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ORIGINAL PAPER

Two-dimensional speckle tracking echocardiography assessed right ventricular function and exercise capacity in pre-capillary pulmonary hypertension

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Abstract

Resting two-dimensional speckle tracking echocardiography (2D-STE) identified right ventricular (RV) systolic function were reported to predict exercise capacity in pulmonary hypertension (PH) patients, but little attention had been payed to 2D-STE detected RV diastolic function. Therefore, we aim to elucidate and compare the relations between 2D-STE identified RV diastolic/systolic functions and peak oxygen consumption (PVO_2) determined by cardiopulmonary exercise testing (CPET) in pre-capillary PH. 2D-STE was performed in 66 pre-capillary PH patients and 28 healthy controls. Linear correlation and multivariate regression analyses were performed to evaluate and compare the relations between RV 2D-STE parameters and PVO_2. Receiver operating characteristic curves were used to compare the predictive value of 2D-STE parameters in predicting the cut-off—$PVO_2 < 11$ ml/min/kg. There were significant differences of all the 2D-STE parameters between PH patients and healthy controls. In patients, RV-peak global longitudinal strain (GLS, $r_s = -0.498$, $P < 0.001$), RV- peak systolic strain rate (GSRs, $r_s = -0.537$, $P < 0.001$) and RV- peak early diastolic strain rate (GSRe, $r_s = 0.527$, $P < 0.001$) significantly correlated with PVO_2, but no significant correlation was observed between RV- peak late diastolic strain rate (GSRa, $r_s = 0.208$, $P = 0.093$) and PVO_2. The first multivariate regression analysis of clinical data without echocardiographic parameters identified WHO functional class, NT-proBNP and BMI as independent predictors of PVO_2 (Model-1, adjusted $r^2 = 0.421$, $P < 0.001$); Then we added conventional echocardiographic parameters and 2D-STE parameters to the clinical data, identified S,(Model-2,adjusted $r^2 = 0.502$, $P < 0.001$), RV-GLS (Model-3, adjusted $r^2 = 0.491$, $P < 0.001$), RV-GSRe (Model-4, adjusted $r^2 = 0.500$, $P < 0.001$) and RV-GSRs (Model-5, adjusted $r^2 = 0.519$, $P < 0.001$) as independent predictors of PVO_2, respectively. The predictive power was increased, and Model-5 including RV-GSRs showed the highest predictive capability. ROC curves found RV-GSRs expressed the strongest predictive value (AUC = 0.88, $P < 0.001$), and RV-GSRs > −0.65/s had a 88.2% sensibility and 82.2% specificity to predict $PVO_2 < 11$ ml/min/kg. 2D-STE assessed RV function improves the prediction of exercise capacity represented by PVO_2 in pre-capillary PH.

Bing-Yang Liu, Wei-Chun Wu and Qi-Xian Zeng have contributed equally to this work.

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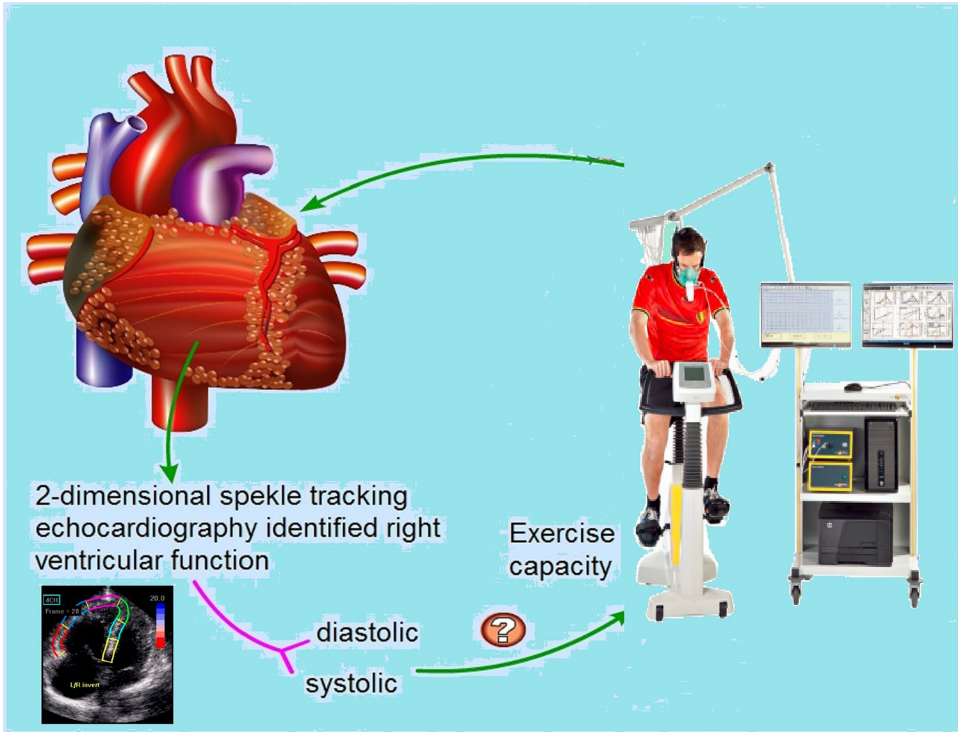
Graphical abstract



