Research Article

Pulmonary Circulation

Left ventricular peak early diastolic strain rate detected by two-dimensional speckle tracking echocardiography and disease severity in pre-capillary pulmonary hypertension

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Abstract

We investigated and compared the correlations between two-dimensional speckle tracking echocardiography detected left ventricular peak early diastolic strain rates (global: left ventricular global peak early diastolic strain rate; septum: left ventricular peak early diastolic strain rate of septum; free wall: left ventricular peak early diastolic strain rate of free wall) and disease severity in pre-capillary pulmonary hypertension. Seventy-four pre-capillary pulmonary hypertension patients (23 males and 51 females, 35 ± 13 years) and thirty healthy controls were consecutively recruited for two-dimensional speckle tracking echocardiography analyses in our study. Medical records of pre-capillary pulmonary hypertension patients were reviewed to capture clinical data; risk assessments were performed based on the 2015 ESC Guidelines. Compared with healthy controls, left ventricular global peak early diastolic strain rate was lower in pre-capillary pulmonary hypertension patients ($1.11 \pm 0.60\,s^{-1}$ versus $1.47 \pm 0.45\,s^{-1}$, $P = 0.001$), especially that of the septum ($1.13 \pm 0.58\,s^{-1}$ versus $1.68 \pm 0.46\,s^{-1}$, $P<0.001$). Linear correlation analyses showed significant but weak correlations between left ventricle diastolic parameters and peak oxygen consumption, N-terminal pro-brain natriuretic peptide, and conventional echocardiographic right ventricle parameters: E/E′, tricuspid annular plane systolic excursion, S′, and fractional area change. No or weak correlations were observed between left ventricle diastolic parameters and hemodynamics. Multivariate logistic regression analyses showed left ventricular global peak early diastolic strain rate (OR: 0.304; 95%CI: 0.101–0.911) and left ventricular peak early diastolic strain rate of septum (OR: 0.252; 95%CI: 0.075–0.848) independently predict intermediate–high risk of pulmonary hypertension patients, even adjusted by age, gender, and body mass index. Receive operating characteristic curves showed that all the three models had the capacity to predict intermediate–high risk of pulmonary hypertension patients, and the model including left ventricular peak early diastolic strain rate of septum showed the strongest predictive capacity (area under the curve = 0.76, 95%CI: 0.59–0.93). Two-dimensional speckle tracking echocardiography detected left ventricle diastolic function parameters are significantly correlated with clinical data and can independently predict intermediate–high risk in pre-capillary pulmonary hypertension patients; the dysfunction of interventricular septum may make major contribution.

Keywords

Pre-capillary pulmonary hypertension, two-dimensional speckle tracking echocardiography, left ventricle, diastolic function, severity

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Introduction

Pre-capillary pulmonary hypertension (PcPH) describes a group of disorders including pulmonary arterial hypertension (PAH), pulmonary hypertension (PH) due to lung diseases, chronic thromboembolic pulmonary hypertension (CTEPH), and PH with unclear and/or multifactorial mechanisms, except for left heart disease.[1] It is well established that chronic pressure and volume overload inevitably result in right heart myocardial remodeling and right heart failure in PH patients.[2,3] In recent years, left ventricular (LV) dysfunction has been gradually detected even in mild idiopathic pulmonary arterial hypertension (IPAH) patients[4] and is reported to be associated with WHO functional class (WHO-FC), hemodynamics, and survival.[5–7] However, almost all of the previous studies focused on LV systolic dysfunction while little attention had been paid to LV diastolic dysfunction in PcPH patients, and the role of ventricular septum and free wall in diastolic dysfunction is unclear.

According to 2016 American Society of Echocardiography (ASE) recommendations and other previous studies,[7,8] conventional echocardiographic parameters like LV relaxation, filling pressure, mitral E/A ratio, average E/e′ ratio, peak tricuspid regurgitation (TR) velocity, and left atrium (LA) volume index are used to estimate diastolic function. However, a concern is that these parameters are angle dependent, less reproducible for nonbasal segments, and highly dependent on probe rotation by the user.[9] For example, the accuracy of mitral E/e′ ratio, one of the most widely used indices, tended to decrease in patients with regional dysfunction at the sampled segments.[10] As a novel measurement of diastolic function, two-dimensional speckle tracking echocardiography (2D-STE) detected LV global peak early diastolic strain rate (LV-GSRe) was reported to predict outcomes in several disease states[11,12] while it has not been investigated in PcPH patients yet.

