Research Article

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Comparison of the capability of risk stratification evaluation between two- and three-dimensional speckle-tracking strain in pre-capillary pulmonary hypertension

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Abstract

To investigate and compare the value of right ventricular longitudinal strain detected by two-dimensional and three-dimensional speckle-tracking echocardiography in risk stratification evaluation in pre-capillary pulmonary hypertension. We consecutively screened 66 patients diagnosed with pre-capillary pulmonary hypertension in our center. According to the risk assessment recommended by 2015 European Society of Cardiology Guidelines, all participants were classified into low- and intermediate-high-risk group. Two-dimensional and three-dimensional strains were measured using off-line softwares (GE EchoPAC version 201 and TomTec, 4D RV Function 2.0). Fifty-seven pre-capillary pulmonary hypertension patients (average 35 years old, 18 males and 39 females) were finally enrolled in our study, 32 (56.1%) were classified in low-risk group, while 25 (43.9%) were in the intermediate-high-risk group. Clinical data associated with disease severity, such as N-terminal pro-brain natriuretic peptide ($r = 0.574$, $P < 0.001$), peak oxygen consumption ($r = -0.484$, $P < 0.001$), and 6-min walking distance ($r = -0.356$, $P = 0.008$) were significantly correlated with two-dimensional right ventricular longitudinal strain; while the correlations with three-dimensional right ventricular longitudinal strain were weaker. Receiver operating characteristic curves for the detection of intermediate-high risk stratification showed two-dimensional right ventricular longitudinal strain had the best predictive capacity (area under curve, 0.82, 95% CI: 0.71–0.93, $P < 0.001$). Univariate and Multivariate Logistic regression analyses identified two-dimensional right ventricular longitudinal strain as an independent predictor (OR: 1.42, 95% CI: 1.18–1.71, $P < 0.001$) of intermediate-high risk stratification in this cohort of pre-capillary pulmonary hypertension patients, the predictive capacity retained (OR: 1.45, 95% CI: 1.18–1.78, $P < 0.001$) after adjusted by age, gender, and body mass index, while three-dimensional speckle-tracking echocardiography parameters were not. In conclusion, when used for the detection of intermediate-high risk stratification in pre-capillary pulmonary hypertension, two-dimensional right ventricular longitudinal strain was better than three-dimensional right ventricular longitudinal strain.

Keywords

strain, two-dimensional speckle-tracking echocardiography, three-dimensional speckle-tracking echocardiography, pulmonary hypertension, risk stratification

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Introduction

Speckle-tracking echocardiography (STE) is currently the widest available technique to quantify myocardial

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deformation.[1] Multiple studies have shown the usefulness of strain quantification of left ventricle (LV) for risk stratification in various cardiac diseases[2,3]; however, data focusing on right ventricular (RV) strain and risk stratification are still limited, especially in population with pulmonary hypertension (PH), who are characterized as RV remodeling and dysfunction.

Pre-capillary PH (PcPH) is a subgroup of PH and share similar hemodynamic characteristics, which is defined as resting mean pulmonary arterial pressure (mPAP) $\geq$25 mmHg and pulmonary artery wedge pressure (PAWP) $\leq$15 mmHg detected by right heart catheterization (RHC).[4] It is well recognized that PH patients often have poor prognosis due to RV dysfunction and failure. The 2015 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of PH recommended using a comprehensive risk stratification to classify PH patients into low-, intermediate-, and high-risk groups, corresponding to estimated one-year mortality <5%, 5–10%, and >10%, respectively.[4] And low-risk state is considered as the goal of treatment. However, the risk stratification is complex, and includes some indices obtained from invasive examinations. Accordingly, in order to adjust treatment regimen timely, an accurate, non-invasive, and convenient evaluation of disease severity is necessary, however, a challenging task.

STE can be applied to two-dimensional (2D), and more recently to three-dimensional (3D) echocardiographic images, while the main limitation remains that strain values vary among methods, modalities, and software version.[5] We have previously reported that 2D-STE detected RV longitudinal strain (RVLS) could improve the prediction of exercise capacity in PcPH.[6] Several other studies also reported the correlations between 2D-STE-RVLS and B-type natriuretic peptide (BNP) levels, 6-min walking distance (6MWD),[7] invasive hemodynamic parameters,[8] and mortality[9,10] in PH patients. Moreover, 3D-STE-RVLS have also been shown to relate to hemodynamic parameters,[11] cardiovascular events, and mortality[12] in PH. However, the comparison of the value of disease severity assessment between 2D- and 3D-STE-RVLS in PcPH has never been investigated before. Therefore, in the present study, we aimed to investigate and further compare the value of 2D- and 3D-STE-RVLS in risk stratification evaluation in PcPH.