Keywords Pulmonary hypertension · 2-dimensional speckle tracking echocardiography · Strain · Strain rate · Cardiopulmonary exercise test · Peak oxygen consumption · Right ventricular function

Introduction

The term pre-capillary pulmonary hypertension (PH) describes a group of patients with pulmonary arterial hypertension (PAH), PH due to lung diseases, chronic thromboembolic PH (CTEPH) and PH with unclear and/or multifactorial mechanisms. They are defined as similar hemodynamic characteristics of a mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg and a pulmonary artery wedge pressure (PAWP) $\leq$ 15 mmHg at rest as assessed by right heart catheterization (RHC) in accordance with 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension [1]. Reports on incidence and mortality of PH at the global level are limited, but a recognized poor prognosis due to right heart failure has been observed in previous studies [2, 3]. Problems of choosing convenient assessment of severity, optimizing individualized therapy and improving survival in PH patients can be challenging for clinicians.

Cardiopulmonary exercise testing (CPET) and/or 6-min walking test (6MWT) were reported to provide diagnostic and prognostic information in PH patients [4–6]. It was recommended that the basic programme of assessment in PAH patients should include at least one measurement of exercise capacity at each visit; Peak oxygen consumption (PVO_2) < 11 ml/min/kg during CPET was corresponding to high risk of mortality (estimated 1-year mortality > 10%) in the comprehensive prognostic evaluation, and was listed as an important factor for high risk stratification of PH in the 2015 ESC/ERS guideline of PH [1]. However, because of the certain absolute and relative contraindications to CPET [7], we need safer measurements to assess the severity and therapeutic effectiveness of PH patients.

Previous studies showed that resting two- dimensional speckle tracking echocardiographic (2D-STE) measurements, such as right ventricular global longitudinal strain (RV-GLS) and RV dyssynchrony parameters, might improve the prediction of exercise capacity and classify PH patients according to 2015 ESC exercise testing risk stratification cut-offs [8]. Hardegree et al. found that RV-GLS assessed by 2D-STE independently predicted clinical deterioration and mortality in PAH patients [9]. Similar conclusions were supported by several previous studies in different groups of PH patients [10–15]. Strain rate (SR) was a derivative of strain and represented the rate of myocardium deformation over time [16]. Kittipovanonth et al. reported that RV systolic strain and SR assessed by Doppler myocardial imaging (DMI) had the potential to recognize early RV dysfunction in PH patients with normal conventional RV systolic parameters [17]. Furthermore, RV diastolic dysfunction was reported to reflect RV filling pressures and thereby be associated with increased mortality [2, 18]. However, little attention had been payed to 2D-STE detected RV diastolic function parameters, and the associations between RV global longitudinal SR, including peak systolic strain rate (RV-GSRs), peak early diastolic strain rate (RV-GSRe), peak late diastolic strain rate (RV-GSRa), and exercise performance in pre-capillary PH patients were still unclear. Given that both RV-GLS and RV-GSRs can be used as novel indices for assessment of RV function and mortality [10, 14], we hypothesize that they also might contribute to non-invasive assessment of exercise capacity and disease severity in pre-capillary PH patients. Therefore, we aimed to elucidate the relations between 2D-STE assessed RV global strain/strain rate and PVO_2 in pre-capillary PH, and to compare the capacity of 2D-STE parameters in predicting $PVO_2 < 11$ ml/min/kg.

Methods

Study population

Sixty-six consecutive patients diagnosed as pre-capillary PH in our center and 28 healthy volunteers were enrolled in this cross-sectional study from April 2017 to March 2018. Table 1 described the diagnosis of all the participants according to 2015 ESC Guidelines. Patients with intra-cardiac shunts, arrhythmia, significant left heart diseases or valve disorders, acute heart failure, renal or hepatic failure, QRS duration > 120 ms or other concomitant diseases including hypertension and diabetes were excluded from the study. All participants in this study signed their written informed consents.

Clinical data collection

Clinical data were obtained by reviewing medical records. Demographic characteristics (age, gender, height and weight), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, etiological classification, WHO functional class (WHO-FC), 6-min walk distance (6MWD) as well as targeted drug usages were acquired from all participants enrolled in this study. Body mass index (BMI, kg/m^2) was calculated as weight/$height^2$.