Moreover, on the basis of 2015 ESC Guidelines for the diagnosis and treatment of PH, the risk assessment strategy contributes to classify PAH patients into low, intermediate, and high-risk groups, corresponding to estimated one-year mortality <5, 5–10, and >10%, respectively.[1] In clinical practice, low-risk classification can be used as treatment goals. In other words, intermediate–high risk classification after PAH-targeted therapy means the specific therapy needs to be re-considered. However, the risk assessment strategy is complicated and contains invasive examinations, such as right heart catheterization (RHC), which might expose patients to operational risks. Boucly et al.[13] put forward a simplified risk assessment tool, which quantified the number of noninvasive low-risk criteria and accurately predicted transplant-free survival in PAH. Therefore, the present study aimed to investigate the correlations between 2D-STE detected LV diastolic function and clinical data in PcPH patients. Additionally, we compared the predictive capacity of 2D-STE assessed LV diastolic parameters in disease severity according to the 2015 ESC Guidelines risk assessment strategy.[1]

Methods

Study population

We consecutively recruited 74 PcPH patients and 30 healthy controls from April 2017 to May 2018 in our center. PcPH was diagnosed according to 2015 ESC Guidelines: mean pulmonary arterial pressure (mPAP) ≥25 mmHg and a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg at rest assessed by RHC.[1] Patients with intra-cardiac shunts, arrhythmia, acute heart failure, renal or hepatic failure, QRS duration >120 ms, or other concomitant diseases like diabetes were excluded from our study. Healthy controls were recruited for echocardiographic analyses and had no previous medical history.

Written informed consents were obtained from all the patients or their legal representatives.

Conventional echocardiography

Conventional transthoracic echocardiographic examinations were performed in 74 PcPH patients by a trained technician using a Vivid S6 equipment (GE Medical Systems) with a 2.5–3.5 mHz probe. Parameters including LV systolic function (LVEF); LV diastolic function (mitral E/A ratio, E: the early diastolic Doppler velocities of the trans-mitral flow; A: the late diastolic Doppler velocities of the trans-mitral flow); right ventricle (RV) systolic function (RV fractional area change, RV-FAC, tricuspid annular plane systolic excursion, TAPSE, the peak systolic Doppler velocities of the tricuspid annulus, S′); and RV diastolic function (RV E/E′, E: the early diastolic Doppler velocities of the trans-tricuspid flow; E′: the early diastolic Doppler velocities of the tricuspid annulus) were obtained. All parameters were measured in accordance to the guidelines of the ASE.[9,10]

Two–dimensional speckle tracking echocardiography

A standard four-chamber view with a frame rate >40 fps was obtained from at least three consecutive beats, and measured by two trained technicians blinded to clinical data using GE EchoPAC version 201. The LV endocardial borders were traced and fine-tuned manually and global peak early diastolic strain rate was then automatically generated (Fig. 1). Additionally, we averaged the peak early diastolic strain rate of the three segments of septum and free wall, referred to as LV peak early diastolic strain rate of septum (LV-S-SRe) and LV peak early diastolic strain rate of free wall (LV-FW-SRe), respectively.

Clinical data

Medical records were reviewed to capture detailed clinical data of the 74 PcPH patients. The patients routinely underwent a symptom-limited cardiopulmonary exercise testing, while eight patients were too weak to perform it.

