Diagnostic and prognostic value of right ventricular eccentricity index in pulmonary artery hypertension

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Abstract
The right ventricle experiences dynamic changes under pressure overload in pulmonary artery hypertension. This study aimed to evaluate the diagnostic and prognostic value of right ventricular eccentricity index (RVEI) in pulmonary artery hypertension. A total of 100 pulmonary artery hypertension patients (mean age, 36.85 (SD, 13.60) years; males, 30.0%) confirmed by right heart catheterization and 147 healthy volunteers (mean age 45.58 (SD, 17.58) years; males, 42.50%) were enrolled in this prospective study. All participants underwent cardiac magnetic resonance imaging (MRI) examination, and balanced steady-state free precession (bSSFP) cine sequences were acquired. RVEI was measured on short-axis cine images at the mid-ventricular level of the right ventricle in end systole. The study found that RVEI was significantly lower in pulmonary artery hypertension patients than in healthy volunteers (1.84 (SD, 0.40) vs. 2.46 (SD, 0.40); p < 0.001). In pulmonary artery hypertension patients, RVEI was correlated with log(NT-proBNP) (r = −0.388; p < 0.001), right ventricular end-diastolic volume index (r = −0.452; p < 0.001), right ventricular end-systolic volume index (r = −0.518; p < 0.001), and right ventricular ejection fraction (r = 0.552; p < 0.001). RVEI could discriminate pulmonary artery hypertension patients from healthy volunteers with 91.8% sensitivity and 68.0% specificity. Over median follow-up of 14.8 months (interquartile range: 6.7–26.9 months), RVEI was demonstrated to be an independent predictor for adverse outcome (HR = 0.076; 95% CI, 0.013–0.458; p = 0.005). In conclusion, MRI-derived RVEI appears to be a useful diagnostic and prognostic value in pulmonary artery hypertension, and it provides incremental value to risk stratification strategy.

Keywords
cardiac magnetic resonance imaging, pulmonary artery hypertension, right ventricular eccentricity index, diagnosis, prognosis

Introduction
The right ventricle has attracted much research interest in recent years, especially with regard to its function in pulmonary artery hypertension (PAH). Recent studies suggest that right ventricular (RV) dysfunction could be a powerful predictor of adverse outcome in PAH.1–3 The dynamic and complicated remodeling process that the right ventricle experiences under pressure overload is distinctly different from that of the left ventricle under systemic hypertension.4,5 In this era of targeted therapy, the period of RV remodeling may be the ideal time for intervention to prevent cardiac failure in PAH patients. However, better understanding of the RV remodeling process and the underlying mechanisms is essential.

In patients with PAH, the circular shape of the left ventricle on cross-sectional images changes to a “D” shape,6 and the crescentic right ventricle assumes a more circular shape.7

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Changes in ventricular geometry can be reflected by the ventricular eccentricity index. Left ventricular eccentricity index (LVEI) has been shown to be associated with myocardial fibrosis and has adverse outcomes in PAH patients. RV eccentricity index (RVEI), however, has not been fully studied. One study reported that echocardiography-derived RVEI is correlated to the degree of tricuspid regurgitation in patients with chronic RV dilation, but changes in RVEI in patients with PAH has not been investigated. Furthermore, echocardiographic assessment of the right ventricle is hampered by inadequate acoustic windows and the complicated three-dimensional geometry. The ideal tool to evaluate the right ventricle would be cardiac magnetic resonance imaging (MRI), as three-dimensional continuous cine images can accurately display right ventricle dimension, volume, geometry, and other advanced mechanical parameters.

The purpose of this study was to assess the diagnostic and prognostic value of cardiac MRI-derived RVEI in PAH patients.

