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Assessment of right ventricle–to–pulmonary artery coupling by three-dimensional echocardiography in pre-capillary pulmonary hypertension: comparison with tricuspid annular plane systolic excursion /systolic pulmonary artery pressure ratio

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Abstract

Background The tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio (TAPSE/sPAP) has limitations in evaluating right ventricle–to–pulmonary artery (RV-PA) coupling, particularly when pulmonary artery pressure cannot be accurately estimated by tricuspid regurgitation or when TAPSE cannot accurately reflect right ventricular systolic function in certain scenarios. Therefore, this study aimed to explore the value of three-dimensional echocardiography (3DE) coupling parameters in assessing RV-PA coupling in patients with pre-capillary pulmonary hypertension (PH).

Methods Fifty-nine patients with pre-capillary PH were retrospectively recruited. The surrogate "gold standard" of RV-PA coupling was derived from right heart catheterization (RHC) and cardiac magnetic resonance imaging (CMR). The relationships between echocardiographic RV-PA coupling parameters and RHC-CMR coupling standard were analyzed by Pearson's test and Bland–Altman test. Additionally, 24 chronic thromboembolic pulmonary hypertension (CTEPH) patients were enrolled to explore the changes in echocardiographic RV-PA coupling parameters before and after PEA. Multivariate ordinal regression analysis was performed to identify echocardiographic parameters associated with prognostic risk stratification in pre-capillary PH patients.

Results 3DE coupling parameters demonstrated strong correlation and good agreement with the RHC-CMR coupling standard. In contrast, TAPSE/sPAP was moderately correlated to the RHC-CMR coupling standard, but showed poor consistency, with a significant bias of 0.44 (95% CI: 0.374, 0.511). Before and after PEA, stroke volume/end-systolic volume (SV/ESV) derived by 3DE remained moderately correlated with pulmonary vascular resistance

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(PVR) and mean pulmonary artery pressure (mPAP) (r =-0.614, -0.655, $P < 0.001$), whereas TAPSE/sPAP was only associated with PVR and mPAP in CTEPH patients before PEA (r=-0.605, -0.758, $P < 0.001$). Multivariate regression analysis revealed TAPSE/sPAP as the strongest predictor of prognostic risk.

Conclusions 3DE-derived coupling parameters offer a noninvasive and reliable approach for assessing RV-PA coupling in patients with pre-capillary PH, especially for patients who cannot accurately estimate pulmonary artery pressure or have undergone cardiac surgery. 3DE SV/ESV is superior to TAPSE/sPAP for assessing postoperative RV-PA coupling in CTEPH patients, TAPSE/sPAP remains a valuable parameter for prognostic risk stratification in pre-capillary PH patients. Echocardiography can provide valuable information for assessing RV-PA coupling and prognosis in patients with pre-capillary PH. However, the application of echocardiographic coupling parameters should be determined based on the specific clinical context.

Keywords Three-dimensional echocardiography, Right ventricular-arterial coupling, Tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio, Pre-capillary pulmonary hypertension, Pulmonary endarterectomy

Background

Right ventricle–to–pulmonary artery (RV-PA) coupling is emerging as a crucial predictor of adverse clinical outcomes in patients with pulmonary hypertension (PH) [1]. It reflects the ability of right ventricle (RV) contractility, measured by end-systolic elastance (Ees), to match the increased afterload on the pulmonary artery (PA), measured by arterial elastance (Ea). The gold standard for assessing RV-PA coupling is the multi-beat or single-beat pressure–volume (P-V) loop, obtained through conductance catheterization, which is technically complex and invasive [2]. Therefore, noninvasive and simpler surrogates for RV-PA coupling have been explored. The tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio (TAPSE/sPAP) has been widely used as a surrogate for RV-PA coupling. It has shown a correlation with the prognosis of pulmonary arterial hypertension (PAH) [3]. However, TAPSE/sPAP may be less effective in certain clinical scenarios, such as the absence of tricuspid regurgitation (TR) or a reduced TAPSE after pulmonary endarterectomy (PEA) in chronic thromboembolic pulmonary hypertension (CTEPH) patients [4]. Previous studies have demonstrated that combining cardiac magnetic resonance imaging (CMR)-derived volumes and right heart catheterization (RHC)-derived pressure measurements offers an effective method for evaluating RV-PA coupling [5]. Three-dimensional echocardiography (3DE) is advantageous as it provides simultaneous volume and pressure data. It has been shown to correlate strongly with CMR in measuring RV volumes [6]. Therefore, this study aimed to explore the value of 3DE-derived coupling parameters in assessing RV-PA coupling in pre-capillary PH and CTEPH patients, comparing them with TAPSE/sPAP.