Methods

Study population

This is a prospective cross-sectional study, and we consecutively screened 66 patients diagnosed as PcPH from April 2017 to March 2018 in our center. Nine patients were excluded due to poor 3D image quality. As a result, we finally enrolled 57 PcPH patients for analysis in the present study. Exclusion criteria include intracardiac shunts, arrhythmia, acute heart failure, and renal or hepatic failure.

All participants signed their written informed consents. The present study was approved by the Ethics Committee of Fuwai Hospital (No. 2018-1063). All procedures performed in our study involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Clinical data collection and risk stratification

We reviewed medical records to capture clinical data of PcPH patients. Age, gender, body mass index (BMI, kg/m^2, calculated as weight/height^2), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, WHO functional class (WHO-FC), 6MWD, peak oxygen consumption (PVO_2) detected by cardiopulmonary exercise testing, and therapies of each patient were obtained. In addition, hemodynamic parameters including right atrial pressure (RAP), mPAP, PAWP, mixed venous oxygen saturation (SvO_2), cardiac index (Ci), and pulmonary vascular resistance (PVR) were recorded during RHC. All the clinical examinations were performed contemporaneously or at a less than three-day interval with the collection of echocardiographic images. However, hemodynamic indices of 10 patients were not available for analysis in the present study because the RHCs were not performed simultaneously with echocardiography.

Risk assessment was performed in accordance with 2015 ESC Guidelines[4] and other two previous reports.[13,14] Patients were classified into low-, intermediate-, and high-risk groups in terms of WHO-FC, NT-proBNP, exercise capacity (6MWD or PVO_2), and hemodynamic parameters detected by RHC (RAP, Ci, and SvO_2), which is described in Table 1. Each variable was graded from 1 to 3, corresponding with low-, intermediate-, and high-risk, respectively. For each patient, we divided the sum of all grades by the number of available variables and rounded the mean grade off to the nearest integer, which was used to define the patient's risk group.[13] Low-risk profile is recommended to be the goal of treatments, hence, we classified patients into low and intermediate-high risk groups for analysis in the present study.

Echocardiography acquisition and measurement protocol

Transthoracic echocardiographic examinations were performed in the 57 PcPH patients using a Vivid S6 equipment (GE Medical Systems). For each participant, at least three cine-loops of 2DE and 3DE images were acquired from an apical RV-focused four-chamber view.

2D-STE acquisitions and measurements. 2D-STE measurement was performed by a well-trained cardiologist, using an off-line software (GE EchoPAC 201). As shown in Fig. 1, the RV endocardial borders were traced and fine-tuned manually to ensure that the six segments were tracked

Table 1. Included variables from the risk assessment instrument from the ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension and their cut-off values.

Variables	Low risk	Intermediate risk	High risk
WHO-FC	I, II	III	IV
NT-proBNP levels	<300 ng/L	300–1400 ng/L	>1400 ng/L
Exercise capacity (6MWD or PVO_2)			
6MWD	>440 m	165–440 m	<165 m
PVO_2	>15 ml/min/kg	11–15 ml/min/kg	<11 ml/min/kg
Hemodynamics			
RAP	<8 mmHg	8–14 mmHg	>14 mmHg
Ci	≥2.5 L/min/m^2	2.0–2.4 L/min/m^2	<2.0 L/min/m^2
SvO_2	>65%	60–65%	<60%

Adopted from the risk assessment instrument from the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH. Reaching a low-risk profile is recommended to be a treatment goal.
6MWD: six-min walking distance; PVO_2: peak oxygen consumption; Ci: cardiac index; NT-proBNP: N-terminal pro- brain natriuretic peptide; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; WHO-FC: World Health Organization functional class.