Table 1 Clinic and echocardiographic characteristics of the 66 pre-capillary PH patients

	Pre-capillary PH (n = 66)
Demographic characteristics	
Age (years)	35 ± 13
Gender (M:F)	19:47
Height (m)	1.62 ± 0.09
Weight (kg)	60.36 ± 12.39
BMI (kg/m^2)	22.58 ± 3.91
Clinical classification	
IPAH	44 (66.7%)
CTEPH	10 (15.2%)
CTD-PAH	8 (12.1%)
PAH after operation of CHD	4 (6.1%)
WHO functional class	
I	8 (12.1%)
II	27 (40.9%)
III	31 (47%)
NT-proBNP (pg/ml)	1113.97 ± 1264.82
Exercise capacity	
PVO_2 (ml/min/kg)	13.97 ± 3.61
6MWD (m)	409.22 ± 107.74
Treatments	
PED-5I	54 (81.8%)
ERA	33 (50%)
PGI	5 (7.6%)
CCB	4 (6.1%)
Echocardiography characteristics	
E/E′	8.98 ± 5.1
RV-FAC (%)	19.8 ± 10.21
TAPSE (mm)	16.61 ± 3.65
S′ (cm/s)	10.44 ± 2.25

Results are represented as mean ± standard deviation or counts and proportions

PH Pulmonary hypertension, *BMI* Body mass index, *PAH* Pulmonary arterial hypertension, *IPAH* Idiopathic PAH, *CTEPH* Chronic thromboembolic pulmonary hypertension, *CTD-PAH* Connective tissue disease induced PAH, *CHD* Congenital heart diseases, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *PVO_2* Peak oxygen consumption, *6WMD* six-minute walk distance, *PED-5I* Phosphodiesterase-5 inhibitors, *ERA* Endothelin-receptor antagonist, *PGI* Prostacyclin, *CCB* Calcium channel blockers, *RV* Right ventricular, *FAC* Fractional area change, *E* Doppler velocities of the trans-tricuspid flow, *E′, S′* Doppler velocities of the tricuspid annulus, *TAPSE* Tricuspid annular plane systolic excursion

Echocardiography acquisition and measurement protocol

Transthoracic echocardiographic examinations were performed in the 66 pre-capillary PH patients and 28 healthy controls by using a Vivid S6 equipment (GE Medical Systems) with a 2.5- to 3.5-mHz probe. All the images were obtained from at least three consecutive beats, and measured using GE EchoPAC version 201 by two trained technicians blinded to clinical data. All the measurements were performed twice according to the guidelines of the American Association of Echocardiography [19] and the average of the two values was used for the analysis.

Standard echocardiographic parameters were described as follows: RV fractional area change (RV-FAC) calculated as:($Area_{max} - Area_{min}$)/$Area_{max}$. $Area_{min}$ was measured at end ventricular systole, which identified as the frame just before tricuspid valve opening, while $Area_{max}$ was measured at end ventricular diastole, corresponding to end atrial systole and identified as the point before the ventricular contraction. Doppler velocities of the trans-tricuspid flow (E, A); Doppler velocities of the tricuspid annulus (E′, S′, pulsed Doppler tissue image) and tricuspid annular plane systolic excursion (TAPSE, M-mode tracings).

2D-STE parameters, such as RV-GLS, RV-GSRs, RV-GSRe and RV-GSRa, were acquired from a RV-focus four-chamber view with a frame rate > 40 fps. The RV endocardial borders were traced and fine-tuned manually to ensure that the six segments (basal, middle and apical of the free wall and interventricular septum) were tracked appropriately as Fig. 1 showed. Figure 1a showed the RV time-strain longitudinal curves of six segments of a PH patient, while Fig. 1b showed the RV time-strain rate longitudinal curves of six segments of a healthy control.

CPET

All the 66 patients underwent a symptom-limited CPET with a 10 W/min incremental cycle ergometer, and PVO_2 was measured breath-by-breath (COSMED Quark PFT Ergo, Italy). The test was considered maximal if peak respiratory exchange ratio (RER) was < 1.1.