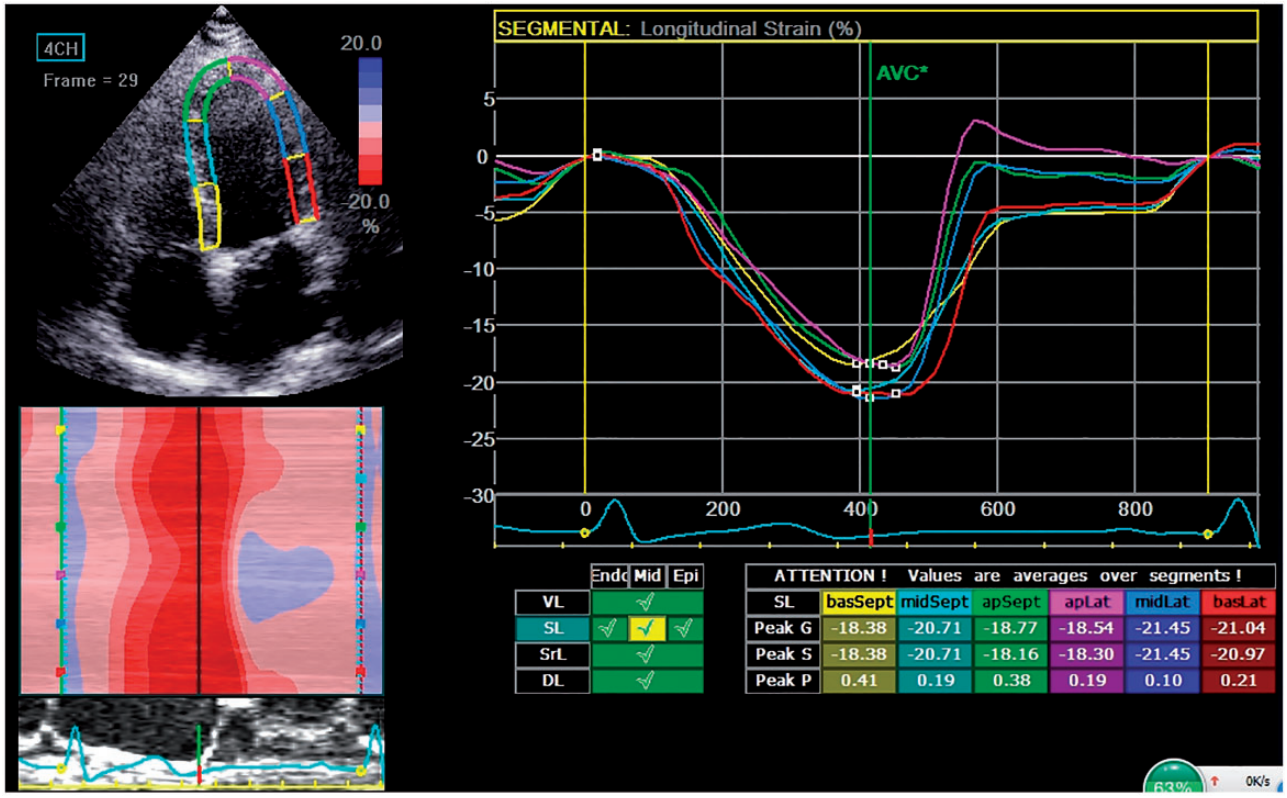

Fig. 1. The left ventricular endocardial borders were traced, and global peak early diastolic strain rate was automatically generated.

Additionally, we captured the demographic characteristics, N-terminal pro-brain natriuretic peptide (NT-proBNP), etiological classification, WHO-FC, six-minute walking distance (6MWD), as well as PAH-targeted therapies of all participants, and all the clinical assessments were performed contemporaneously with the echocardiography testing.

Risk assessment

On the basis of the risk assessment strategy of 2015 ESC Guidelines, all the PcPH patients were classified into low risk or intermediate–high risk groups. Low risk was considered when a patient fulfilled all the following criteria simultaneously: the absent of clinical signs of right heart failure, no progression of symptoms or syncope, WHO-FC I–II, 6MWD > 440 m, peak oxygen consumption (PVO_2) > 15 ml/min/kg, NT-proBNP < 300 pg/ml, no pericardial effusion, right atrial pressure (RAP) < 8 mmHg, cardiac index ≥ 2.5 l/min/m^2, and SvO_2>65%. It was worth noting that among the 74 patients, 55 patients were treatment-naïve and the intervals between echocardiography and RHC were within 24 h. RHC parameters of other 19 patients could not be taken into account in our study because this was a cross-sectional risk assessment. Coincidentally, irrespective of RHC parameters, other clinical data of those 19 patients could not meet the criteria of low risk. Therefore, these patients were all classified into intermediate–high risk group and not excluded from the present study.

In addition, we quantified the number of noninvasive low-risk criteria: WHO-FC I or II; 6MWD > 440 m; NT-proBNP < 300 pg/ml, patients were then classified into four groups (0, 1, 2, and 3 criteria) as a previous study described.[13]

Statistical analysis

Continuous variables were described as mean ± standard deviation and compared using two-tailed t-tests if they were normally distributed, while those with skewed distribution were described as median (interquartile range) and compared using Mann–Whitney U and Kruskal–Wallis tests; categorical data were expressed as counts and percentages. Chi-squared tests were used to analyze the categorical data. Linear correlation analyses were performed to evaluate the correlations between LV-GSRe and clinical data, expressed as a Pearson or Spearman correlation coefficient (r). In addition, univariate and multivariate logistic regression analyses were performed to identify independent variables associated with the intermediate–high risk assessment, and the results were expressed as odds ratio and 95% confidence interval (CI). Receive operating characteristic (ROC) curves were used to compare the predictive capability of logistic regression models for the detection of intermediate–high risk. Bland–Altman method and intraclass correlation coefficient (ICC) were used to assess intra- and inter-observer variability of LV-GSRe measurements.

