-derived parameters.

| Variables | r | p value |
|-------------------------------|-------|------------------|
| RAP | -0.01 | 0.110 |
| mPAP | -0.41 | <0.001 |
| PAWP | 0.12 | 0.102 |
| CI | 0.33 | <0.001 |
| S _v O ₂ | 0.34 | <0.001 |
| PVR | -0.48 | <0.001 |
| TPR | -0.44 | <0.001 |
| PAC | 0.45 | <0.001 |

CI, cardiac index; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; S_vO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TPR, total pulmonary resistance.
Values in bold are significant (*p* < 0.05).

ROC curve analysis revealed that the optimal cutoff value of TAPSE/PASP for clinical worsening prediction was 0.17 mm/mmHg (specificity 79%, sensitivity 67%), with an area under the ROC curve of 0.78 (95% CI 0.72–0.84, *p* < 0.0001; Supplemental Figure S2). As shown in Figure 3, restricted cubic

spline confirmed the linear relationship between TAPSE/PASP and clinical worsening (Nonlinear *p* = 0.797). Kaplan–Meier event-free survival curves verified that patients with higher TAPSE/PASP had a significantly better prognosis (Log-rank *p* < 0.001; Figures 4 and Supplemental Figure S3).

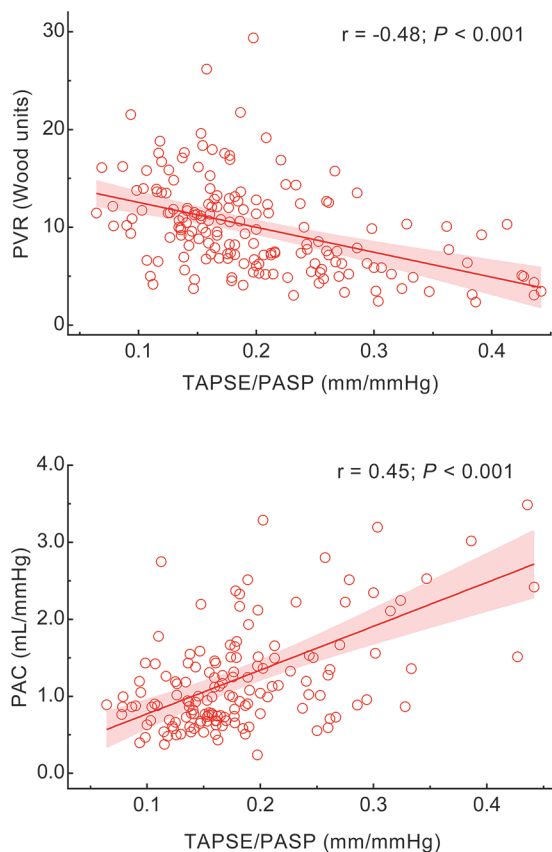


Figure 2. Relationship of the TAPSE/PASP ratio with PVR and PAC.

PAC, pulmonary arterial compliance; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion.

We further explored the value of TAPSE/PASP in predicting follow-up hemodynamics and clinical worsening. Given the invasive nature of RHC and the requirement for readmission, follow-up hemodynamics and exercise data were available for only 55 (26.8%) patients. We performed exploratory analyses and found that TAPSE/PASP independently predicted follow-up hemodynamics (mPAP and PVR) and exercise capacity (VO₂@Peak; Supplemental Tables S5–S6).

Discussion

To our knowledge, this study is the largest to examine the relationship between the echo-derived TAPSE/PASP ratio and clinical worsening in patients with CTEPH. We found TAPSE/PASP to be an independent marker for assessing disease severity and predicting outcomes in

CTEPH. In addition, significant correlations between TAPSE/PASP and invasive hemodynamic variables, such as PVR or PAC, were observed.

In recent years, RV-PA coupling has emerged as a valuable marker that can powerfully detect occult RV dysfunction. The idea of coupling allows for investigating the cardiopulmonary unit as a whole and focusing on RV performance at different levels of afterload. Traditionally, the gold standard for assessing RV-PA coupling is Ees/Ea derived from the P-V loop using a conductance catheter. Several pilot studies have demonstrated impaired RV-PA coupling by Ees/Ea in patients with CTEPH.^{18,19} However, the invasive nature and technical complexity of P-V loop analysis have largely limited its clinical application. Recently, noninvasive parameters reflecting RV-PA coupling have been proposed, among which the TAPSE/PASP ratio has been proven to be the most valid surrogate of invasively measured Ees/Ea.⁴