Methods

Study population

This study included patients diagnosed with pre-capillary PH according to the 2022 ESC/ERS guidelines at China Japan Friendship Hospital between July 2018 and October 2022. The inclusion criteria were: (1) RHC, CMR and 3DE performed within 7 days; (2) High-quality images suitable for post-processing analysis; (3) An intact tricuspid regurgitation (TR) spectrum for pulmonary arterial pressure estimation; and (4) Absence of arrhythmia. To further assess the changes in RV-PA coupling parameters before and after PEA, another cohort of CTEPH patients was selected. These patients underwent RHC and echocardiography both before surgery (within 7 days) and 3 months after surgery. Patient demographic and clinical data were extracted from electronic medical records. The institutional review board of the China–Japan Friendship Hospital waived the need for written informed consent, as the study involved the retrospective analysis of clinically acquired data. The Ethics Committee of China-Japan Friendship Hospital in Peking, China, approved this study (No. 2020–95-K59).

Clinical data

Baseline clinical parameters included the World Health Organization (WHO) functional class, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and the 6-minute walk distance (6MWD). The patient's prognostic risk assessment was identified by reference to the comprehensive risk assessment of PAH (three-strata model) in the 2022 ESC/ERS guidelines of pulmonary hypertension [7].

Echocardiography

Echocardiography was performed using a GE Vivid E95 machine (GE Healthcare, General Electric Healthcare), equipped with M5S phased-array transducers. Following the guidelines for cardiac chamber quantification in adults [8], right ventricular (RV) structural and functional parameters were measured using EchoPAC software (GE Healthcare, version 204). These parameters included: right atrium area (RA area), ratio of right ventricular and left ventricular (RV/LV) basal diameter, RV outflow tract

acceleration time (RVOT-act), TAPSE, RV fractional area change (FAC), systolic annular tissue velocity of the lateral tricuspid annulus (S') and global longitudinal strain of the right ventricle (RV GLS). The tricuspid regurgitation pressure gradient (TR-PG) was calculated from the peak velocity of TR (TR Vmax) according to the simplified Bernoulli equation: TR-PG = 4 (TR Vmax)^2. The TR mean pressure gradient (TR-mPG) was obtained by tracing the time–velocity integral of the TR. The sPAP and mean pulmonary artery pressure (mPAP) were calculated by adding the estimated RAP to the TR-PG and TR-mPG, respectively. The RAP was divided into three categories (3, 8, and 15 mm Hg) based on the inferior vena cava diameter and its respiratory variation [9].

Three-dimensional echocardiography

3DE images were acquired by the same experienced doctor (AL.L) using the 4 V probe. 3DE images of the RV were acquired from the four-chamber apical view during a single breath hold and six heartbeats. Postprocessing for the quantification of RV volumes was performed offline using EchoPAC Software (4D Auto RVQ, EchoPAC version 204, GE Healthcare) by another two doctors (GJ.L and YN.Z). The process is as follows: (1) First, the data were aligned to identify the RV long axis from the tricuspid valve (TV) center to the RV apex in the RV-4 chamber view and in the orthogonal view. (2) Then, the following landmarks were manually defined: the RV apex, the free wall and septal wall of the tricuspid annulus in the 4-chamber view, the RV endocardial border corresponding to the left ventricle and right ventricle (LV/RV) posterior junction, the LV/RV anterior junction and the RV free wall point in the short-axis view. (3) Based on these landmarks, the software automatically extracted the RV-focused four-chamber view and a series of end-systolic and end-diastolic short-axis views from the base to the apex, from which a 3D model of the RV was generated. The 3D endocardial surface was then tracked throughout the cardiac cycle. If the boundary position was not optimal, the software allowed manual corrections of tracking. (4) A 3D model of the RV was created with calculations of the volume and right ventricular ejection fraction (RV EF), as shown in Fig. 1.