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

Results

Clinical characteristics of the 74 PcPH patients (23 male and 51 female, average age 35 ± 13 years old) enrolled in our study were described in Table 1. There were 50 (67.6%) patients diagnosed with IPAH, 11 (14.9) patients with CTEPH, 9 (12.2%) with connective tissue disease associated PAH, and 4 (5.4%) with PAH after operation of congenital heart diseases. Approximately 85% of the participants had a WHO-FC I–III. LV ejection fraction ($63.07 \pm 6.36\%$) was normal in all of the participants. In addition, the hemodynamic parameters of 55 treatment-naïve patients are also shown in Table 1, and their mean PCWP is 7 mmHg. As shown in Table 2, there were 30 age- and sex-matched healthy controls (8 male and 22 female, average age 34 ± 11 years old) recruited for echocardiographic analyses. LV-GSRe ($1.47 \pm 0.45\,s^{-1}$ versus $1.11 \pm 0.60\,s^{-1}$, $P = 0.001$) and LV-S-SRe ($1.68 \pm 0.46\,s^{-1}$ versus $1.13 \pm 0.58\,s^{-1}$, $P = 0.001$) of them were significantly higher than PcPH patients. Furthermore, though the LV-FW-SRe of healthy controls tended to be higher than PH patients ($1.94 \pm 0.60\,s^{-1}$ versus $1.70 \pm 0.83\,s^{-1}$, $P = 0.152$), no significant difference was observed.

Table 3 shows the correlations between 2D-STE detected LV diastolic parameters and clinical data. First, there were significant but weak correlations between LV diastolic parameters and clinical data, such as NT-proBNP, PVO_2, and WHO-FC. Compared with LV-FW-SRe, LV-S-SRe showed stronger correlations with clinical data. Second, we compared 2D-STE detected and conventional (mitral E/A ratio) measurements of LV diastolic function, and significant correlations were observed. Additionally, 2D-STE detected LV diastolic function parameters were significantly correlated with conventional echocardiographic parameters of RV systolic function (RV-FAC, RV-S′, TAPSE) and diastolic function (RV E/E′). As regards the subgroup analyses of RHC assessed hemodynamic parameters, no correlations were noted between 2D-STE detected LV diastolic function parameters and RAP, mPAP, cardiac index, or PCWP. A relatively weak correlation was observed between LV-S-SRe and pulmonary vascular resistance (PVR).

Among the 74 pre-capillary PH patients, 11 patients met the predefined criteria for low-risk classification. Figure 2 shows that all the three parameters were higher in low-risk group than intermediate–high risk group. The results were described as follows: LV-GSRe, 1.60 (1.10–1.90)s^{-1} versus 0.90 (0.60–1.40)s^{-1}, $P = 0.021$; LV-S-SRe, 1.33 (0.91–2.00)s^{-1} versus 0.93 (0.62–1.50)s^{-1}, $P = 0.029$; LV-FW-SRe, 2.17 (1.54–2.50)s^{-1} versus 1.61 (1.02–2.11)s^{-1}, $P = 0.056$. Figure 3 shows that as the number of noninvasive

Table 1. Baseline characteristics of the 74 pre-capillary pulmonary hypertension population.

Characteristics	
Age (years)	35 ± 13
Gender (male)	23 (31.08%)
Height (m)	1.63 ± 0.09
Weight (kg)	60.17 ± 12.62
BMI (kg/m^2)	22.57 ± 3.86
WHO functional class	
I–II	36 (48.6%)
III–IV	38 (51.4%)
NT-proBNP (pg/ml)[a]	990.05 (491.33, 2155.5)
NT-proBNP < 300 pg/ml	23 (31.1%)
PVO_2 (ml/min/kg) (n = 66)	13.97 ± 3.61
PVO_2 > 15 ml/min/kg	23 (34.8%)
6MWD (m)	408.39 ± 114.75
6MWD > 440 m	29 (39.2%)
Hemodynamics (n = 55)	
mPAP (mmHg)	54 ± 14
RAP (mmHg)[a]	3 (2, 6)
cardiac index ($l/min/m^2$)	3.2 ± 0.8
PVR (dyn s/cm^5)	779.7 ± 288.3
PCWP (mmHg)	7 ± 3
Mixed venous oxygen saturation (%)	70.2 ± 5.5
Treatments	
PDE-5i	57 (77%)
ERA	38 (51.4%)
PGI	9 (12.2%)
CCB	4 (5.4%)
Echocardiography characteristics	
LVEF (%)	63 ± 6
LV-GSRe (s^{-1})	1.11 ± 0.60
Mitral E/A ratio	1.0 ± 0.4
RV E/E′[a]	7.5 (5.4, 11.0)
RV-FAC (%)	19.4 ± 10.0
TAPSE (mm)	16.3 ± 3.8
RV S′ (cm/s)	10.3 ± 2.2
Risk assessment	
Low risk	11 (14.9%)
Intermediate–high risk	63 (85.1%)

BMI: body mass index; CCB: calcium channel blockers; E,A: Doppler velocities of trans-tricuspid/-mitral flow; EF: ejection fraction; ERA: endothelin-receptor antagonist; E′, S′: Doppler velocities of the tricuspid annulus; FAC: fractional area change; GSRe: global peak early diastolic strain rate; LV: left ventricle; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; PCWP: pulmonary capillary wedge pressure; PDE-5i: phosphodiesterase-5 inhibitors; PGI: prostacyclin; PVO_2: peak oxygen consumption; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RV: right ventricle; 6MWD: six-minute walk distance; TAPSE: tricuspid annular plane systolic excursion.