The TAPSE/PASP ratio is a combination of RV contractility and afterload. As a novel marker of RV-PA coupling, the prognostic value of TAPSE/PASP has been investigated in acute PE,¹⁰ which is pathophysiologically connected to CTEPH. Interestingly, compared with the previously suggested value for identifying adverse outcomes in acute PE (0.4 mm/mmHg), the TAPSE/PASP ratios observed in our study were much lower, which is in agreement with experimental models of acute and chronic PH. In animal models assessed by pressure–volume curves, RV-PA coupling was preserved in acute PE,²⁰ whereas after 3 months of chronic PA occlusion, the overloaded RV decompensated, and RV-PA uncoupling was observed.²¹ CTEPH is suspected in patients with persistent dyspnea after 3 months of anticoagulation, and this chronic overload process may explain the common mismatch between RV function and afterload.²² Moreover, the cut-off value established in our study (0.17 mm/mmHg) is comparable to that of PAH in systemic lupus erythematosus (0.184 mm/mmHg),⁷ with both being far below the normal limits,²³ indicating a common RV-PA coupling impairment in chronic PH. In this regard, our findings further support the idea that RV-PA uncoupling is a primary component of the phenotype of patients with chronic PH.

Table 4. Multivariate Cox regression models for clinical worsening prediction.

| Variables | HR | 95% CI | p value |
|---|-------|-------------|------------------|
| Model 1 | | | |
| Female | 0.456 | 0.269–0.773 | 0.004 |
| NT-proBNP ^a | 1.315 | 1.056–1.638 | 0.015 |
| TAPSE/PASP ^a | 0.313 | 0.197–0.499 | <0.001 |
| Model 2 | | | |
| RVEDD | 1.036 | 1.000–1.073 | 0.054 |
| TAPSE | 0.901 | 0.812–1.011 | 0.076 |
| Pericardial effusion | 1.946 | 1.037–3.652 | 0.038 |
| TAPSE/PASP ^a | 0.543 | 0.302–0.974 | 0.041 |
| Model 3 | | | |
| RAP | 1.051 | 0.994–1.110 | 0.079 |
| S _v O ₂ | 0.968 | 0.926–1.011 | 0.142 |
| TAPSE/PASP ^a | 0.323 | 0.201–0.519 | <0.001 |
| Model 4 | | | |
| P _{ET} CO ₂ @AT | 0.889 | 0.812–0.974 | 0.011 |
| TAPSE/PASP ^a | 0.405 | 0.214–0.767 | 0.006 |
| Model 5 | | | |
| NT-proBNP ^a | 1.431 | 1.094–1.873 | 0.009 |
| Pericardial effusion | 2.777 | 1.719–5.116 | 0.003 |
| TAPSE/PASP ^a | 0.402 | 0.239–0.676 | <0.001 |
| <p>AT, anaerobic threshold; CI, cardiac index; LVEDD, left ventricular end-diastolic diameter; NT-proBNP, N-terminal pro-brain natriuretic peptide; PASP, pulmonary arterial systolic pressure; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide; RAP, right atrium pressure; RVEDD, right ventricular end-diastolic diameter; S_vO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TPR, total pulmonary resistance; VCO₂, carbon dioxide output; VE, minute ventilation; VO₂, oxygen uptake; WHO FC, World Health Organization functional class; WR, work rate. Model 1: Stepwise regression analysis was applied to age, sex, WHO FC, NT-proBNP, and TAPSE/PASP. Model 2: Stepwise regression analysis was applied to LVEDD, RVEDD, TAPSE, pericardial effusion, and TAPSE/PASP. Model 3: Stepwise regression analysis was applied to RAP, CI, TPR, S_vO₂, and TAPSE/PASP. Model 4: Stepwise regression analysis was applied to WR, VO₂@Peak, Lowest VE/VCO₂, PETCO₂@AT, Oxygen pulse@Peak, and TAPSE/PASP. Model 5: Stepwise regression analysis was applied to sex, NT-proBNP, pericardial effusion, PETCO₂@AT, and TAPSE/PASP. Values in bold are significant (<i>p</i> < 0.05). ^aPer standard deviation increase.</p> | | | |

In this retrospective study, we observed that patients with RV-PA uncoupling had worse exercise capacity (lower VO₂@Peak and WR) and stroke volume reserve (reduced oxygen pulse@Peak), with poorer pulmonary perfusion and ventilatory efficiency (higher VE/VCO₂ slope and

lower P_{ET}CO₂@Peak). As mentioned above, the contractile reserve of the RV is one major determinant of RV-PA coupling. In patients with reduced TAPSE/PASP, the RV fails to increase its contractile ability to compensate for elevated pulmonary arterial pressure during exercise.