Participants and methods

Participants

Between March 2013 and December 2018, a total of 142 pulmonary hypertension patients underwent right heart catheterization (RHC) examination at our hospital. Patients were eligible for inclusion in this prospective study if they had (1) mean pulmonary artery pressure (mPAP) \( \geq 25 \) mm Hg; (2) pulmonary capillary wedge pressure (PCWP) \(< 15 \) mm Hg; (3) pulmonary vascular resistance (PVR) \( > 3 \) Wood units at rest; and (4) undergone cardiac MRI examination within 72 h of RHC. Patients were excluded if they had (1) not undergone cardiac MRI examination (n = 8); (2) pulmonary hypertension due to left heart disease (World Health Organization (WHO) Group 2; n = 7); (3) pulmonary hypertension due to lung disease (WHO Group 3; n = 7); (4) pulmonary hypertension due to chronic blood clots in the lungs (WHO Group 4; n = 3); (5) pulmonary hypertension due to unknown causes (WHO Group 5; n = 2); or (6) age \(< 18 \) years (n = 15). Finally, a total of 100 PAH patients (Group 1) who met all criteria were enrolled into this study. Another 147 healthy volunteers from our database without any known cardiac disease or chronic systemic disease were recruited to form a comparison group and also underwent cardiac MRI scans. The study was approved by the ethics committee of our institution. All participants provided written informed consent.

Clinical evaluation and laboratory tests

All included patients underwent a comprehensive clinical evaluation. Any symptoms (dyspnea, edema, syncope, and so on) were recorded. The WHO functional class (WHO-FC) was evaluated for each patient. The 6-minute walk test (6MWT) was performed in a 30-m-long corridor according to a standardized protocol, and the 6-minute walk distance (6MWD) was recorded. Serum N-terminal pro-brain natriuretic peptide (NT-ProBNP) and troponin T levels were measured. Routine echocardiographic and RHC examination were performed.

Cardiac MRI

Cardiac MRI was acquired on a 3.0T scanner (Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany). Balanced steady-state free precession (bSSFP) cine images were acquired during breath-holds using the electrocardiogram (ECG)-gated technique, with a 32-channel dedicated cardiac phase-array receiver coil. Short-axis stacks of cine images were acquired from the base of the ventricle to the apex. Cine images were acquired with the following parameters: field of view, 320–340 mm\(^2\); repetition time, 3.4 ms; echo time, 1.3 ms; flip angle, 50°; matrix size, 256 × 144; spatial resolution, \( 1.4 \times 1.3 \) mm\(^2\); temporal resolution, 42 ms; slice thickness, \( 8 \) mm with no gap; and frames reconstructed per cardiac cycle, 25. Phase-sensitive inversion recovery (PSIR) turbo-flash pulse sequence was performed on consecutive short-axis and 2- and 4-chamber views 10–15 min after gadolinium injection with 0.15 mm/kg per bolus.

Image analysis

Blinded analysis of cardiac MR images was performed offline. Conventional functional parameters of the ventricle were analyzed using the postprocessing software Qmass 8.2 (Medis Medical Imaging Systems, Leiden, The Netherlands). The endocardial and epicardial contours of left ventricle were manually delineated at end diastole and end systole for the calculation of left ventricular volume, mass, and ejection fraction (EF). The endocardial contour of the right ventricle was delineated at end diastole and end systole for the calculation of RV volume and EF.

RVEI was calculated as follows: On short-axis cine images at the mid ventricular level of the right ventricle in end systole, a line was drawn perpendicularly from the midpoint of the interventricular septum to the right ventricle free wall; this distance was measured (D1). Another line was drawn (D2) perpendicular to D1 to mark the largest width of the right ventricle (Fig. 1). RVEI was the ratio of D2 to D1. LVEI was calculated as Thomas RM et al. did: the ratio of LV diameter perpendicular to the IVS to LV diameter parallel to the IVS.

Late gadolinium enhancement (LGE) was considered present if there was bright signal within the myocardium, and were also visible in another plane that cut the area in question (Supplementary Fig. S1).

Right heart catheterization

RHC was performed using a 5F transfemoral catheter according to the standard procedure. Transducers were
positioned at the patient’s mid-chest level, and the pressures in the inferior vena cava, right atrium, right ventricle, and pulmonary artery were recorded successively. Blood was sampled from intracardiac chambers and great vessels for the measurement of oxygen saturation, and from the main pulmonary artery for the measurement of mixed venous saturation (SvO₂). The cardiac output was determined using the Fick method. Cardiac index was calculated by dividing CO by the body surface area (BSA). PVR was calculated using the formula (mPAP−PCWP)/CO.

**Risk stratification of PAH patients**

Risk stratification of patients was based on WHO-FC, 6MWD, NT-proBNP, right atrial pressure, cardiac index, and SvO₂. Each variable was first scored on a scale of 1 to 3 (where 1 = low risk, 2 = intermediate risk, and 3 = high risk). The sum of all scores was divided by the number of available variables to get the mean score, which was rounded off to the nearest integer to define the risk group.