Cardiac magnetic resonance imaging

CMR was conducted using a 1.5T clinical scanner (MAGNETOM Area, Siemens Healthcare, Erlangen, Germany) with an 18-channel phased-array surface coil. Images were acquired during end-expiratory breath holding, with retrospective electrocardiographic gating. Standard CINE images in long-axis 4-chamber and contiguous short-axis slices covering both ventricles from base to apex were acquired with true fast imaging with a steady-state free precession sequence in the holding

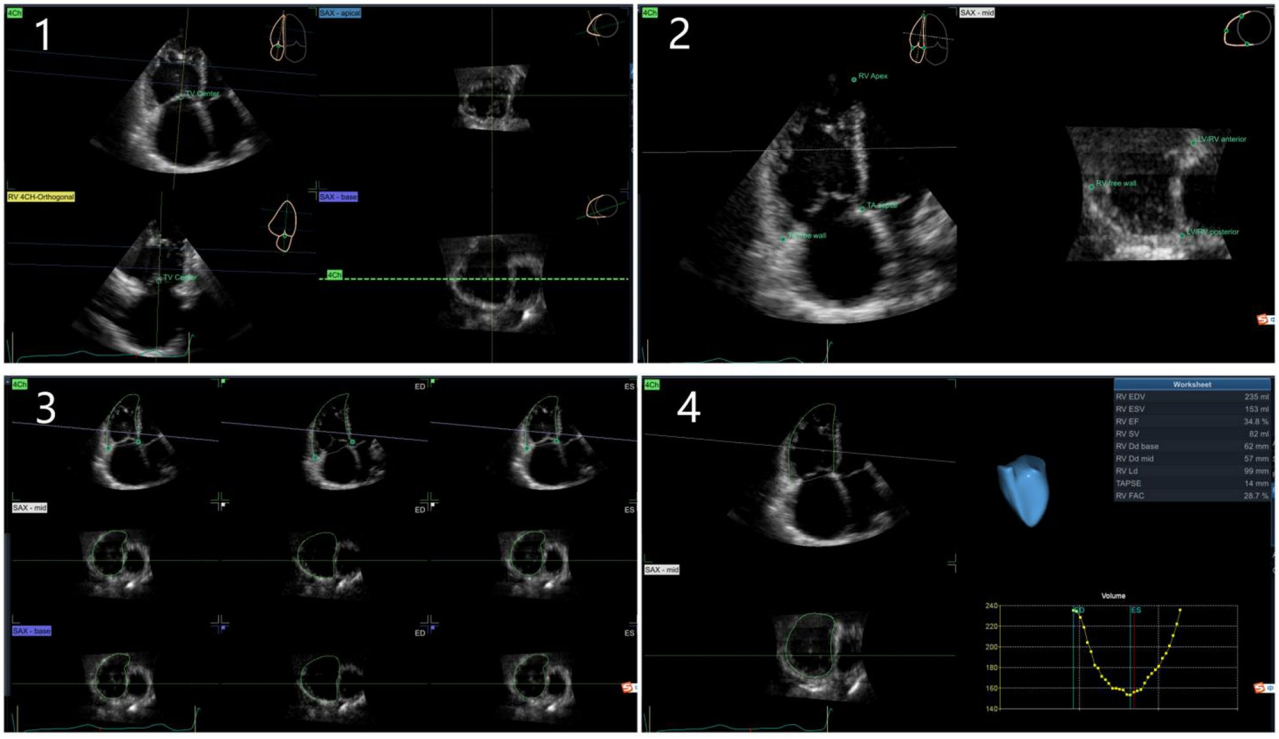

Fig. 1 Postprocessing for quantification of RV volumes and function using offline 3D echocardiographic analysis software. (**1**) Data alignment to identify the RV long axis. (**2**) Define landmarks. (**3**) Software was used to automatically extract the 3D endocardial surface. (**4**) A 3D model of the RV was generated. RV: right ventricle; 4Ch: four-chamber view; SAX: short-axis

breath. The right ventricular end-diastolic volume (RV EDV), RV ESV and RV EF were independently analyzed on CINE images by a radiologist with years of experience with cardiac function on the SyngoVia platform (Siemens Healthcare, Erlangen, Germany).