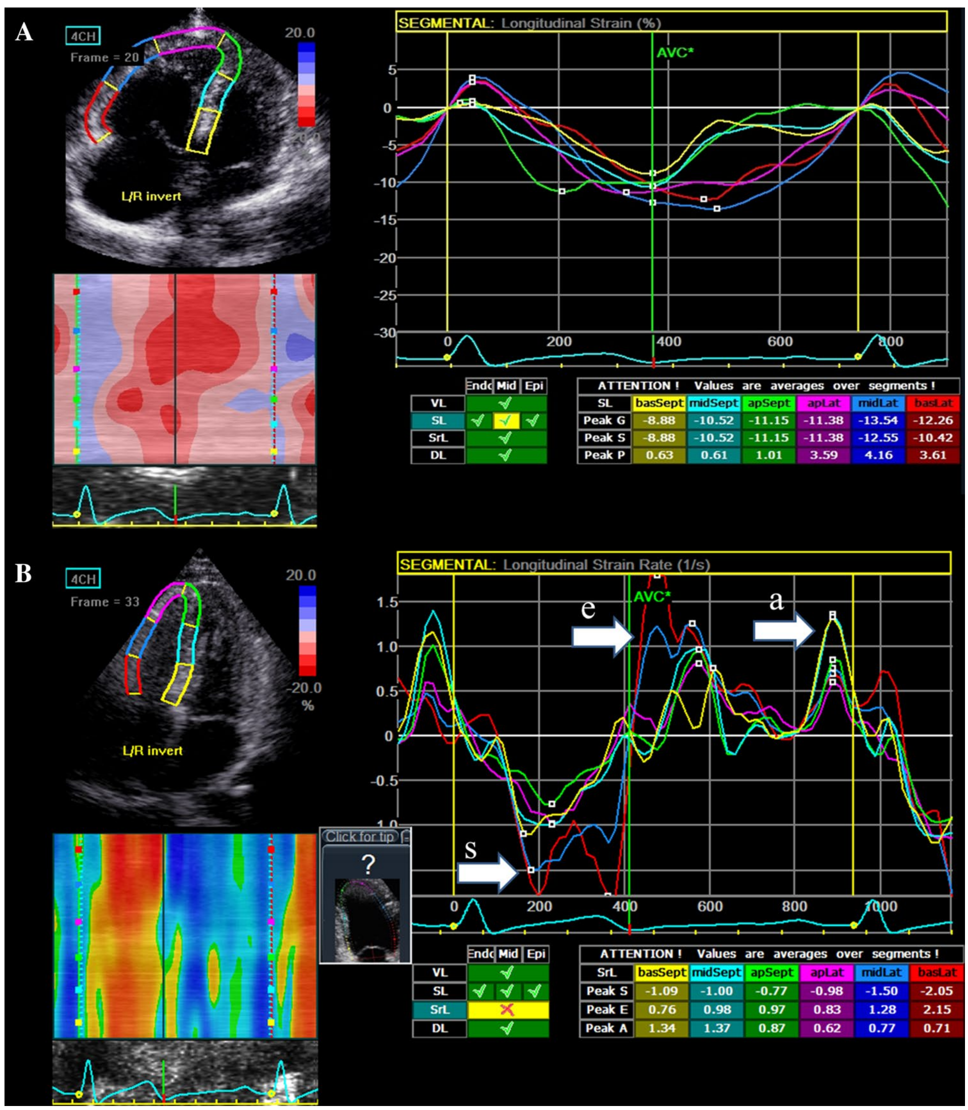


Fig. 1 The right ventricular endocardial border were traced and fine-tuned manually and time-strain longitudinal curves of each segment were generated. **a** time-strain longitudinal curves of six segments in a pre-capillary pulmonary patient; **b** time-strain rate longitudinal curves of six segments in a healthy control; s: peak systolic strain rate; e: peak early diastolic strain rate; a: peak late diastolic strain rate

Statistical analysis

Continuous data were described as mean ± standard deviation (SD), and categorical data were expressed as counts and percentages. Two-group comparisons were performed with unpaired, two-tailed t-tests for means if the data were normally distributed and Chi squared tests were used to analyze the categorical data. Linear correlation analyses were performed to evaluate the correlations between PVO_2 and clinical data, including echocardiographic parameters and 2D-STE characteristics, expressed as a Spearman correlation coefficient (r_s).

Multivariate regression analyses were performed to identify the independent predictors of PVO_2 by a stepwise variable selection method with significant level to entry 0.1 and significant level to stay 0.05. Five models were constructed, and details for each model were described as corresponding adjusted R^2, constant, regression coefficient and P value. Model-1 was constructed by the first multivariate regression analysis which included clinical data only and took no account of echocardiographic parameters. Then the second analysis limited clinical data and conventional echocardiographic indices, without 2D-STE parameters, identified Model-2. Then we added 2D-STE parameters to the clinical and conventional echocardiographic data, respectively, and Model-3,4,5 were constructed. The adjusted R^2 was used to compare the predictive accuracy of the models.

In addition, receive operating characteristic (ROC) curves were used to compare the predictive values of the 2D-STE parameters and identify the optimal cut points for the detection of $PVO_2 < 11$ ml/min/kg.

For 2D-STE parameters, inter-observer variability were assessed for 20 randomly selected patients by the Bland–Altman method, and the results were described as follows: RV-GLS: − 0.13 ± 1.47%, 95% confidence interval (CI): − 3.02 to 2.76%, intra-class correlation coefficients (ICC): 0.953, 95% CI 0.881–0.981; RV-GSRs: 0.01 ± 0.14 s^{-1}, 95% CI − 0.26 to 0.28 s^{-1}, ICC 0.900, 95% CI 0.746–0.960; RV-GSRe: − 0.04 ± 0.12 s^{-1}, 95% CI − 0.29 to 0.21 s^{-1}, ICC 0.933, 95% CI 0.830–0.973; RV-GSRa: 0.02 ± 0.13 s^{-1}, 95% CI − 0.25 to 0.29 s^{-1}, ICC 0.923, 95% CI 0.805–0.969; which can be considered acceptable for our clinical purpose.