Risk assessment was assessed according to 2015 ESC Guidelines.

Continuous variables were described as mean ± standard deviation if they were normally distributed and categorical data were described as counts (proportions).

[a]Continuous variables with skewed distribution were described as median (interquartile range).

low-risk criteria increased, the three LV diastolic parameters also increased (Supplemental Table S1).

Univariate (Supplemental Table S2) and multivariate logistic regression analyses were performed to identify independent predictive factors for intermediate–high risk group. As described in Table 4, LV-GSRe and LV-S-SRe independently predicted intermediate–high risk of PH patients after adjusting for age, gender, and BMI, and LV-S-SRe expressed the strongest predictive capacity. Furthermore, ROC curves showed that all the three models had the capacity to predict intermediate–high risk of PcPH patients, and Model-2 including LV-S-SRe showed the strongest predictive capacity (area under the curve $=0.76$, 95%CI: 0.59–0.93) (Fig. 4).

For LV-GSRe measurement, intra- and inter-observer variability were assessed for 20 randomly selected patients by the Bland–Altman method, and the results were 0.025 ± 0.18, 95%CI: -0.33 to 0.38 and 0.04 ± 0.19, 95%CI: -0.34 to 0.42, respectively; ICC: 0.98, 95%CI: 0.95–0.99 and 0.97, 95%CI: 0.93–0.99, respectively, which can be considered acceptable for our clinical purpose.

Table 2. Two-dimensional speckle tracking echocardiography detected LV global peak early diastolic strain rate of the 74 pre-capillary pulmonary hypertension patients and 30 healthy controls.

	Pre-capillary PH (n = 74)	Healthy controls (n = 30)	P value
Age (years)	35 ± 13	34 ± 11	0.676
Gender (male)	23 (31.1%)	8 (26.7%)	0.814
LV-GSRe (s^{-1})	1.11 ± 0.60	1.53 ± 0.47	0.001
LV-S-SRe (s^{-1})	1.13 ± 0.58	1.68 ± 0.46	<0.001
LV-FW-SRe (s^{-1})	1.70 ± 0.83	1.94 ± 0.60	0.152

FW-SRe: peak early diastolic strain rate of free wall; GSRe: global peak early diastolic strain rate; LV: left ventricular; S-SRe: peak early diastolic strain rate of septum.
Results are represented as mean ± standard deviation or counts and proportions.

Discussion

Since quite a number of PH patients presented with LV functional impairment as reported previously,[4,7] our study first investigated the correlations between LV diastolic function and clinical data in pre-capillary PH patients and further compared the role of LV septum and free wall in the diastolic dysfunction. We noted significant correlations between 2D-STE detected LV diastolic parameters and clinical data, such as WHO-FC, PVO_2, and conventional

Table 3. Linear correlation analyses of LV diastolic parameters and clinical data in PH patients.

	LV-GSRe		LV-S-SRe		LV-FW-SRe	
Characteristics	r	P value	r	P value	r	P value
Clinical data						
NT-proBNP (pg/ml)[a]	−0.49	<0.01*	−0.57	<0.01*	−0.44	<0.01*
WHO-FC	−0.26	0.03*	−0.32	<0.01*	−0.24	0.04*
PVO_2 (ml/min/kg)	0.36	<0.01*	0.28	0.03*	0.28	0.03*
Conventional echocardiographic parameters						
Mitral E/A ratio	0.43	<0.01*	0.37	<0.01*	0.41	<0.01*
RV E/E′[a]	−0.36	<0.01*	−0.43	<0.01*	−0.33	<0.01*
RV-FAC (%)	0.50	<0.01*	0.45	<0.01*	0.46	<0.01*
TAPSE (mm)	0.36	<0.01*	0.54	<0.01*	0.29	0.01*
RV S′ (cm/s)	0.44	<0.01*	0.44	<0.01*	0.42	<0.01*
Hemodynamic parameters						
mPAP (mmHg)	−0.05	0.70	−0.10	0.46	−0.13	0.36
RAP (mmHg)[a]	−0.07	0.62	−0.08	0.55	−0.06	0.70
cardiac index (l/min/m^2)	0.18	0.19	0.21	0.12	0.12	0.39
PVR (dyn s/cm^5)	−0.15	0.31	−0.29	0.04*	−0.13	0.39
PCWP (mmHg)	0.20	0.16	0.18	0.21	0.20	0.17