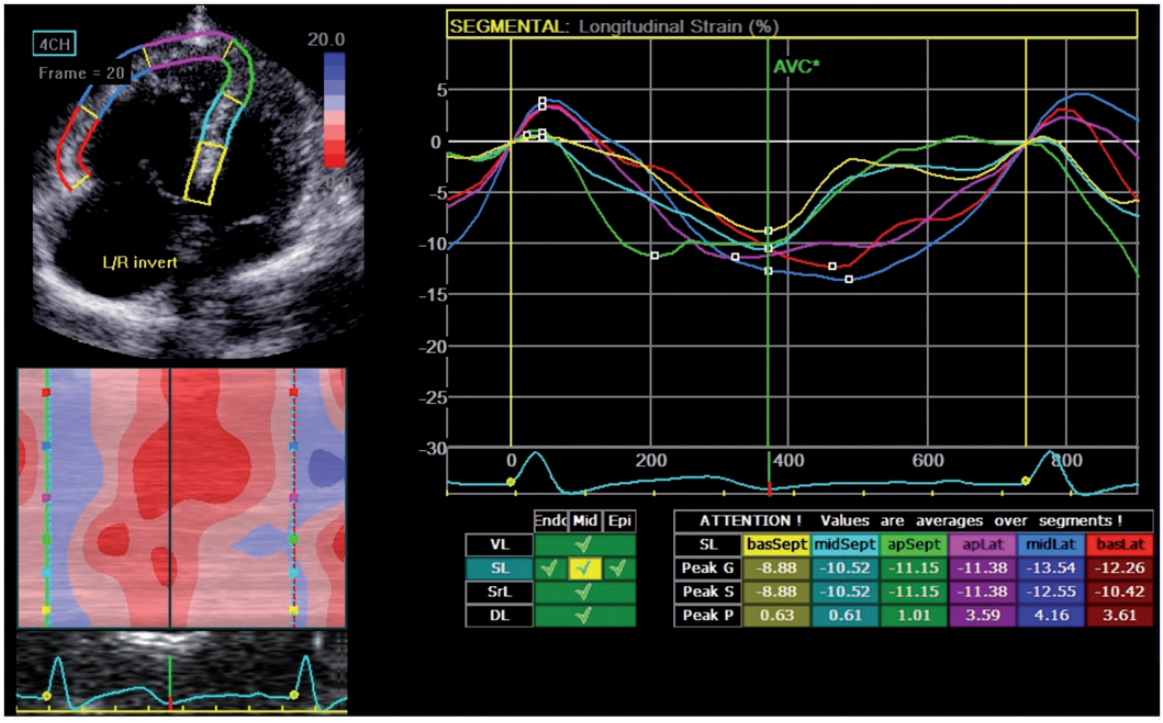

Fig. 1. The right ventricular endocardial borders were traced and fine-tuned manually using GE EchoPAC version 201, and time–strain longitudinal curves of each segment were generated.

appropriately, the 2D RV time-strain curves were then automatically generated. Of all the parameters, the global longitudinal strain (GLS) was used for analysis in our study.

3DE acquisitions and measurements. For 3DE images, full-volume acquisition over two heartbeats was performed during a quiet breath-hold, by the same cardiologist, using an off-line software (TomTec, 4D RV Function 2.0). As shown in Fig. 2, three orthogonal planes and various landmarks were selected to define the end-diastolic and end-systolic frames. It automatically supplies four-chamber, sagittal, and coronal RV views on the basis of the initial view adjustment and allows tracking the RV endocardium