Right heart catheterization

Hemodynamic measurements were performed using a 7 F Swan-Ganz Philips Allura X-PER FD20 fatplate angiography system (Baxter Inc). The system was zeroed and referenced at the patients' heart level as previously described [10]. RAP, sPAP, and PAWP were recorded at end-expiration at baseline over at least three heart cycles. Cardiac output (CO) was obtained using Fick's method directly. The pulmonary vascular resistance (PVR), cardiac index (CI), SV, pulse pressure, and diastolic pressure gradient were calculated using standard formulas.

Calculation of right ventricular-arterial coupling parameters

End-systolic elastance (Ees) was used as the gold standard for RV contractility, defined by the relationship between end-systolic pressure (ESP) and ESV [11]. Arterial elastance (Ea) was calculated as the ratio of ESP to SV [12]. RV-PA coupling was quantified as the ratio of Ees/Ea. It is assumed that mPAP could be a reasonable approximation of ESP [13], so the equation becomes Ees = mPAP/ESV, Ea = mPAP/SV and Ees/Ea = SV/ESV. RV ESV and SV were obtained from CMR and adjusted to body surface area. RHC provided mPAP. 3DE SV and 3DE ESV were measured using 3D echocardiographic volumetric analysis, mPAP was obtained through the TR-mean PG method as described above. The corresponding 3DE-derived RV-PA coupling parameters (3DE Ees, 3DE Ea and 3DE Ees/Ea) were then calculated. The TAPSE/sPAP was calculated by M-mode imaging and Doppler echocardiography.

Table 1 Clinical characteristics of the study cohort

Variables	Value
Age, years	52.9 ± 13.6
Male, %	34 (57.6%)
Body surface area (m^2)	1.75 ± 0.16
Heart rate, bpm	79 ± 14
NT-pro BNP, pg/ml	667.5 (182.5, 2105.5)
6-minute walking distance, m	399.5 ± 110.6
WHO functional class	
I Class, %	2 (3.4%)
II Class, %	24 (40.7%)
III Class, %	28 (47.5%)
IV Class, %	5 (8.5%)
Prognostic risk stratification	
Low risk, %	16 (27.1%)
Intermediate risk, %	32 (54.3%)
High risk, %	11 (18.6%)

The data are expressed as the number (percentage) of patients, mean ± standard deviation for normally distributed data, or median (interquartile range) for skewed data. NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class

Statistical analysis

Data were analyzed using SPSS (version 26 for Windows, SPSS, Chicago, IL, USA) and MedCalc (version 18.11.6, Belgium). The data are expressed as the mean ± standard deviation for quantitative variables with a normal distribution or as the median (interquartile range) for variables without a normal distribution. Pearson's test and the Bland–Altman test were used to analyze the correlation and consistency between echocardiographic coupling parameters and the RHC–CMR coupling standard. A paired t test was used to compare the changes in RHC and echocardiographic parameters before and after PEA. Pearson's test was used to analyze the relationships between 3DE SV/ESV, TAPSE/sPAP and hemodynamic indices (mPAP, PVR) before and after PEA. Univariate and multivariate ordinal regression analyses identified echocardiographic parameters most strongly associated with prognostic risk stratification. Intraclass correlation coefficient assessed inter- and intra-observer reproducibility for 3DE SV/ESV and TAPSE/sPAP from 20 randomly selected patients. For all the statistical tests, a P value < 0.05 indicated statistical significance.

Results

Study cohort: From July 2018 to October 2022, a total of 73 patients diagnosed with pre-capillary PH underwent RHC, CMR and 3DE within 7 days. Ten patients without an intact TR spectrum and 3 patients with poor image quality were excluded. One patient was excluded because of pulmonary stenosis, which is not suitable for estimating pulmonary pressure via the TR spectrum. Ultimately, 59 patients were retrospectively identified. The 59 patients (34 men [57.6%]; mean age, 52.9 ± 13.6 years old) had a wide range of mPAP (46.4 ± 2.2 mm Hg; range, 25–66 mm Hg). There were 10 patients with idiopathic pulmonary arterial hypertension, 1 patient with pulmonary capillary hemangiomatosis and 48 patients with CTEPH. The baseline characteristics of the study population are summarized in Table 1. The RHC, CMR and echocardiographic variables are shown in Table 2.