E,A: Doppler velocities of trans-tricuspid/-mitral flow; E′, S′: Doppler velocities of the tricuspid annulus; FAC: fractional area change; FW-SRe: peak early diastolic strain rate of free wall; GSRe: global peak early diastolic strain rate; LV: left ventricle; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; PCWP: pulmonary capillary wedge pressure; PVO_2: peak oxygen consumption; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RV: right ventricle; S-SRe: peak early diastolic strain rate of septum; TAPSE: tricuspid annular plane systolic excursion; WHO-FC: WHO functional class.
r: Pearson correlation coefficient.
*$P < 0.05$ was level of significance.
[a]NT-proBNP, RV E/E′, and RAP were skewed distributed and described as a Spearman correlation coefficient.

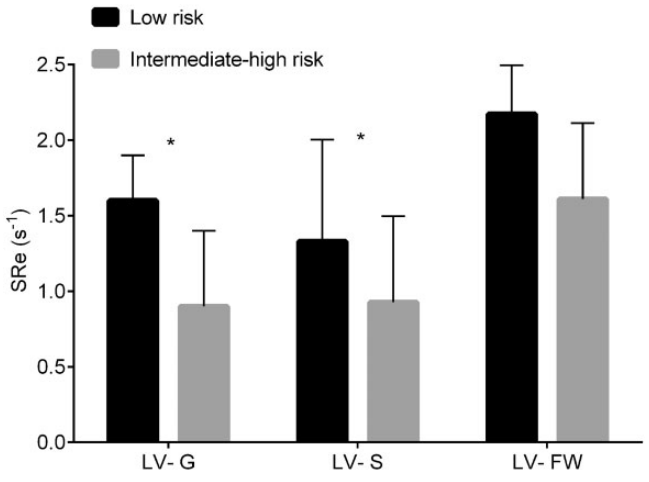

Fig. 2. Histograms of 2D-STE detected LV diastolic parameters based on risk assessment according to 2015 ESC Guidelines. *P<0.05. Comparisons were performed with Mann–Whitney U tests. Means and interquartile ranges are displayed by boxes and whiskers. FW: free wall; G: global; LV: left ventricle; S: septum; SRe: peak early diastolic strain rate.

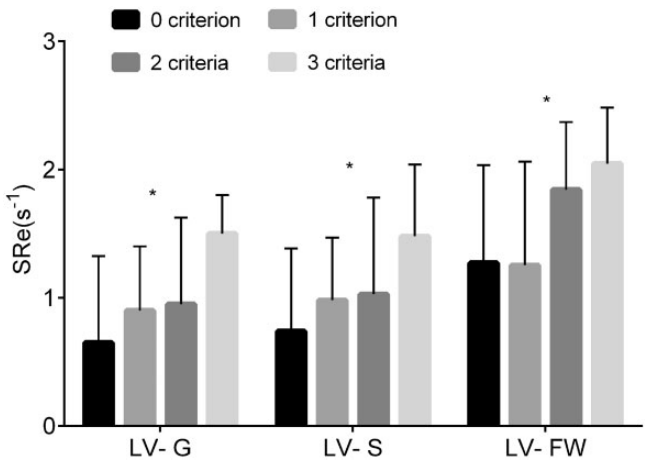

Fig. 3. Histograms of 2D-STE detected LV diastolic parameters based on the number of noninvasive low-risk criteria (World Health Organization functional class I or II; 6 min walking distance >440 m; N-terminal pro-brain natriuretic peptide <300 pg/ml). *P < 0.05. Comparisons were performed with Kruskal–Wallis tests. Means and interquartile ranges are displayed by boxes and whiskers. FW: free wall; G: global; LV: left ventricle; S: septum; SRe: peak early diastolic strain rate.

echocardiographic parameters of RV function, furthermore, the septum may make major contribution; however, correlations between LV diastolic parameters and hemodynamic characteristics measured by RHC were not observed. Additionally, to the best of our knowledge, we had shown for the first time that 2D-STE detected LV diastolic parameters might independently predict intermediate–high risk of pre-capillary PH patients.