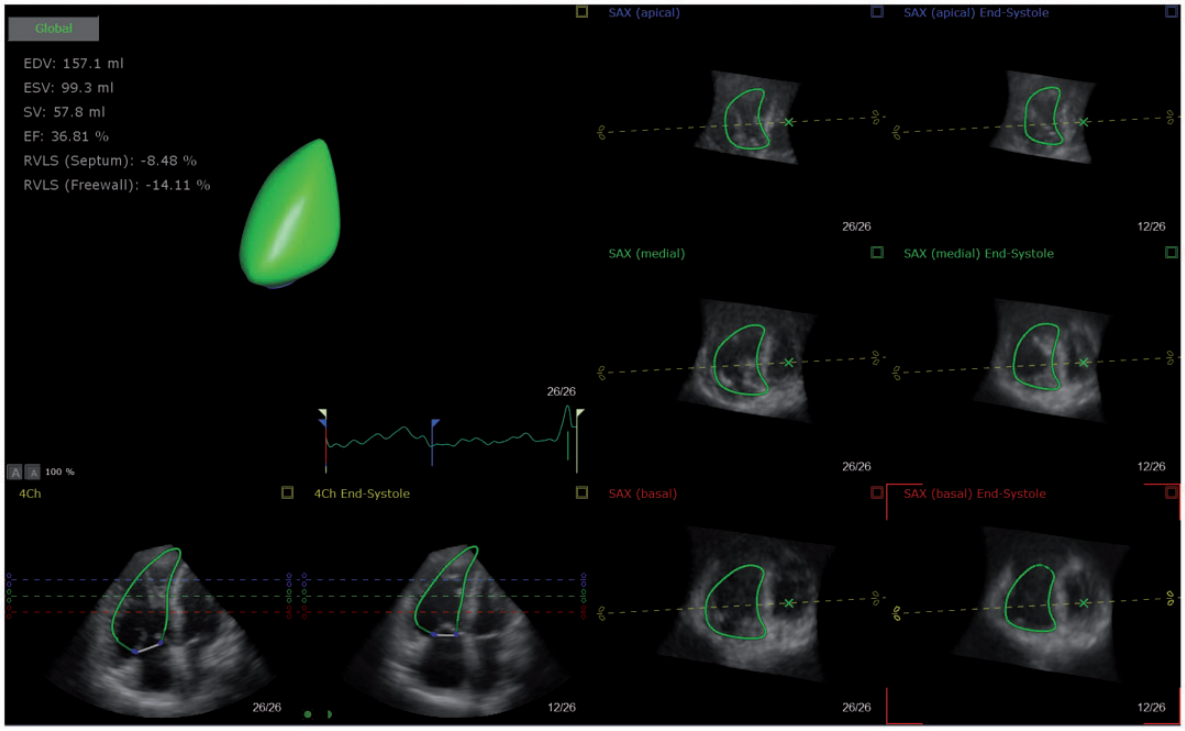

Fig. 2. End-systolic verification and editing of endocardial RV borders using TomTec 4D RV function 2.0.
RVLS: right ventricular longitudinal strain; EDV: end-diastolic volume; ESV: end-systolic volume; EF: ejection fraction.

along the cardiac cycle using 3D speckle-tracking. RVLS of septum (S) and free wall (FW) were automatically generated. We average the RVLS of S and FW, referred to as 3DE-GLS.

The protocol of measurements was in accordance with the guidelines of the American Association of Echocardiography[15] and another current report.[16] Inter-operator variability was assessed in a randomly selected group of 10 PH patients, respectively.

Statistical analysis

Continuous variables were described as mean ± standard deviation if they were normally distributed, while those with skewed distribution were described as median and interquartile range; categorical data were expressed as counts and percentages. Linear correlation analyses were performed to evaluate the correlations between 2D-/3D-STE-RVLS and clinical data, expressed as a Spearman correlation coefficient (r). Receiver operating characteristic (ROC) curves were used to investigate and compare the predictive capability of 2D-/3D-STE-RVLS for the detection of intermediate-high risk. Finally, Univariate and Multivariate Logistic regression analyses were performed to further identify independent predictors of intermediate-high-risk stratification, and the results were expressed as odd ratio (OR) and 95% confidence interval (CI). Intra-class Correlation Coefficient (ICC) was used to assess inter-observer variability of STE measurements.

$P < 0.05$ was considered as statistically significant. SPSS software (version 19.0, IBM) and GraphPad Prism software (version 6.01) were used for analysis.

Results

As described in Table 2, there were 57 PcPH patients (average 35 years old, 18 males and 39 females) enrolled in our study, which included 48 (84.2%) group 1 (PAH) patients and 9 (15.8%) group 4 (chronic thromboembolic PH, CTEPH) patients. All patients were treated with advanced targeted PAH therapy at baseline, except for CTEPH patients. WHO-FC was graded I–II in about 50% patients. Hemodynamic characteristics were available in 47 patients, the mean mPAP was 57 mmHg and mean pulmonary capillary wedge pressure was 7 mmHg. According to the risk assessment described in detail above, 32 (56.1%) patients were classified in low-risk group, while 25 (43.9%) were in intermediate-high-risk group.