All statistical analyses were performed using SPSS software (version 19.0, IBM), GraphPad Prim software (version 6.01) and MedCalc (version 15.2). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

The clinical and conventional echocardiographic characteristics of the 66 pre-capillary PH patients (19 male and 47 female, 35 ± 13 years old) were described in Table 1. More than 80% of the study population were II–III in WHO functional class. 2D-STE parameters of the 66 patients and 28 healthy controls (eight male and 20 female, 34 ± 12 years old) were showed in Table 2, there were significant differences of all the 2D-STE measurements between the two groups.

Linear correlation analyses were used to evaluate correlations between PVO_2 and clinical data, which were described in Table 3. In addition, correlations between PVO_2 and 2D-STE parameters were showed in Fig. 2. Among all the 2D-STE measurements, RV-GSRs approaching RV systolic function seemed to have the strongest correlation with PVO_2 ($r_s = -0.537$, $P < 0.001$), and RV-GLS also significantly correlated with PVO_2 ($r_s = -0.498$, $P < 0.001$). As for RV diastolic function, RV-GSRe showed a relatively stronger correlation with PVO_2 ($r_s = 0.527$, $P < 0.001$), but no significant correlation was observed between RV-GSRa and PVO_2 ($r_s = 0.208$, $P = 0.093$).

As described in Table 4, the first multivariate regression analysis was limited to clinical data without echocardiographic parameters, and identified WHO-FC, NT-proBNP and BMI as independent predictors of PVO_2 (Model-1, adjusted $r^2 = 0.421$, $P < 0.001$). The second analysis included clinical and conventional echocardiographic data, but excluded 2D-STE parameters, Model-2 was constructed and the adjusted r^2 was improved to 0.502 ($P < 0.001$), and

Table 2 Two-dimensional speckle tracking echocardiographic characteristics of the 66 pre-capillary pulmonary hypertension patients and healthy controls

	Pre-capillary PH (n = 66)	Healthy controls (n = 28)	P value
Age (years)	35 ± 13	34 ± 12	0.787
Gender (M:F)	19:47	8:20	0.983
RV-GLS (%)	− 11.67 ± 4.26	− 21.70 ± 4.31	< 0.001
RV-GSRs (s^{-1})	− 0.724 ± 0.26	− 1.2 ± 0.19	< 0.001
RV-GSRe (s^{-1})	0.49 ± 0.31	1.4 ± 0.44	< 0.001
RV-GSRa (s^{-1})	0.77 ± 0.36	0.95 ± 0.29	0.024

Results are represented as mean ± standard deviation or counts and proportions

RV Right ventricular, *GLS* Global longitudinal strain, *GSRs* Global peak systolic strain rate, *GSRe* Global peak early diastolic strain rate, *GSRa* Global peak late diastolic strain rate

Table 3 Linear correlation analyses showed correlations between PVO_2 and clinical data in the 66 pre-capillary PH patients

	Spearman correlation coefficient	P value
Clinical data		
BMI (kg/m^2)	−0.214	0.085
WHO functional class	−0.512	<0.001
NT-proBNP (pg/ml)	−0.493	<0.001
Conventional echocardiography characteristics		
E/E′	−0.41	0.001
RV-FAC (%)	0.369	0.002
TAPSE (mm)	0.187	0.133
S′ (cm/s)	0.35	0.004

PH Pulmonary hypertension, *BMI* Body mass index, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *PVO_2* Peak oxygen consumption, *RV* Right ventricular, *FAC* Fractional area change, *E* Doppler velocities of the trans-tricuspid flow, *E′, S′* Doppler velocities of the tricuspid annulus, *TAPSE* Tricuspid annular plane systolic excursion

identified WHO-FC, NT-proBNP, BMI and S' as independent predictors of PVO_2. Finally, 2D-STE measurements were added to clinical and conventional echocardiographic data in the multivariate regression analysis. Model-3,4,5 were constructed and RV-GLS(Model-3, adjusted $r^2=0.491$, $P<0.001$), RV-GSRe (Model-4, adjusted $r^2=0.500$, $P<0.001$) and RV-GSRs (Model-5, adjusted $r^2=0.519$, $P<0.001$) were identified as independent predictors of PVO_2, respectively. Among all the models constructed in our study, Model-5 including RV-GSRs showed the strongest predictive capability of PVO_2.

ROC curves were performed to compare the predictive capacity for $PVO_2<11$ ml/min/kg among 2D-STE RV global systolic and diastolic strain rate as showed in Fig. 3. RV-GSRs seemed to have the strongest predictive value (area under curve, AUC = 0.88, $P<0.001$). Furthermore, optimal cut-offs of RV-GSRs > −0.65 s^{-1} had a 88.2% sensibility and 82.2% specificity to predict $PVO_2<11$ ml/min/kg, which classified patients into intermediate or high risk according to 2015 ESC Guidelines [1].