Correlation and consistency between echocardiographic RV-PA coupling parameters and the RHC-CMR coupling standard

As illustrated in Figs. 2 and 3DE coupling parameters (3DE SV/ESV, 3DE Ees, and 3DE Ea) showed strong correlation with the RHC-CMR coupling standard (Ees/Ea, Ees and Ea) (r = 0.87, 0.80, 0.77, P < 0.001). The 3DE coupling parameters and RHC-CMR coupling standard also

Table 2 Right heart catheterization and echocardiographic and cardiac magnetic resonance imaging-derived parameters in the study cohort

Variables	Value
Right heart catheterization	
mPAP, mmHg	45.6 ± 11.0
RAP, mmHg	4.3 ± 3.3
PVR, Wood Units	11.8 ± 5.3
CI, L/min per m^2	1.94(1.6,2.4)
PAWP, mmHg	9.0 ± 3.2
Cardiac magnetic resonance imaging	
RV EDV, mL/m^2	120.8 ± 33.1
RV ESV, mL/m^2	75.3 ± 25.0
RV SV, mL/m^2	45.5 ± 10.6
RV EF, %	39.3 ± 9.6
2D Echocardiography	
RA area, cm^2	24.3 ± 7.4
RV basal diameter, mm	46.9 ± 7.1
RV/LV basal diameter	1.4 ± 0.4
FAC, %	28.2 ± 8.1
TAPSE, mm	16.4 ± 3.9
S', cm/sec	10.4 ± 2.8
RV GLS, %	-12.5 ± 4.5
RVOT-act, ms	66.2 ± 19.5
sPAP mmHg	81.1 ± 20.2
mPAP mmHg	51.3 ± 12.4
3D Echocardiography	
RV EDV, mL/m^2	115.5 ± 33.5
RV ESV, mL/m^2	74.0 ± 28.9
RV SV, mL/m^2	41.3 ± 9.0
RVEF, %	37.4 ± 8.8
Right ventricular pulmonary artery coupling surrogates	
RHC-CMR Ea, mmHg/mL/m^2	1.06 (0.63, 1.49)
RHC-CMR Ees, mmHg/mL/m^2	0.69 ± 0.24
RHC-CMR Ees/Ea	0.68 ± 0.26
3DE Ea, mmHg/mL/m^2	1.31 (0.95, 1.47)
3DE Ees, mmHg/mL/m^2	0.74 ± 0.22
3DE SV/ESV	0.60 ± 0.21
TAPSE/sPAP, mm/mmHg	0.22 ± 0.08

Normally distributed data are expressed as the mean ± standard deviation, and skewed data are expressed as the median (interquartile range)

mPAP: mean pulmonary artery pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance; CI: cardiac index; PAWP: pulmonary arterial wedge pressure; 2D: two-dimensional; RV EDV: right ventricular end-diastolic volume; RV ESV: right ventricular end-systolic volume; RV SV: right ventricular stroke volume; RV EF: right ventricular ejection fraction; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; S': systolic velocity of the tricuspid lateral annulus; RV GLS: right ventricular global longitudinal strain; RVOT-act: right ventricular outflow tract acceleration time; sPAP: systolic pulmonary artery pressure; Ea: pulmonary artery effective elasticity; Ees: right ventricular end-systolic maximum elasticity; Ees/Ea: right ventricular-arterial coupling; RHC: right heart catheterization; CMR: cardiac magnetic resonance imaging; 3DE: three-dimensional echocardiography; SV/ESV: stroke volume/end-systolic volume

exhibited good agreement with low bias values (3DE SV/ESV vs. Ees/Ea: -0.05, 3DE Ees vs. Ees: 0.07 mmHg/mL/m^2, 3DE Ea vs. Ea: 0.21 mmHg/mL/m^2) and satisfactory limits of agreement. TAPSE/sPAP showed a moderate correlation with Ees/Ea ($r = 0.61$, $P < 0.001$). However, the consistency between TAPSE/sPAP and Ees/Ea was less satisfactory, with a significant bias of 0.44 (95% CI: 0.37, 0.51), as shown in Fig. 3. Intra- and inter-observer reproducibility for the 3DE SV/ESV was high, with intraclass correlation coefficients (ICCs) of 0.89 (95% CI: 0.41–0.98) and 0.86 (95% CI: 0.54–0.96), respectively. TAPSE/sPAP demonstrated good reproducibility as well, with ICCs of 0.93 (95% CI: 0.74–0.98) for intra-observer and 0.87 (95% CI: 0.54–0.97) for inter-observer reproducibility.