The results of linear correlation analyses were shown in Table 3. First, we found that 3D-RV-GLS ($r = 0.288$, $P = 0.049$) and 3D-RVLS (FW) ($r = 0.329$, $P = 0.024$) were significantly and weakly correlated with BMI, and 3D-RVLS (FW) also significantly correlated with age ($r = 0.312$, $P = 0.033$). However, similar correlations were not observed between 2D-RV-GLS and demographic data, such as age and BMI. Second, clinical data associated with disease severity, such as NT-proBNP ($r = 0.574$, $P < 0.001$), PVO_2 ($r = -0.484$, $P < 0.001$), and 6MWD

Table 2. Baseline characteristics of the 57 pre-capillary pulmonary hypertension population.

Characteristics	
Age (years)	35 ± 13
Gender (Male)	18 (31.6%)
BMI (kg/m^2)	22.13 ± 3.38
WHO functional class	
I–II	29 (50.9%)
III–IV	28 (49.1%)
NT-proBNP (pg/ml)	658.6 (149.3, 1780.5)
PVO_2 (ml/min/kg)	13.87 ± 3.55
6MWD (m) ($n = 54$)	413 ± 107
Hemodynamics ($n = 47$)	
mPAP (mmHg)	54 ± 13
RAP (mmHg)	3 (2, 6)
Ci (L/min/m^2)	2.94 (2.49, 3.74)
PVR (dyn · s · cm^{-5})	755.84 ± 275.61
PCWP (mmHg)	7 ± 3
SVO_2 (%)	70.17 ± 5.66
Treatments	
PDE-5i	48 (84.2%)
ERA	28 (49.1%)
PGI	4 (7.0%)
CCB	4 (7.0%)
Echocardiography characteristics	
2D-RV-GLS (%)	−11.74 ± 4.05
3D-RV-GLS (%)	−9.15 (−11.15, −7.06)
3D-RVLS (S) (%)	−6.21 (−8.05, −4.94)
3D-RVLS (FW) (%)	−11.09 (−14.31, −9.34)
Risk assessment	
Low risk	32 (56.1%)
Intermediate-high risk	25 (43.9%)

Notes: Continuous variables were described as mean ± standard deviation (SD) if they were normally distributed, while those with skewed distribution were described as median (interquartile range, IQR); categorical data were expressed as counts (percentages).

Risk assessment was assessed according to 2015 ESC Guidelines.

BMI: body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; PVO_2: peak oxygen consumption; 6WMD: six-min walk distance; mPAP: mean pulmonary arterial pressure; RAP: right atrial pressure; Ci: cardiac index; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; SVO_2: mixed venous oxygen saturation; PDE-5i: phosphodiesterase-5 inhibitors; ERA: endothelin-receptor antagonist; PGI: prostacyclin; CCB: calcium channel blockers; 2D: two-dimensional; 3D: three-dimensional; RV: right ventricle; RVLS: right ventricular longitudinal strain; GLS: global longitudinal strain; S: septum; FW: free wall.

($r = -0.356$, $P = 0.008$) were significantly correlated with 2D-RV-GLS; while the correlations with 3D-RV-GLS were weaker. In addition, 3D-RVLS (FW) showed an association with NT-proBNP ($r = 0.330$, $P = 0.012$), while 3D-RVLS (S) did not. As for hemodynamic parameters, only weak correlations were observed between Ci ($r = -0.307$, $P = 0.036$), PVR ($r = 0.396$, $P = 0.009$), SVO_2 ($r = -0.299$, $P = 0.041$), and 2D-RV-GLS. Finally, all STE parameters showed intermediate correlations with 3DE-RVEF. The correlation coefficients with 3DE RV volumes were 2D-RV-GLS > 3D-RV-GLS > 3D-RVLS (FW) > 3D-RVLS (S).

Fig. 3 showed the ROC curves for the detection of intermediate-high risk stratification. Among all the STE measurements, 2D-RV-GLS showed the best predictive capacity (area under curve, AUC: 0.82, 95% CI: 0.71–0.93, $P < 0.001$). Furthermore, 2D-RV-GLS < −10.8% had an 80% sensitivity and 78.1% specificity of predicting intermediate-high-risk stratification.