**Follow-up and endpoints**

Patients were followed up regularly by clinical visit or telephone contact according to our usual follow-up protocol. Final follow-up was on February 2019. Major events were defined according to the REVEAL Registry and included death, lung transplantation, or atrial septostomy. Clinical worsening was defined as worsening of WHO-FC, a ≥15% decrease in 6MWD, hospitalization for any cause, or the introduction of a parenteral prostacyclin analog for any reason. The composite of major events and clinical worsening was defined as the primary endpoint. Time to event was defined as the period from RHC examination to the event. Patients who did not experience the primary endpoint were censored at the time of last follow-up.

**Reproducibility**

The observers who measured the RVEI were blinded to the clinical data. Random samples of 20 patients and 30 healthy volunteers were selected to examine intra- and interobserver variability; the first observer measured the RVEI of the selected sample at one month later. Another observer performed analysis for inter-observer variability on the selected sample.

**Statistical analysis**

Categorical variables were expressed as numbers and percentages and evaluated by chi-square test. Normally distributed continuous variables were expressed as means and standard deviation (SD) and evaluated by the independent-sample t test. Non-normally distributed continuous variables are presented as median and interquartile ranges. Normality was tested with Kolmogorov-Smirnov method. We analysed NT-proBNP by a logarithmic transformation (base10). Differences in continuous variables among healthy volunteers and PAH patients were evaluated by analysis of variance (ANOVA). Pearson correlation coefficients were calculated to determine the strength of the relationship between variables. Univariable Cox proportional hazards regression analysis was performed to identify the variables associated with the primary endpoint, and prognostic value of RVEI was corrected by variables included into risk stratification, respectively. The Kaplan–Meier method was used for survival analysis, and the differences between groups were assessed with the log-rank test. Receiver operating characteristic (ROC) curve analysis was used to discriminate

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**Fig. 1.** Measurement of RVEI in a PAH patient (a) and a healthy volunteer (b) on balanced-SSFP cine images. RVEI: right ventricular eccentricity index; SSFP: steady-state free precession.
PAH patients from normal volunteers and to identify the optimum cutoff value of RVEI for discriminating patients with adverse events. To evaluate the incremental prognostic value of RVEI, sequential Cox regression analysis was utilized. The improvement of global chi-square was calculated to assess incremental prognostic value of each model. For the agreement of RVEI measurement, Bland-Altman analysis was used. Statistical analysis was performed using Stata SE, (version 15.1; Stata Corp; College Station, TX, USA) and SPSS (version 17.0; IBM Corp; Armonk, NY, USA). Two-tailed p < 0.05 was considered statistically significant.

**Results**

**Demographic, clinical, and cardiac MRI characteristics**

Among the enrolled patients, 33/100 (33%) had idiopathic PAH, 58/100 (58%) had congenital heart disease-associated PAH, 8/100 (8%) had connective tissue disease-associated PAH, and 1/100 (1%) had human immunodeficiency infection-associated PAH. Among 58 who had congenital heart disease-associated PAH, 21 with atrial septal defect (ASD), 23 with ventricular septal defect (VSD), and 14 with patent ductus arteriosus (PDA). While 8/100 (8.0%) had connection tissue disease-associated PAH, 21 with atrial septal defect (ASD), 23 with ventricular septal defect (VSD), and 14 with patent ductus arteriosus (PDA). Among the enrolled patients, 33/100 (33%) had idiopathic PAH, 58/100 (58%) had congenital heart disease-associated PAH, 8/100 (8%) had connective tissue disease-associated PAH, and 1/100 (1%) had human immunodeficiency infection-associated PAH. Among 58 who had congenital heart disease-associated PAH, 21 with atrial septal defect (ASD), 23 with ventricular septal defect (VSD), and 14 with patent ductus arteriosus (PDA). While 8/100 (8.0%) had connection tissue disease-associated PAH, 21 with atrial septal defect (ASD), 23 with ventricular septal defect (VSD), and 14 with patent ductus arteriosus (PDA).

**Diagnostic value of RVEI for discriminating PAH patients from normal volunteers**

ROC analysis identified 1.96 as the optimum RVEI cutoff for discriminating PAH patients from normal volunteers; this value had sensitivity of 91.8%, specificity of 68.0%, and area under the curve (AUC) 0.870 (Supplementary Fig. S2).