Changes in RV function and hemodynamics before and after PEA

Among 88 patients who underwent PEA for CTEPH, 51 patients completed RHC and echocardiography both within 7 days before and 3 months after PEA. Of these, 47 (53.4%) had complete TR spectra before PEA, while only 24 (27.3%) maintained complete TR spectra post-surgery. Finally, 24 patients were retrospectively identified. As shown in Table 3, echocardiographic parameters (RA area, RV basal diameter, RV/LV basal diameter, TAPSE, S', FAC, 3DE SV/ESV, TAPSE/sPAP) and RHC parameters (mPAP, PVR) presented the significant changes before and after 3 months of PEA. Before PEA, the TAPSE/sPAP ratio showed a strong association with disease severity markers such as PVR and mPAP (r = -0.61, -0.76, $P < 0.001$). However, these associations weakened post-surgery, with weaker correlations (r = -0.47, -0.32, $P > 0.001$). On the other hand, the 3DE SV/ESV ratio remained moderately correlated with PVR and mPAP both before (r = -0.57, -0.61, $P < 0.001$) and after surgery (r = -0.61, -0.66, $P < 0.001$), as shown in Table 4.

Association between echocardiographic parameters and prognostic risk stratification

There were 16 pre-capillary PH patients (27.1%) in the low-risk group, 32 patients (54.3%) in the intermediate-risk group, and 11 patients (18.6%) in the high-risk group. Univariate ordinal regression analysis revealed that several echocardiographic parameters were associated with prognostic risk stratification, including the RA area, RV basal diameter, RV/LV basal diameter, sPAP, TAPSE, FAC, 3DE SV/ESV, and TAPSE/sPAP. As a composite index composed of TAPSE and sPAP, TAPSE/sPAP showed obvious collinearity with TAPSE and sPAP (variance inflation factor of>10,Tolerance<1), so we manually eliminated TAPSE and sPAP in multivariate ordinal regression analysis. The final model identified TAPSE/sPAP as an independent predictor of prognosis ($P < 0.05$), as shown in Table 5.