Univariate and Multivariate Logistic regression analyses for risk stratification were further performed and results were shown in Table 4. 2D-RV-GLS was identified as an independent predictor (OR: 1.42, 95% CI: 1.18–1.71, $P < 0.001$) of intermediate-high risk stratification in this cohort of PcPH patients, the predictive capacity retained (OR: 1.45, 95% CI: 1.18–1.78, $P < 0.001$) after adjusted by age, gender, and BMI, while 3DE-STE parameters were not.

ICC for inter-observer variability were 0.94 (95% CI: 0.85–0.98) for 2D-RV-GLS, 0.72 (95% CI: 0.55–0.94) for 3D-RVLS (S), and 0.71 (95% CI: 0.52–0.92) for 3D-RVLS (FW), respectively.

Discussion

To the best of our knowledge, this is the first study for comparison between 2D- and 3D-STE strains in the evaluation of risk stratification in PcPH. Novel findings include: (1) 3D-RV strains might be affected by demographic data, such as age and BMI, while 2D-RV-GLS was not; (2) compared with 3D-RV strains, 2D-RV-GLS showed closer correlations with clinical data, hemodynamic characteristics detected by RHC, and 3DE detected RVEF and volumes; (3) 3DE-RVLS of FW showed closer correlations with clinical data than that of S; (4) among all the STE measurements, 2D-RV-GLS showed the best predictive capacity and was identified as an independent predictor of intermediate-high risk stratification in this cohort of PcPH patients, the predictive capacity retained after adjusted by age, gender, and BMI, while 3DE-STE parameters were not.

Speckle tracking provides information about global and segmental myocardial deformation by tracking frame-to-frame over the cardiac cycle, distances between speckles, or their spatiotemporal displacement. And the deformational change of myocardium during the cardiac cycle was referred to as strain.[3] Though there is no established gold standard method to assess strain, STE has been validated in comparison with cardiac magnetic resonance.[17] To date, a number of clinical strain data illustrated that reduction of absolute strain is a marker of decreased RV function,[18] exercise capacity,[6] and poor prognosis[19] in PH patients, either detected by 2D-STE or by 3D-STE. However, due to the paucity of data, this technique is not recommended for routine clinical use according to 2010 Guidelines from American Society of Echocardiography.[15]

Table 3. Linear correlation analyses of 2D/3D-RV strain and clinical data in PH patients.

	2D-RV-GLS		3D-RV-GLS		3D-RVLS (S)		3D-RVLS (FW)	
Characteristics	*r*	*P* values	*r*	*P* values	*r*	*P* values	*r*	*P* values
Clinical data								
Age (year)	–0.040	0.792	0.227	0.125	–0.080	0.594	0.312	0.033[a]
BMI (kg/m^2)	–0.162	0.278	0.288	0.049[a]	0.081	0.587	0.329	0.024[a]
NT-proBNP (pg/ml)	0.574	<0.001[a]	0.341	0.010[a]	–0.231	0.084	0.330	0.012[a]
PVO_2 (ml/min/kg)	–0.484	<0.001[a]	–0.261	0.05[a]	–0.243	0.068	–0.205	0.126
6MWD (m)	–0.356	0.008[a]	0.003	0.983	–0.007	0.961	–0.050	0.719
Hemodynamic parameters ($n = 47$)								
mPAP (mmHg)	0.183	0.218	0.142	0.342	0.251	0.089	0.116	0.436
RAP (mmHg)	–0.070	0.641	–0.195	0.189	–0.100	0.503	–0.178	0.231
Ci (L/min/m^2)	–0.307	0.036[a]	–0.092	0.537	–0.066	0.659	–0.066	0.660
PVR(dyn · s · cm^{-5})	0.396	0.009[a]	0.016	0.920	0.177	0.256	–0.041	0.794
PCWP (mmHg)	–0.143	0.365	0.113	0.475	0.083	0.601	0.061	0.701
SVO_2 (%)	–0.299	0.041[a]	–0.038	0.800	0.024	0.88	–0.045	0.76
3DE-RV parameters								
RVEF	–0.502	<0.001[a]	–0.632	<0.001[a]	–0.571	<0.001[a]	–0.563	<0.001[a]
RV-EDV	0.363	0.006[a]	0.274	0.039[a]	0.168	0.212	0.266	0.046[a]
RV-ESV	0.461	<0.001[a]	0.418	0.001[a]	0.313	0.018[a]	0.391	0.003[a]

[a]$P < 0.05$ was level of significance.

r: Spearman correlation coefficient; 2D: two-dimensional; 3D: three-dimensional; RV: right ventricle; GLS: global longitudinal strain; S: septum; FW: free wall; BMI: body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; PVO_2: peak oxygen consumption; 6MWD: six-min walk distance; mPAP: mean pulmonary arterial pressure; RAP: right atrial pressure; Ci: cardiac index; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; SVO_2: mixed venous oxygen saturation; RVEF: right ventricular ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume.