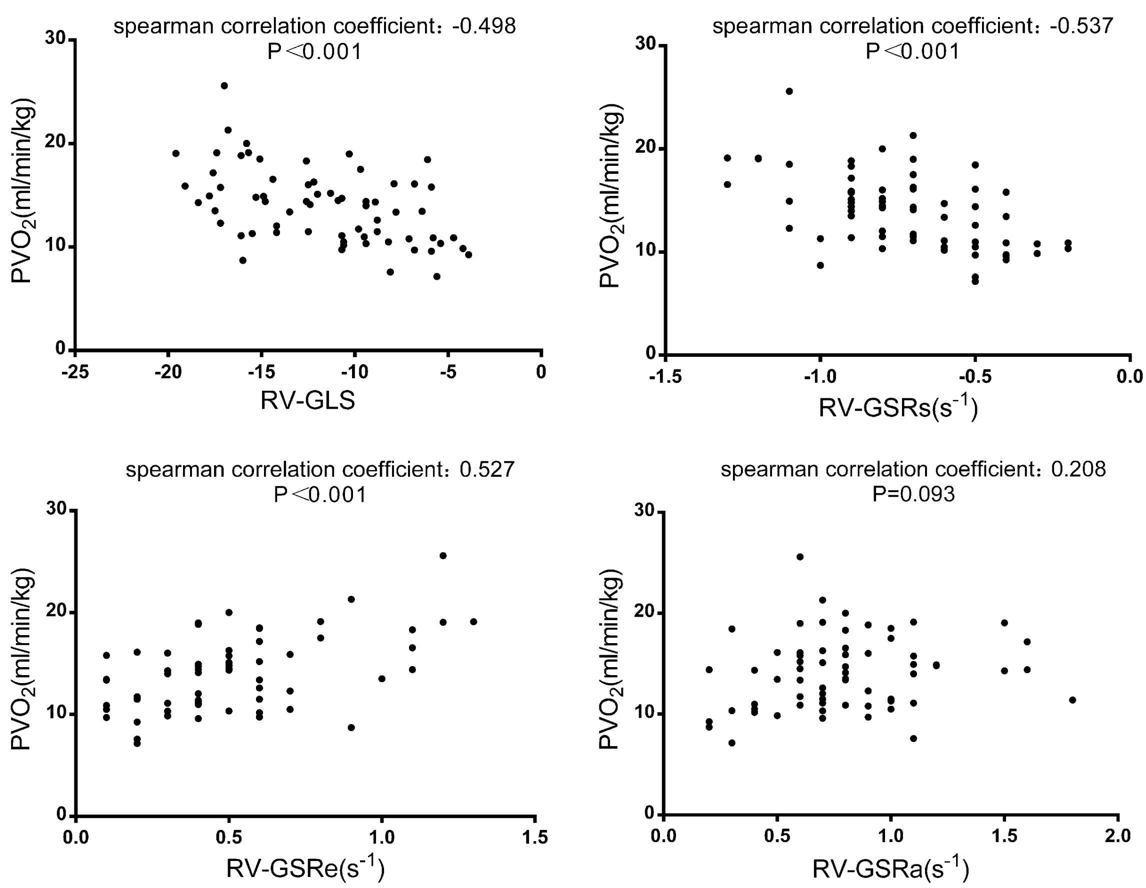


Fig. 2 Relations between resting RV function identified by 2-dimensional speckle tracking echocardiography strain/strain rate and exercise performance. *RV* right ventricle, *GLS* Global longitudinal strain, *GSRs* Global peak systolic strain rate, *GSRe* Global peak early diastolic strain rate, *GSRa* Global peak late diastolic strain rate, *PVO_2* Peak oxygen consumption

Table 4 Multivariate regression analysis of echocardiographic and clinical variables associated with PVO_2

	B	SE	β	P value	Adjusted R^2
Model-1					
Intercept	26.454	2.399		< 0.001	0.421
WHO-FC	− 1.819	0.560	− 0.348	0.002	
NT-proBNP	− 0.001	0.000	− 0.403	< 0.001	
BMI	− 0.307	0.089	− 0.332	0.001	
Model-2					
Intercept	23.037	2.870		< 0.001	0.502
WHO-FC	− 1.829	0.544	− 0.347	0.001	
NT-proBNP	− 0.001	0.000	− 0.365	0.001	
BMI	− 0.336	0.087	− 0.357	< 0.001	
S′	0.384	0.153	0.236	0.015	
Model-3					
Intercept	23.173	2.997		< 0.001	0.491
WHO-FC	− 1.756	0.556	− 0.333	0.003	
BMI	− 0.298	0.089	− 0.317	0.001	
NT-proBNP	− 0.001	0.000	− 0.352	0.031	
RV-GLS	− 0.221	0.100	0.255	0.032	
Model-4					
Intercept	23.108	2.886		< 0.001	0.500
WHO-FC	− 1.554	0.569	− 0.294	0.008	
BMI	− 0.262	0.091	− 0.279	0.006	
NT-proBNP	− 0.001	0.000	− 0.333	0.004	
RV-GSRe	3.108	1.273	0.260	0.018	
Model-5					
Intercept	21.542	3.009		< 0.001	0.519
WHO-FC	− 1.630	0.544	− 0.309	0.004	
BMI	− 0.260	0.088	− 0.277	0.005	
NT-proBNP	− 0.001	0.000	− 0.293	0.010	
RV-GSRs	-4.313	1.477	-0.303	0.005	