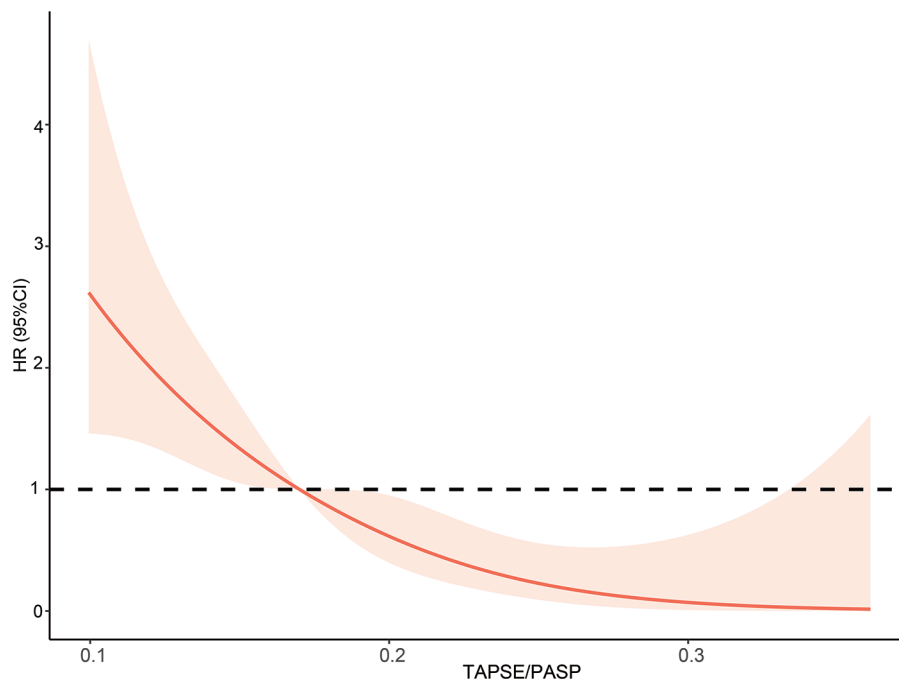
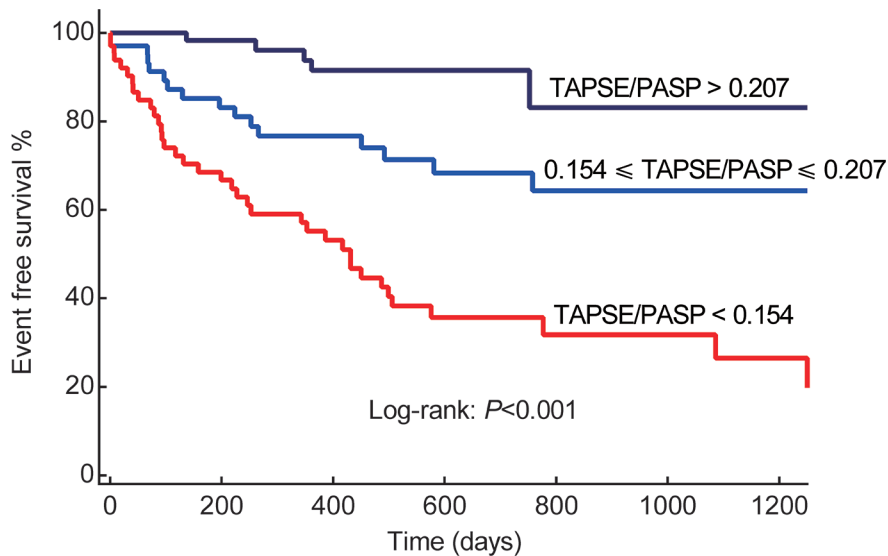


Figure 3. Association between the TAPSE/PASP ratio and clinical worsening of CTEPH patients. CI, confidence interval; HR, hazard ratio; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion.



| No. at risk | | | | | | | |
|-------------------------|----|----|----|----|----|----|---|
| TAPSE/PASP: <0.154 | 69 | 36 | 26 | 14 | 8 | 6 | 5 |
| TAPSE/PASP: 0.154-0.207 | 68 | 40 | 31 | 22 | 15 | 11 | 5 |
| TAPSE/PASP: >0.207 | 68 | 51 | 36 | 20 | 10 | 5 | 3 |

Figure 4. Kaplan-Meier event-free survival curves based on the tertiles of the TAPSE/PASP ratio. PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

The insufficient increase in CO and pulmonary blood flow eventually leads to exaggerated ventilation–perfusion mismatch and reduced exercise capacity.