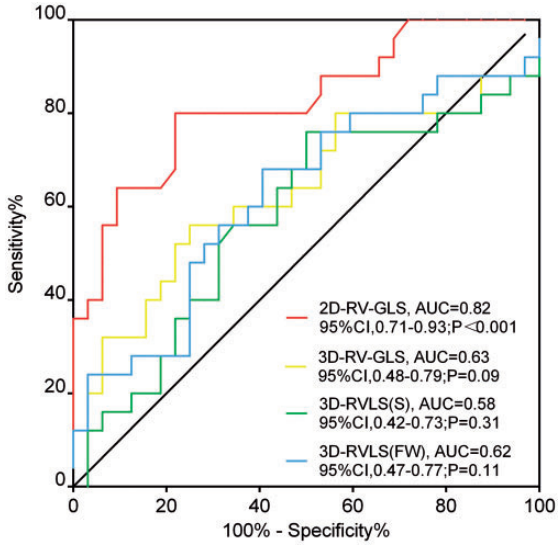

Fig. 3. Receiver operating characteristics curves and area under curves of 2DE and 3DE-RVLS for the prediction of intermediate-high risk stratification in PcPH patients.
2D: two-dimensional; 3D: three-dimensional; RVLS: right ventricular longitudinal strain; S: septum; FW: free wall; GLS: global longitudinal strain; AUC: area under curves; CI: confidence interval.

Therefore, further investigation and evidence should be provided before it is widely used in clinical practice.

The gross anatomy of the RV differs from the LV as it has a more complex geometrical shape. Additionally, the RV epicardial fibers are oriented obliquely, the midwall circumferential layer is poorly developed and the endocardial fibers are oriented longitudinally. This structure explains why RV contraction is mainly determined by longitudinal shortening rather than by circumferential deformation.[20] This is also the possible mechanism of the associations between RVLS and clinical data in PH patients, which were observed in numerous previous studies.[21]

It is worth noting that, however, most of previous studies on disease severity in PH patients used 2D-STE to detect RV strain, while reports focused on 3D-STE parameters were limited. Vitarelli et al. explored the relationships between 2D-/3D-STE echocardiographic parameters with hemodynamic variables indicative of heart failure in PH patients, suggesting that the predictive accuracy for RV failure has no difference between 2D-RVLS (FW) (AUC: 0.88, 95% CI: 0.69–0.98) and 3D-RVLS (FW) (AUC: 0.88, 95% CI: 0.71–0.97).[11] However, the etiology of the population in their study was quite different with those in our study, and

Table 4. Univariate and Multivariate Logistic regression analyses for risk stratification of 57 pulmonary hypertension patients.

Variables	Univariate			Multivariate		
	OR	95% CI	*P* values	OR	95% CI	P values
Age (year)	1.01	0.97–1.06	0.59			
Gender (M)	2.81	0.89–8.88	0.08			
BMI (Kg/m^2)	0.96	0.82–1.12	0.58			
2D-RV-GLS (%)	1.42	1.18–1.71	<0.001[a]	1.45	1.18–1.78	<0.001[a]
3D-RV-GLS (%)	1.01	0.89–1.14	0.91	0.99	0.87–1.13	0.91
3D-RVLS (S) (%)	0.97	0.86–1.10	0.63	0.96	0.85–1.09	0.55
3D-RVLS (FW) (%)	1.04	0.92–1.17	0.52	1.02	0.90–1.16	0.72

[a]$P < 0.05$ was level of significance.