WHO-FC WHO functional class, *BMI* Body mass index, *NT-proBNP* N-terminal pro-brain natriuretic peptide; *S′* Doppler velocities of the tricuspid annulus, *RV* Right ventricular, *GLS* Global longitudinal strain; *GSRs* Global peak systolic strain rate, *GSRe* Global peak early diastolic strain rate, *GSRa* Global peak late diastolic strain rate

Discussion

The results of the study demonstrated that RV global systolic function (RV-GLS and RV-GSRs) and early diastolic function (RV-GSRe) assessed by two-dimensional speckle tracking echocardiography significantly correlated with exercise performance identified by PVO_2 during CPET in pre-capillary PH patients, but similar correlation was not observed between RV-GSRa and PVO_2. In addition, to the best of our knowledge, this study was the first time to illustrate that 2D-STE detected RV-GSRs might improve the prediction of PVO_2, and contribute to the evaluation of risk stratification.

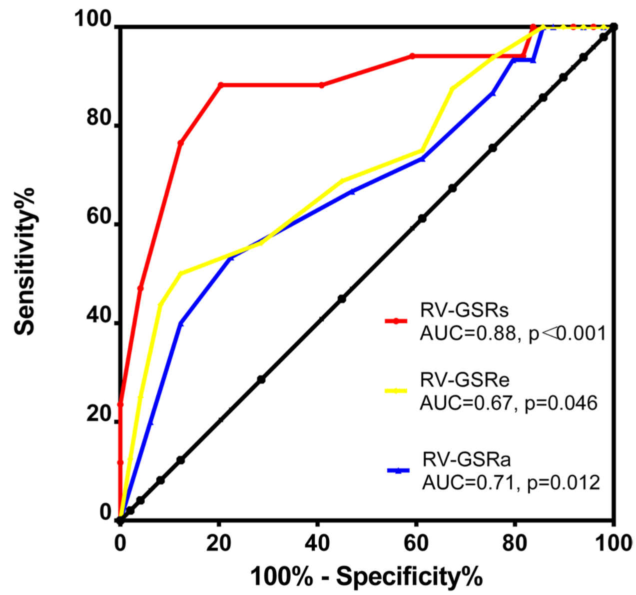


Fig. 3 Comparisons of the Receiver-operator curves for the prediction of $PVO_2 < 11$ ml/min/kg between all the two-dimensional speckle tracking echocardiography parameters: RV-GSRs, RV-GSRe and RV-GSRa. *RV* right ventricle, *GSRs* Global peak systolic strain rate, *GSRe* Global peak early diastolic strain rate, *GSRa* Global peak late diastolic strain rate

2D-STE detected RV systolic and diastolic functions in pre-capillary PH patients and healthy controls

We found that there were significant differences in all of the 2D-STE parameters between pre-capillary PH patients and healthy controls in this study, which illustrated that both systolic and diastolic functions of RV were impaired in PH patients. These findings were partly in according with previous studies [10, 11, 20, 21], and it was well established that the development of PH leaded to the increase of RV afterload and eventually resulted in RV systolic dysfunction, but the RV global diastolic strain rate identified RV diastolic function was not mentioned in their studies. During the development of PH, hypertrophy, fibrosis and stiffening of the RV cardiomyocytes all appeared to contribute to the observed RV diastolic dysfunction [22], which was related to clinical progression in both baseline and treated PAH patients [23], and reported to reflect RV filling pressures and thereby be associated with increased mortality [2, 19]. Therefore, the exact assessment of RV functions, both in systole and diastole, are of great importance to PH patients.

RV global and free wall strain in PH patients

Most of studies in the early days used RV free wall (RVFW) strain and strain rate to reflect RV function [9, 14, 20], illustrated the correlations between RV-FW strain and 6MWD, NT-proBNP, hemodynamic characteristics detected by right heart catheterization, clinical deterioration and mortality in PH patients. A meta analysis conducted by Malay Shukla [24] showed that among the ten publications included in their study, 40% publications reported RV-GLS, which calculated with free wall and interventricular septum, to predict prognosis in PH patients, while others analyzed RV-FWS only. RV-GLS reflects not only RV but also LV function, because the interventricular septum could not be divided into separate left and right ventricular septum; and it was so highly variable in existing reports that we still need further investigations on the best approach. In two recent studies [25, 26], researchers compared the RV-GLS and RV-FWS, suggested that there were no obvious differences between RV-GLS and RV-FWS when compared with RV function and hemodynamics in PH patients. However, in details, RV-GLS showed slightly stronger correlations with 6MWD (correlation coefficient: -0.492 vs. -0.483) and NT-proBNP levels (correlation coefficient: 0.632 vs. 0.627) than RV-FWS [25]; in addition, the Pearson correlation coefficient with RV ejection fraction (RVEF) derived from cardiac magnetic resonance imaging was stronger for echocardiography detected RV-GLS than RV-FWS (0.814 vs. 0.778) [26]. Therefore, we chose RV-GLS instead of RV-FWS to express RV function in the present study.