**Relationship between RVEI and LVEI, RV function and clinical severity of PAH**

RVEI was significantly correlated to RVEDVi (r = -0.452; p < 0.001), RVESVi (r = -0.518; p < 0.001), RVEF (r = 0.552, p < 0.001), and log (NT-proBNP) (r = -0.388; p < 0.001), as well correlated to echocardiographic-derived tricuspid regurgitation velocity (r = -0.213, p = 0.048). RVEI was not significantly correlated to 6MWD and invasive hemodynamic parameters such as mPAP, right atrial pressure, PCWP, PVR, cardiac index, and SvO2 (Table 2). And RVEI significantly correlated to LVEI (r = 0.372, p < 0.001). LVEI was significantly correlated to RVEDVi (r = 0.482; p < 0.001), RVESVi (r = 0.499; p < 0.001), RVEF (r = -0.351, p < 0.001), and log (NT-proBNP) (r = -0.337; p = 0.001). LVEI also correlated to echocardiographic-derived tricuspid gradient and tricuspid regurgitation velocity (r = 0.328, p = 0.002; r = 0.348, p = 0.001, respectively). Except mPAP (r = 0.237, p = 0.018), LVEI was not significantly correlated to other invasive hemodynamic parameters such as right atrial pressure, PCWP, PVR, cardiac index SvO2, and 6MWD (Supplementary Table S1). The mean RVEI varied significantly between healthy volunteers and the three PAH risk subgroups (healthy volunteers: 2.46 (SD, 0.40); low-risk patients: 2.10 (SD, 0.27); intermediate-risk patients: 1.62 (SD, 0.27); high-risk patients: 1.50 (SD, 0.37); ANOVA, p < 0.001). RVEI showed steady decrease with increase in risk stratification, with the high-risk group having significantly lower RVEI than the other groups. Fig. 2 shows a box-and-whisker plot of RVEI in the three risk groups.

**Relationship between RVEI and LGE presence**

In the 92 patients who underwent contrast cardiac MRI imaging scan, LGE was identified in 66 (72%) patients. There was no difference of RVEI between absent and present LGE groups (1.95 (SD, 0.35) vs. 1.79 (SD, 0.38); p = 0.063).

**Outcomes during follow-up**

Over the median follow-up period of 14.8 months (interquartile range: 6.7–26.9 months), 30/100 (30%) patients experienced the primary endpoint: this included 9 cardiac deaths, 19 heart failure readmissions, and 2 worsening WHO-FC. Univariate Cox analysis showed RVEI, LVEI, 6MWD, log (NT-proBNP), cardiac index, SvO2, RVESVi, RVEF, LVESVi, and LVEF to be significantly associated with the composite endpoint (Table 3). After correcting the prognostic value of RVEI with variables included into risk stratification respectively, RVEI predicted outcome independent of WHO FC, 6MWD, log (NT-proBNP), RAP, CI, and SvO2 (Table 4).
Additional value of RVEI for predicting primary endpoints

RVEI < 1.59 could differentiate patients with adverse outcome from the total enrolled patients with 81.4% sensitivity and 63.3% specificity; the AUC for this cutoff RVEI value was 0.721 (Supplementary Fig. S3). Using the cutoff value of 1.59, patients were separated into a high RVEI group (69/100) and low RVEI group (31/100). Fig. 3a and b shows the Kaplan–Meier survival curves for the different risk groups and the high and low RVEI groups. Patients in high-risk group had significantly more adverse outcomes (log-rank test, p = 0.035). However, there was no significant difference between the low-risk and intermediate-risk groups. Low RVEI group had significantly more adverse outcomes than the high RVEI group (log-rank test, p < 0.001). Further, we analyzed survival curves of the primary endpoint according to RVEI in intermediate risk group; the result is presented in Fig. 3c. In the intermediate-risk group, patients with RVEI < 1.59 were more likely to reach the primary endpoint (log-rank test, p = 0.001).

In addition, we found that the models based on risk stratification ($\chi^2 = 6.680$, df = 1) can be improved by RVEF ($\chi^2 = 11.288$, df = 1, p < 0.05) and RVEI.
The model (including risk stratification and RVEF) can be further improved by the addition of RVEI ($\chi^2 = 15.511$, df = 1, $p < 0.05$); the results are shown in Supplementary Fig. S4.