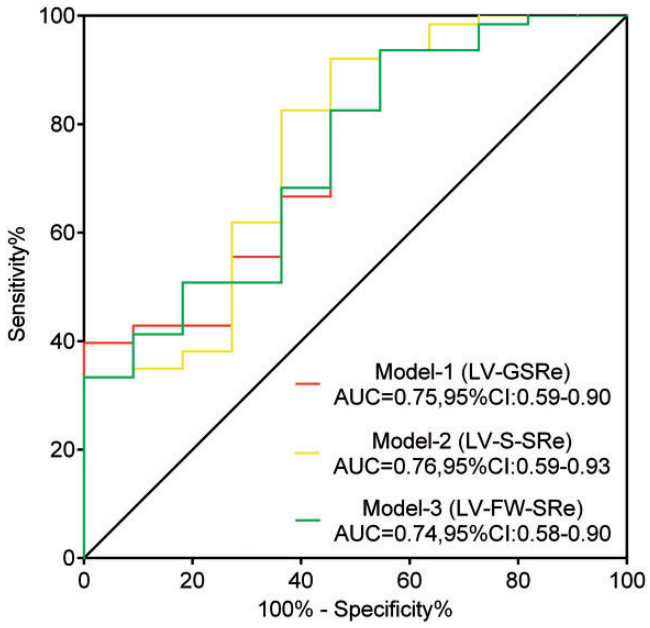

Fig. 4. Receiver operating characteristic curves showed the predictive capacity of logistic regression models for the detection of intermediate–high risk according to 2015 ESC Guidelines. AUC: area under the curve; CI: confidence interval; FW-SRe: peak early diastolic strain rate of free wall; GSRe: global peak early diastolic strain rate; LV: left ventricle; S-SRe: peak early diastolic strain rate of septum.

Table 4. Multivariate logistic regression analyses for risk assessment in pre-capillary pulmonary hypertension.

Variables	OR	95%CI	P value
Model-1			
LV-GSRe (s^{-1})	0.30	0.10–0.91	0.03*
Age (year)	1.05	0.98–1.12	0.18
Gender (M)	0.67	0.14–3.24	0.61
BMI (kg/m^2)	1.13	0.90–1.43	0.28
Model-2			
LV-S-SRe (s^{-1})	0.25	0.08–0.85	0.03*
Age (year)	1.05	0.98–1.13	0.14
Gender (M)	0.57	0.12–2.78	0.49
BMI (kg/m^2)	1.15	0.92–1.45	0.22
Model-3			
LV-FW-SRe (s^{-1})	0.51	0.23–1.15	0.10
Age (year)	1.05	0.98–1.12	0.20
Gender (M)	0.67	0.15–3.11	0.61
BMI (kg/m^2)	1.15	0.92–1.45	0.22

BMI: body mass index; CI: confidence interval; FW-SRe: peak early diastolic strain rate of free wall; GSRe: global peak early diastolic strain rate; LV: Left ventricle; OR: odds ratio; S-SRe: peak early diastolic strain rate of septum. *P<0.05 was level of significance.

Numerous studies reported LV diastolic dysfunction and its possible mechanism in PH patients previously.[4,8,14–19] Lamberts et al.[15] found that an increase in RV volume significantly increased LV end-diastolic pressure in rats with monocrotaline-induced RV hypertrophy while similar response was not observed in controls, suggesting that impaired left ventricular diastolic function may be caused by RV hypertrophy. Menzel et al.[8] showed that the interventricular septal motion and pulmonary venous return to the LA were improved after pulmonary thromboendarterectomy in CTEPH patients, which resulted in a normalization of LV diastolic function. Research by Marcus et al.[17] suggested RV pressure overload led to leftward ventricular septal bowing, reduced RV output, and blood delivery of pulmonary vascular, thereby impaired the LV filling in primary PH patients, and similar conclusions were obtained from other researches on PAH or CTEPH patients.[18,19] Microscopically, Manders et al.[14] performed LV biopsy in PAH patients and found an increase in myofilament Ca^{2+} sensitivity in cardiomyocytes, which may contribute to LV diastolic dysfunction. In the present study, we found that LV-S-SRe showed stronger correlations with clinical data and risk assessment than LV-FW-SRe, and the PCWP of these patients was normal, suggesting that interventricular septum may make the direct and major contribution to the diastolic dysfunction in pre-capillary PH patients; on the other hand, no or weak significant correlations were observed between LV-GSRe and RV pressure overload parameters, such as mPAP, RAP, and PVR, suggesting an indirect and relatively weak effect of pulmonary circulation on LV diastolic function. To sum up, LV diastolic dysfunction in PcPH patients may be a comprehensive result of RV hypertrophy, leftward ventricular septal bowing, reduced LV preload, as well as increased myofilament Ca^{2+} sensitivity in its cardiomyocytes, while the dysfunction of interventricular septum due to the RV hypertrophy likely makes the major contribution.