In addition to the RV contractile reserve, the condition of the pulmonary vasculature appears to be as important in determining the state of RV-PA coupling. Prior findings have highlighted that PVR and PAC are the two major components of RV afterload, representing the static load and pulsatile load, respectively.²⁴ Normal pulmonary circulation is a low-resistance, high-compliance system that can accommodate dramatic changes in blood flow. In CTEPH, thrombus organization and extracellular matrix deposition in pulmonary arteries lead to an abnormal PVR and PAC²⁵ and then contribute to RV impairment through the increased afterload. In our study, we showed that the TAPSE/PASP ratio was significantly related to PVR and PAC, which are both strong predictors of adverse outcomes in PH.¹⁵ Furthermore, PAC has been proven to be an important predictor of outcome after pulmonary endarterectomy (PEA).²⁶ Several studies have also demonstrated a significant correlation between TAPSE/PASP and these afterload-associated parameters. For example, Guazzi *et al.*²⁷ described a strong correlation between TAPSE/PASP and PAC in patients with heart failure with preserved ejection fraction. A similar result was obtained by Tello *et al.*⁶ in 290 patients with PAH, which additionally suggested the potential role of pulmonary vascular stiffness in RV-PA uncoupling. In line with previous results, our findings provide more information on the associations between pulmonary vasculopathy and RV-PA uncoupling in CTEPH.

In the current study, we also found that TAPSE/PASP correlated linearly with clinical worsening and that each standard deviation increase in TAPSE/PASP reduced the risk of clinical worsening by 60%. Previous studies have found that TAPSE/PASP is an independent prognostic predictor in patients with HF^{5,28} and PAH,^{6,7} and we extend this knowledge to patients with CTEPH. Current PH guidelines recommend a dynamic risk stratification encompassing hemodynamic parameters,¹³ and repetitive RHC is needed during follow-up, which is invasive and technically demanding. Therefore, noninvasive tools are believed to be important additions to RHC in PH.²⁹ As a noninvasive echo-derived parameter,

TAPSE/PASP has the advantage of clinical availability, cost-effectiveness, and high predictive value and therefore may be included in routine examinations for risk assessment and goal-oriented treatment in CTEPH. Given the availability of multiple treatment options, including PEA, balloon pulmonary angioplasty, and PAH-specific therapy, risk assessment in CTEPH is much more complex than in PAH. In this study, treatment options did not affect outcomes, which may be explained by the limited sample size and follow-up time. Of note, the RV-PA loop analysis has been applied in assessing treatment response in experimental models of PAH. Recently, a pilot study has also suggested its role in screening chronic thromboembolic disease patients indicated for PEA.¹⁹ These findings invite us to consider the possibility that TAPSE/PASP, as a surrogate for Ees/Ea, may also provide important information regarding treatment options. Larger-scale, prospective studies are warranted to properly evaluate the value of TAPSE/PASP in CTEPH patients receiving different treatment regimens.

Limitations

We have to acknowledge a few limitations. First, a major limitation of our study is the retrospective design, and 15% of patients were not included due to the lack of PASP or TAPSE. Measurement of TAPSE/PASP might be affected by an inadequate acoustic window or lack of a tricuspid regurgitation signal. Therefore, we compared baseline characteristics between included and excluded participants (Supplemental Table S1) and found that they were similar with regard to demographic factors and disease severity, which indicated that the lack of PASP and TAPSE was random. Second, as a parameter of RV longitudinal contractility, TAPSE is unable to reflect radial or apical contractility and reaches a minimum with the deterioration of RV function (floor effect).³⁰ Nonetheless, considering its prognostic value, TAPSE is recommended to be included in comprehensive echocardiographic evaluation of PH.¹³ Third, the current study is a single-center experience, and the rate of PEA therapy is much lower than that reported in the latest international registration,³¹ which may be related to socioeconomic and cultural factors or the single-center study design.³² Hence, the generalizability of our conclusion is limited. However, considering that Fuwai Hospital is the national center for

cardiovascular diseases, our patients were from all over China. Moreover, CTEPH is a rare complication of acute PE, and this study had the largest sample size in the context of exploring RV-PA coupling in CTEPH.

Conclusion

The results of our study indicate that the non-invasive metric of RV-PA coupling, as estimated by echo-derived TAPSE/PASP, reflects disease severity and functional capacity and correlates with hemodynamic parameters. Overall, TAPSE/PASP may serve as a valuable prognostic predictor for clinical worsening in patients with CTEPH. Therefore, we suggest TAPSE/PASP to be included in routine risk assessment of CTEPH.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki and approval was granted by the Fuwai Hospital Ethics Committee (Approval No. 2009-193). Written informed consent was obtained from all participants.

Consent for publication

The participant has consented to the submission of this article to the journal.

Author contributions

Anqi Duan: Conceptualization; Writing – original draft; Writing – review & editing.

Xin Li: Data curation; Formal analysis; Software; Writing – review & editing.

Qi Jin: Methodology; Writing – original draft; Writing – review & editing.

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Availability of data and materials

The data will be shared on reasonable request to the corresponding author.


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Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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