### Table 2. Correlation between RVEI and exercise capacity, biomarker, invasive hemodynamics, and cardiac MRI–determined right ventricular volume and function.

| Variables                  | Correlation with RVEI (Pearson r) | p         |
|----------------------------|----------------------------------|-----------|
| Exercise capacity          |                                   |           |
| 6MWD                       | 0.171                            | 0.102     |
| Biomarker                  |                                   |           |
| log(NT-proBNP)             | -0.388                           | <0.001    |
| Hemodynamics               |                                   |           |
| mPAP, mm Hg                | 0.075                            | 0.459     |
| RAP, mm Hg                 | -0.041                           | 0.689     |
| PCWP, mm Hg                | 0.110                            | 0.303     |
| PVR, Woods units           | -0.038                           | 0.712     |
| Cardiac index, L/min/m²    | 0.110                            | 0.284     |
| SvO₂, %                    | 0.109                            | 0.290     |
| Echocardiographic index    |                                   |           |
| Transticuspid gradient, mmHg | -0.203                          | 0.059     |
| TR velocity, m/s           | -0.213                           | 0.048     |
| Cardiac MRI                |                                   |           |
| RVEDVi, mL/m²              | -0.452                           | <0.001    |
| RVESVi, mL/m²              | -0.518                           | <0.001    |
| RVEF, mL/m²                | 0.552                            | <0.001    |
| LVEI                       | -0.372                           | <0.001    |

Note: Values in bold indicate statistically significant p values.

6MWD: 6-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary artery pressure; RAP: right atrial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SvO₂: mixed venous oxygen saturation; MRI: magnetic resonance imaging; RVEDVi: right ventricular end-diastolic volume index; RVESVi: right ventricular end-systolic volume index; RVEF: right ventricular ejection fraction; RVEI: right ventricular eccentricity index in end systole.

### Table 3. Univariate Cox regression analysis of factors associated with the composite endpoint.

| Demographic factors | HR (95% CI) | p     |
|---------------------|-------------|-------|
| Age, y              | 0.933 (0.964–1.022) | 0.628 |
| Male sex            | 0.979 (0.448–2.140)  | 0.958 |
| BMI, kg/m²          | 1.005 (0.899–1.123)  | 0.934 |
| BSA, m²             | 1.818 (0.186–17.735) | 0.607 |
| WHO-FC              |             |       |
| I                   |             |       |
| II                  | 0.839 (0.087–8.078)  | 0.879 |
| III                 | 0.660 (0.086–5.004)  | 0.689 |
| IV                  | 0.914 (0.118–7.064)  | 0.931 |
| 6MWD, m             | 0.996 (0.993–0.999)  | 0.011 |
| log(NT-proBNP)      | 2.057 (1.218–3.473)  | 0.007 |
| Troponin T, ng/L    | 1.007 (0.988–1.026)  | 0.437 |

### Cardiac MRI

| Variables                  | HR (95% CI) | p     |
|----------------------------|-------------|-------|
| RVEDVi, mL/m²              | 1.005 (1.000–1.011) | 0.054 |
| RVESVi, mL/m²              | 1.008 (1.002–1.013)  | 0.005 |
| RVEF, %                    | 0.955 (0.928–0.982)  | 0.001 |
| LVEDVi, mL/m²              | 0.976 (0.959–0.993)  | 0.006 |
| LVESVi, mL/m²              | 0.972 (0.949–0.996)  | 0.023 |
| LVMass, g/m²               | 0.988 (0.973–1.003)  | 0.122 |
| LVEF, %                    | 0.993 (0.960–1.027)  | 0.671 |
| RVEI                       | 0.104 (0.026–0.409)  | 0.001 |
| LVEI                       | 1.477(1.014–2.153)   | 0.042 |

Note: Values in bold indicate statistically significant p values.

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; BSA: body surface area; WHO-FC: World Health Organization functional class; 6MWD: 6-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; RV: right ventricular; PVR: pulmonary vascular resistance; MRI: magnetic resonance imaging; RVEDVi: right ventricular end-diastolic volume index; RVESVi: right ventricular end-systolic volume index; RVEF: right ventricular ejection fraction; RVEI: right ventricular eccentricity index in end systole.

### Intra- and inter-observer agreement in RVEI measurement

The bias and limits of agreement on intra- and inter-observer variability are shown in Supplementary Fig. S5.
Discussion

This study was performed to assess the diagnostic and prognostic value of RVEI in PAH patients. We found that cardiac MRI-derived RVEI was closely related with RV function and clinical severity of PAH and could serve as a noninvasive diagnostic imaging parameter and as a predictor of prognosis.