CI: confidence interval; OR: odd ratio; BMI: body mass index; RV: right ventricular; 2D: two-dimensional; 3D: three-dimensional; RV: right ventricle; GLS: global longitudinal strain; RVLS: right ventricular longitudinal strain; S, septum; FW, free wall.

they included patients with post-capillary PH. Furthermore, the methods used to measure 3DE-RVLS were different. Another research reported by Moceri et al. also assessed the implications of 3D-RVLS on clinical condition in PH patients, illustrating that absolute 3D-RVLS significantly decreased as WHO-FC becoming worse, but they use WHO-FC as a single sign of disease severity.[19] The present study used the comprehensive indices in risk stratification according to 2015 ESC Guidelines, whose prognostic accuracy was previously verified.[13,14] Additionally, several studies have evaluated the prognostic value of RV function detected by 3DE or 2DE.[22,23] For example, Ryo et al.[23] classified PH patients into RV adapted, RV adapted–remodeled, and RV adverse–remodeled groups according to 3D wall motion tracking and suggested their associations with clinical outcomes. However, prognostic studies have a common limitation that outcomes can be affected and may vary in different PH subgroups, which were often combined together by researchers. Given that the PH-targeted therapy of some PH subgroups were still controversial, especially for CTEPH,[24] therefore, we could not exclude the effects of therapeutic factors on prognostic analysis. The present study is a cross-sectional study, the evaluation of risk stratification may contribute to guide patient administration, and rarely affected by the treatment.

One of the novel findings in our study was that 2D-RV-GLS had a better predictive capacity for intermediate-high risk stratification than 3D-RVLS. It may be caused by imaging modality related factors, software-related factors, and operator-related factors.[5] One of the possible explanations is that the temporal resolution of 3D-STE is lower than that of 2D-STE,[5] meaning that 3D-STE is more prone to miss the short-lived events during the isovolumic period. In addition, previous studies suggested that LV strain may be affected by age,[25] sex,[26] and obesity;[27] as for RV strain in our study, correlations were also observed between 3D-STE parameters and demographic data. To eliminate these confounding factors, we adjusted age, gender, and BMI in the Multivariate Logistic regression analyses, suggesting that the predictive capacity for risk stratification of 2D-RV-GLS retained, while predictive value of 3DE-STE parameters were still not observed.

In clinical practice, an accurate and timely evaluation of disease severity in PH patients is of great importance. However, the risk assessment strategy recommended by 2015 ESC Guidelines was complicated and included invasive hemodynamic parameters.[4] Therefore, we have dedicated to explore easier and safer ways to evaluate disease severity in PH patients. We previously reported the predictive capacity of 2D-RV-GLS for high risk in PcPH[6]; in the present study, we further illustrated that 2D-RV-GLS was better than 3D-RVLS when used for the detection of intermediate-high risk stratification in PcPH patients. We are looking forward that STE could be a routine examination to evaluate RV function in PH patients in the future.

In conclusion, when used for the detection of intermediate-high risk stratification in PcPH, RVLS detected by 2D STE was better than that detected by 3D STE.

Limitations

Some limitations should be acknowledged. First, a major limitation of this research is our small sample size, which may represent a selection bias. Second, the lack of correlation between hemodynamic parameters and RVLS can be confusing. However, this could be expected as the number of patients with invasive data was relatively low. In addition, though the intervals of RHC and echocardiographic measurements were less than three days, potentially measurements in different hemodynamic states might have occurred. We use a comprehensive risk assessment strategy instead of single hemodynamic data, thus, it is very unlikely that conclusions were affected by this delay. Third, there were inevitable heterogeneity and variability of the echocardiographic measurements, so we used ICC to assess inter-observer variability, and the results were considered

acceptable for our clinical purpose. Finally, given the relatively small cohort of patients, no etiological subgroup analysis was performed. Larger studies are still needed to provide more evidences for clinical applications of STE parameters in PH patients.

Author contributions

B-YL, W-CW, Q-XZ, Z-HL, HW, J-GH, and C-MX contributed to the conception and design of the study. B-YL, W-CW, Q-XZ, L-LN, YT, R-LQ, QL, Z-HZ, J-RL, and C-MX contributed to the acquisition, analyses, and interpretation of data. B-YL drafted the manuscript together with W-CW, Q-XZ, and C-MX and all authors critically revised it. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

Conflict of interest

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

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Ethical approval

Our study was complied with the 1964 Declaration of Helsinki and its later amendments, and approved by the Ethics Committee of Fuwai Hospital (No. 2018-1063).

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