2D-STE detected RV systolic function and exercise capacity

RV contraction primarily resulted in longitudinal shortening of RV myocytes [27], so the 2D-STE detected RV global longitudinal strain and peak systolic strain rate had the potential to reflect the contraction function of RV. Considering that RV contraction function closely correlated with RV cardiac output and exercise capacity [28], it was not surprising that 2D-STE detected RV-GLS and RV-GSRs significantly correlated with PVO_2.

As regards the models constructed in the present study, higher BMI was reported as a protective factor for death in PAH [29], but there was no evidence to support a direct association with RV function; WHO-FC was also one of the parameters in the risk assessment strategy in 2015 ESC Guidelines of PH [1], while it was to a great extent depended on the subjective sensation of patients; An increase in NT-proBNP reflected RV dilatation concomitant to hypertrophy and deterioration of systolic function [30], however, it was effected by age, gender, ethnicity and renal function [31]. Therefore, the prediction capacity of PVO_2 was significant but low for model-1 including these parameters. 2D-STE detected RV-GLS and RV-GSRs directly reflected the RV contraction function, so that they could improve the prediction capacity of exercise capacity. A recent study [28] showed that 2D-STE derived RV dyssynchrony improved the prediction of exercise capacity in IPAH, which was similar with our results, but strain and strain rate were not mentioned in this study.

2D-STE detected RV early and late diastolic function and exercise capacity

With respect to RV diastolic function, it was well established that chronic RV pressure overload in PH patients causes RV myocardial hypertrophy and fibrosis, which resulted in reduced ventricular compliance [32]. An interesting finding of the present study was that a significant correlation was observed between PVO_2 and early diastolic function (RV-GSRe) assessed by 2D-STE, rather than late diastolic strain rate (RV-GSRa). This finding was never reported before, and the possible mechanism were as follows: RV-GSRe corresponding to isovolumic and early rapid filling periods, which depends largely on the active diastole of RV and filling pressures, while the subsequent RV-GSRa mainly relies on atrial contraction [33]. The active diastole contributes 70–80% of the whole filling quantity [34], and plays a dominating role in the ventricular diastole. In other words, RV-GSRe identified RV early diastole contributed a large proportion of the complete diastole, while RV-GSRa identified RV early diastole just contributed a small part of diastole. These might result in the finding of our study that RV-GSRe, rather than RV-GSRa, significantly correlated with PVO_2.

2D-STE parameters and risk assessment in PH

2015 ESC risk assessment strategy was complicated and included invasive methods such as right heart catheterization (RHC) [1]. In our study, 2D-STE parameters, especially RV-GSRs, showed a predictive capacity of high risk assessment in pre-capillary PH patients. This non-invasive measurement could make the risk assessment strategy more convenient and safer in clinical practice, especially in patients with contraindications to RHC or intolerance to CPET. Michaela et al. reported [35] 2D-STE detected RV global longitudinal strain and RV free-wall longitudinal strain had the similar capacity to classify IPAH patients into different risk groups, but RV longitudinal systolic and diastolic strain rate was not mentioned in their study. No study, before us has designed to use 2D-STE detected strain rate to classify PH patients according to PVO_2 risk stratification cut-offs.

Understanding the implications of 2D-STE measurements, including systolic and diastolic parameters, was the first step for their future applications in clinical practice. Consequently, we need further more researches to provide application guidance, and we are looking forward 2D-STE to be used as a routine measurement for risk assessment and therapeutic strategies in patients with pre-capillary PH in the future.

In conclusion, RV systolic function and early diastolic function assessed by 2D-STE improves the prediction of exercise capacity in pre-capillary PH patients and 2D-STE detected RV peak systolic strain rate may have the potential to classify pre-capillary PH patients according to the exercise testing risk stratification cut-offs.

Limitations

We acknowledge several limitations of our study. First, as a single center study, selectional bias was possible, and the correlations between 2D-STE parameters and PVO_2 were weak to moderate, which may due to the small sample size in our study. Second, all the echocardiographic measurements were performed twice according to the guidelines by an experienced physician to improve the data quality in our study, but there were inevitable heterogeneity and variability of the quality, so we assessed inter-observer variability by the Bland–Altman method, and the results were considered acceptable for our clinical purpose. Third, WHO-FC IV patients were not enrolled in the study, because they were intolerance to exercise testing. Therefore, the aim of our study was of great importance for these patients. Finally, as a cross-sectional study, it was hard to demonstrate the cause-effect relationships. It means that regular follow-up need to be performed in the future.

Author contributions All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval 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.

Informed consent Written informed consent was obtained from all participants in this study.

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