In PAH patients, flattening or leftward deviation of the interventricular septum is considered an imaging marker of maladaptive RV remodeling.\textsuperscript{20–22} It is caused by increased RV pressure, prolonged RV shortening, and interventricular mechanical asynchrony.\textsuperscript{20–22} Under pressure overload, the right ventricle assumes a circular shape on cross-sectional images,\textsuperscript{7,23} and this change can be reflected by the RVEI. Echocardiography-derived RVEI has been previously shown to be correlated with the severity of tricuspid regurgitation.\textsuperscript{10,17,24} In the present study, we measured RVEI on conventional cardiac MRI cine images and found significant association of this parameter with PAH severity. RVEI was also shown to be a predictor of outcome of PAH.

In our study, there was no significant association of RVEI with hemodynamic parameters. In previous studies, we found that parameters related with RV remodeling

Table 4. Adjusted Cox regression analysis for the composite endpoint.

| Model          | Variables          | HR      | p       |
|----------------|--------------------|---------|---------|
| Model 1 WHO FC + RVEI |                   |         |         |
| WHO FC I       | Ref                |         |         |
| WHO FC II      | 0.926 (0.096–8.913) | 0.947   |         |
| WHO FC III     | 0.953 (0.124–7.296) | 0.963   |         |
| WHO FC IV      | 1.297 (0.166–10.104) | 0.804  |         |
| RVEI           | 0.100 (0.025–0.404) | 0.001   |         |
| Model 2 6MWD + RVEI |               |         |         |
| 6MWD           | 0.997 (0.993–1.000) | 0.028   |         |
| RVEI           | 0.098 (0.021–0.447) | 0.003   |         |
| Model 3 log (NT-proBNP) + RVEI |   |         |         |
| log (NT-proBNP) | 1.610 (0.902–2.873) | 0.107   |         |
| RVEI           | 0.157 (0.035–0.714) | 0.017   |         |
| Model 4 RAP + RVEI |            |         |         |
| RAP            | 0.953 (0.874–1.039) | 0.272   |         |
| RVEI           | 0.089 (0.021–0.380) | 0.001   |         |
| Model 5 CI + RVEI |             |         |         |
| CI             | 0.924 (0.718–1.187) | 0.534   |         |
| RVEI           | 0.108 (0.027–0.427) | 0.002   |         |
| Model 6 SvO2+RVEI |           |         |         |
| SvO2           | 0.973 (0.946–1.002) | 0.068   |         |
| RVEI           | 0.103 (0.026–0.406) | 0.001   |         |

Note: Values in bold indicate statistically significant p values.
HR: hazard ratio; WHO-FC: World Health Organization functional class; 6MWD: 6-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; RAP: right atrial pressure; SvO2: mixed venous oxygen saturation; RVEI: right ventricular eccentricity index in end systole.

Fig. 3. Kaplan–Meier curves for the traditional PAH risk groups (a). Kaplan–Meier curves for primary endpoint based on RVEI in total PAH patients (b) and in intermediate-risk patients (c).
(RVESV, RVmass/RVEDV, T1 time in RV insertion point, and septum) were also not related with pulmonary artery hemodynamic parameters in PAH. RVEI also was one of the parameters related with RV remodeling and this could be in consistent with previous studies. It could be explained that: (1) In our study, most enrolled patients with PAH concentrated into high range of pulmonary artery pressure (median mPAP: 56 mmHg, interquartile range: 45–74 mmHg); (2) RV remodeling response to increased pressure afterload is a complex process, and RV remodeling process could more likely correlate with the duration of increased afterload; (3) In the complicated process of RV remodeling, individual differences in response to even the same increased pressure afterload could be diverse.

Direct measurement of pulmonary arterial pressure by RHC is the “gold standard” for the diagnosis of PAH. The diagnostic utility of noninvasive imaging in PAH is still not established. Various RV geometrical imaging parameters have been claimed to have some diagnostic value for PAH. A recent study found that ventricular mass index (i.e. right ventricle mass divided by left ventricle mass) ≥0.45 measured by cardiac MRI has 85% sensitivity and 82% specificity for the diagnosis of PAH. Another showed that the systolic leftward deviation of the interventricular septum has 86% sensitivity and 91% specificity for the diagnosis of PAH. Septal angle ratio derived from MRI cine images was shown to have good correlation to be a sensitive index of RV enlargement in PAH. Thus, it is not surprising that RVEI is also a powerful indicator of PAH.