Given that LV diastolic dysfunction in PH patients was possibly caused by the dysfunction of interventricular septum and RV hypertrophy, which simultaneously led to RV systolic and diastolic dysfunction,[3] there was no surprise that LV diastolic dysfunction was significantly correlated with RV dysfunction parameters, as confirmed in our study. Lazar et al.[20] and Moustapha et al.[21] also supported the similar view. Reduced LV filling subsequently resulted in reduced cardiac output of LV, which was considered as the major cardiac contributor of poor adaption to exercise.[22,23] This may be one of the possible mechanisms for LV diastolic parameters significantly correlated with PVO_2 in our study.

Interestingly, there were no significant correlations between LV diastolic parameters and hemodynamic data measured by RHC in the present study, only a weak correlation was observed between LV-S-SRe and PVR. The results were controversial in previous studies. Adriano showed PAH patients with normal LV diastolic function often had a higher cardiac index, lower RAP and PVR, suggesting that impaired LV relaxation was more likely to occur in patients with advanced IPAH. Nevertheless, findings from Kasner et al.[4] suggested nonsevere IPAH patients (mPAP 29 ± 5 mmHg) also suffered an impaired LV diastolic compliance. In addition, Adriano reported correlations between LV peak early diastolic velocity (E) and PVR ($r = 0.26$, $P = 0.05$), RAP ($r = 0.27$, $P = 0.04$), cardiac index ($r = 0.35$, $P = 0.007$), but the correlation coefficients were not high; other echocardiographic diastolic parameters, such as LV peak late diastolic velocity (A), tissue Doppler measured early (e′) and late (a′) diastolic velocities, E/e′ and e′/a′ ratios at the septal and lateral areas of the mitral annulus, showed no relationships with hemodynamic data, and the possible reasons were not detailed.[7] One possible explanation was that the LV diastolic dysfunction in PcPH patients was mainly caused by the dysfunction of interventricular septum and RV hypertrophy rather than the abnormal pulmonary circulation, as mentioned above; another possible reason was that PH patients often had a normal LVEF, a serious TR (TR velocity>2.8 m/s), and a reduced LV filling, so that the conventional parameters of LV diastolic function may not be completely suitable for PH patients. Therefore, the relationships between LV diastolic function and hemodynamic parameters still need further investigations.

A novel finding of our study was that the 2D-STE detected LV diastolic parameters were associated with disease severity in PH patients, either assessed by 2015 ESC risk assessment strategy or by the number of noninvasive low-risk criteria. Additionally, LV-GSRe and LV-S-SRe had the potential to independently predict intermediate–high risk of PH patients, even after adjusting for age, gender, and BMI. We defined low-risk criteria according to the 2015 ESC Guidelines but excluded for right atrium (RA) area. That was mainly because RA area was a static and angle-dependent data, and less reproducible. Previous studies investigated the relationships between LV diastolic dysfunction and disease severity of PH; however, hemodynamic data were used to express disease severity in their studies.[7,21,24] Later researches illustrated that severity and prognosis evaluation of PH patients should contain clinical assessment, exercise tests, biochemical markers, and echocardiographic and hemodynamic parameters, rather than single RHC measurements.[25–28] Moreover, as an invasive examination, it was unrealizable to perform RHC at frequent follow-up. Therefore, in clinical practice, a safer and easier assessment scheme, such as LV-GSRe and LV-S-SRe, was hopefully used in risk evaluation of PH patients in the future.

In conclusion, LV diastolic function detected by 2D-STE was significantly correlated with clinical data in pre-capillary PH patients, and the dysfunction of interventricular septum may make the major contribution. Furthermore, LV-GSRe and LV-S-SRe had the potential to independently predict intermediate–high risk of PH patients, even after adjusting for age, gender, and BMI.

Limitation

We also had several limitations. First, selection bias was possible as this was a single center study. The second limitation was the small sample size in our study, but PH was a relatively orphan disease, worldwide large-scale study was still limited to date. In addition, there were inevitable heterogeneity and variability of the echocardiographic parameters. Accordingly, to improve the data quality, all of the measurements were performed twice by an experienced physician and in strict accordance with the guidelines in our study, and the intra- and inter-observer variability were considered acceptable for our clinical purpose. Finally, this was a cross-sectional study. Neither cause–effect relationships nor outcome was demonstrated, and regular follow-up needs to be performed in the future.

Authors' note

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

Authors' contributions

BL, WW, QZ, ZL, HW, JH, and CX contributed to the conception and design of the study. BL, WW, QZ, LN, YT, XC, QL, ZZ, LH, and CX contributed to the acquisition, analyses, and interpretation of data. BL drafted the manuscript together with WW, QZ, and CX and all authors critically revised it. All authors gave final approval and agree 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.

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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