Targeted therapy in PAH aims to maintain right ventricle function or to reverse dysfunction. A best surrogate marker of RV function for use in the clinical setting needs to be identified. Recent studies have identified some RV remodeling indices that are associated with prognosis in PAH. RV EDVi >84 mL/m² has been shown to be significantly associated with poor prognosis in PAH (HR = 4.20; 95% CI: 1.31–8.30; p = 0.011). Right ventricle/left ventricle volume ratio ≥2.3 was shown to reflect severe RV dilation and to indicate a significantly higher risk of mortality in patients with PAH. Apical traction has also been demonstrated to be associated with poor outcome (HR = 14.826, 95% CI: 1.696–129.642; p = 0.015). Fractal dimension measured by fractal analysis as a marker of RV trabecular complexity was associated with elevated afterload (r = 0.30, p < 0.001) and was also a predictor of all-cause mortality (HR = 1.256; 95% CI: 1.011–1.560; p = 0.04). RVEI, which we identified as an important indicator of RV geometrical remodeling and an independent predictor for PAH, is more easily measured in the clinic than by using the above parameters.

Current guidelines recommend risk stratification-driven targeted therapy for PAH. With the conventional risk-stratification methods, reliable prediction of prognosis was possible in PAH patients classified as “low-risk” and “high-risk”, however, leaving scope for interpretation of patients classified as “intermediate-risk” since there was wide variation in severity of PAH. The present study shows that RVEI could be used to classify intermediate-risk patients into different prognostic groups. The use of RVEI in clinical decision making and prognosis prediction merits further study.

**Study limitations**

Some limitations of the study must be mentioned. First, this was a single-center study. Second, the follow-up duration was not very long. Third, the number of patients in the low-risk and high-risk groups were rather small.

**Conclusion**

In summary, RVEI derived from routine cardiac MR cine images is correlated with severity of PAH. RVEI appears to have valuable diagnostic and prognostic value for PAH, especially in intermediate-risk patients, and could be a new and convenient parameter for noninvasive diagnosis of PAH severity.

**Authors’ contribution**

All authors contributed equally to the research design and writing of the article. All authors developed, revised critically for important intellectual content, approved and agree to be accountable for all aspects of the article.

**Ethical approval**

The study was approved by the ethics committee of our institution.

**Guarantor**

Yucheng Chen accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish the work.

**Conflicts of interest**

The author(s) declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. Vonk Noordegraaf A and Galie N. The role of the right ventricle in pulmonary arterial hypertension. Eur Respir Rev 2011; 20: 243–253.
2. Van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011; 58: 2519–2519.
3. Voelkel NF, Quaife RA, Leinwand LA, et al. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. Circulation 2006; 114: 1883–1891.
4. Badagliacca R, Poscia R, Pezzuto B, et al. Right ventricular remodeling in idiopathic pulmonary arterial hypertension: adaptive versus maladaptive morphology. J Heart Lung Transplant 2015; 34: 395–403.
5. Drazner MH. The progression of hypertensive heart disease. Circulation 2011; 123: 327–334.
6. Karas MG and Kizer JR. Echocardiographic assessment of the right ventricle and associated hemodynamics. Progr Cardiovasc Dis 2012; 55: 144–160.
7. Werther Evaldsson A, Ingvarsson A, Smith JG, et al. Echocardiographic right ventricular strain from multiple apical views is superior for assessment of right ventricular systolic function. Clin Physiol Funct Imaging 2018; 39: 168–176.
8. Reiter U, Reiter G, Kovacs G, et al. Native myocardial T1 mapping in pulmonary hypertension: correlations with cardiac function and hemodynamics. Eur Radiol 2017; 27: 157–166.
9. Ghiyo S, Klersy C, Magrini G, et al. Prognostic relevance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension. Int J Cardiol 2010; 140: 272–278.
10. Kim HK, Kim YJ, Park JS, et al. Determinants of the severity of functional tricuspid regurgitation. Am J Cardiol 2006; 98: 236–242.
11. Robert OC, Richard C, Allan LC, et al. ATS statement: guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685–713; quiz 86–88.
12. Callan P and Clark AL. Right heart catheterisation: indications and interpretation. Heart 2016; 102: 147–157.
13. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685–713; quiz 86–88.
14. Schulz-Menger J BD, Bremerich J, Flamm SD, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing Journal of Cardiovascular Magnetic Resonance. J Cardiovasc Magn Reson 2013; 15: 35.
15. Thomas RM, Olivera P, James CD, et al. An echocardiographic index for separation of right ventricular volume and pressure overload. JACC 1985; 5: 918–924.
16. Leuchte HH, ten Freyhaus H, Gall H, et al. Risk stratification strategy and assessment of disease progression in patients with pulmonary arterial hypertension: updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol 2018; 272S: 20–29.
17. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 2018; 39: 4175–4181.
18. Frost AE, Badesch DB, Miller DP, et al. Evaluation of the predictive value of a clinical worsening definition using 2-year outcomes in patients with pulmonary arterial hypertension: a REVEAL Registry analysis. Chest 2013; 144: 1521–1529.
19. Bland JM and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307–310.
20. Palau-Caballero G, Walmsley J, Van Empel V, et al. Why septal motion is a marker of right ventricular failure in pulmonary arterial hypertension: mechanistic analysis using a computer model. Am J Physiol Heart Circ Physiol 2017; 312: H691–H700.
21. Marcus JT, Gan CT, Zwanenburg JJ, et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. J Am Coll Cardiol 2008; 51: 750–757.
22. Tanaka H, Tei C, Nakao S, et al. Diastolic bulging of the interventricular septum toward the left ventricle. An echocardiographic manifestation of negative interventricular pressure gradient between left and right ventricles during diastole. Circulation 1980; 62: 558–563.
23. Grapsa J, Gibbs JS, Cabrita IZ, et al. The association of clinical outcome with right atrial and ventricular remodelling in patients with pulmonary arterial hypertension: study with real-time three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging 2012; 13: 666–672.
24. Sagie A, Schwammenthal E, Paladil LR, et al. Determinants of functional tricuspid regurgitation in incomplete tricuspid valve closure: Doppler color flow study of 109 patients. J Am Coll Cardiol 1994; 24: 446–453.
25. Ryo K, Goda A, Onishi T, et al. Characterization of right ventricular remodeling in pulmonary hypertension associated with patient outcomes by 3-dimensional wall motion tracking echocardiography. Cardiovasc Imaging 2015; 38: e003176.
26. Chen YY, Yun H, Jin H, et al. Association of native T1 times with biventricular function and hemodynamics in precapillary pulmonary hypertension. Int J Cardiovasc Imaging 2017; 33: 1179–1189.
27. Rajaram S, Swift AJ, Capener D, et al. Comparison of the diagnostic utility of cardiac magnetic resonance imaging, computed tomography, and echocardiography in assessment of suspected pulmonary arterial hypertension in patients with connective tissue disease. J Rheumatol 2012; 39: 1265–1274.
28. Alunni JP, Degano B, Arnaud C, et al. Cardiac MRI in pulmonary artery hypertension: correlations between morphological and functional parameters and invasive measurements. *Eur Radiol* 2010; 20: 1149–1159.

29. Swift AJ, Rajaram S, Hurdman J, et al. Noninvasive estimation of PA pressure, flow, and resistance with CMR imaging: derivation and prospective validation study from the ASPIRE registry. *JACC Cardiovasc Imaging* 2013; 6: 1036–1047.

30. Altmayer SP, Patel AR, Addetia K, et al. Cardiac MRI right ventricle / left ventricle (RV/LV) volume ratio improves detection of RV enlargement. *J Magn Reson Imaging* 2016; 43: 1379–1385.

31. Van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2007; 28: 1250–1257.

32. Altmayer SPL, Han QJ, Addetia K, et al. Using all-cause mortality to define severe RV dilation with RV/LV volume ratio. *Sci Rep* 2018; 8: 7200.

33. Unlu S, Farsalinos K, Ameloot K, et al. Apical traction: a novel visual echocardiographic parameter to predict survival in patients with pulmonary hypertension. *Eur Heart J Cardiovasc Imaging* 2016; 17: 177–183.

34. Dawes TJW, Cai J, Quinlan M, et al. Fractal analysis of right ventricular trabeculae in pulmonary hypertension. *Radiology* 2018; 288: 386–395.