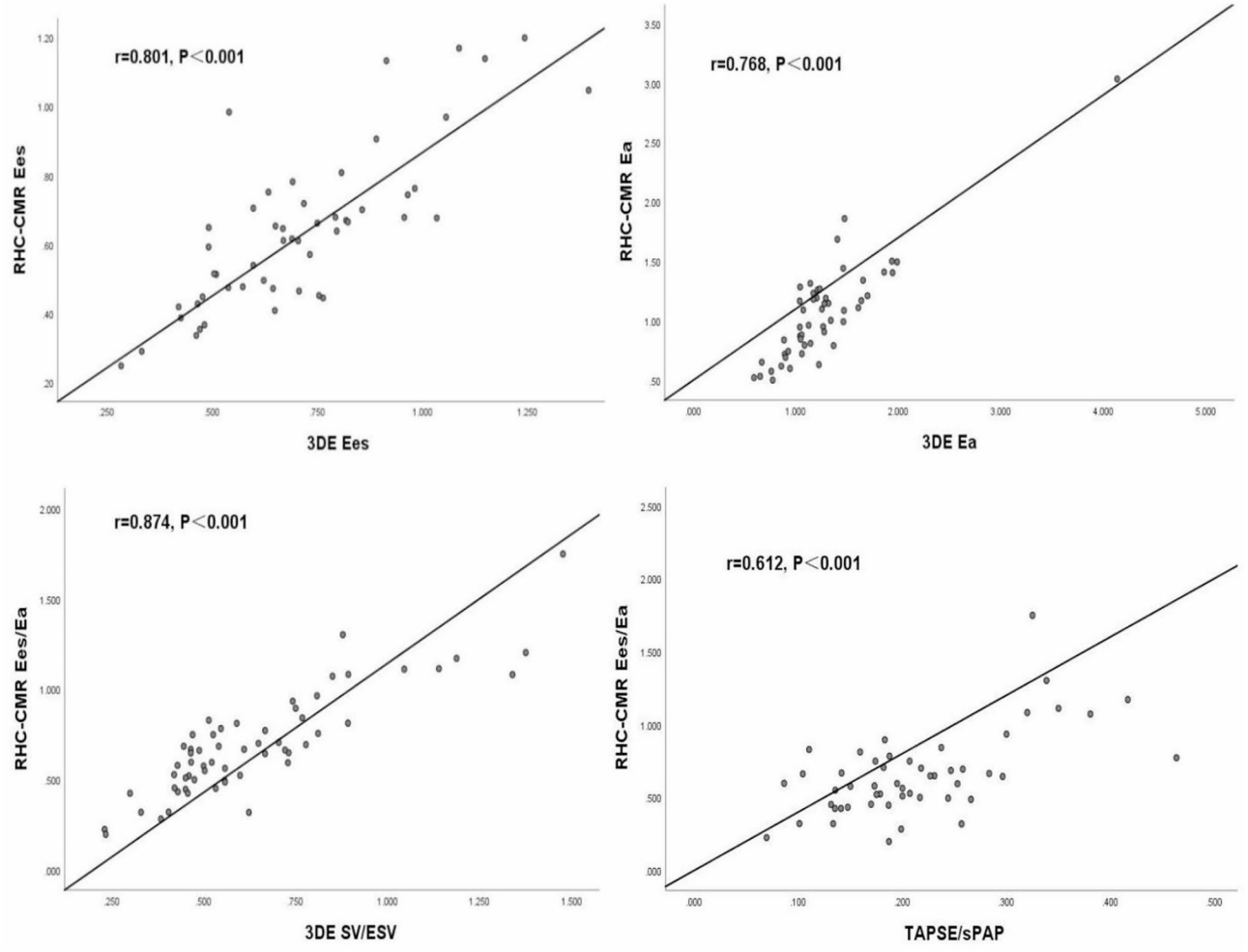

Fig. 2 Correlations between echocardiographic RV-PA coupling parameters and the RHC-CMR coupling standard. The correlations between echocardiographic coupling parameters and the RHC-CMR coupling standard were analyzed using the Pearson test. RHC-CMR Ees/Ea, RHC-MR Ees and RHC-CMR Ea refer to the right ventricular- arterial coupling index, right ventricular end-contraction elasticity and pulmonary arterial elasticity derived from right heart catheterization and cardiac magnetic resonance parameters, respectively; 3DE Ees: right ventricular end-contraction elasticity calculated by echocardiographic parameters; 3DE Ea: pulmonary arterial elasticity calculated by echocardiographic parameters; 3DE SV/ESV: three-dimensional echocardiography-derived stroke volume/end-systolic volume; TAPSE/sPAP: the ratio of tricuspid annular plane systolic excursion and systolic pulmonary artery pressure estimated by echocardiography

Discussion

The present study validated the feasibility of using 3DE-derived volume and pressure measured by Doppler echocardiography to assess RV-PA coupling in pre-capillary PH patients. The results showed that 3DE SV/ESV is a valuable parameter for assessing RV-PA coupling, particularly in evaluating postoperative condition of CTEPH patients. In contrast, the TAPSE/sPAP remains superior for prognostic assessment in pre-capillary PH patients.

Our results demonstrated that 3DE-derived parameters, such as 3DE SV/ESV, 3DE Ees (RV contractility), and 3DE Ea (pulmonary arterial elastance), strongly correlated with RHC-CMR coupling standards, indicating their utility in noninvasively evaluating RV-PA coupling. As previously shown, increased arterial load is a hallmark of disease progression in PH, while contractility does not increase in parallel, leading to severe uncoupling of the RV and PA [14].This uncoupling can be evaluated through 3DE parameters, which represent RV contractility and PA elastance more accurately than conventional parameters like TAPSE. However, our use of mPAP to approximate ESP for calculating 3DE Ees and Ea may have led to an underestimation of these parameters. Recent studies suggest that as PH progresses, the RV-PA loop shape changes, this assumption of using mPAP to approximate ESP remains a limitation, particularly in severe PH cases where ESP may closely align with sPAP [15, 16]. Therefore, caution is advised when interpreting these findings.

As a three-dimensional parameter, 3DE SV/ESV captures more volumetric data, overcoming the challenges posed by the complex geometry of the RV, thus enabling

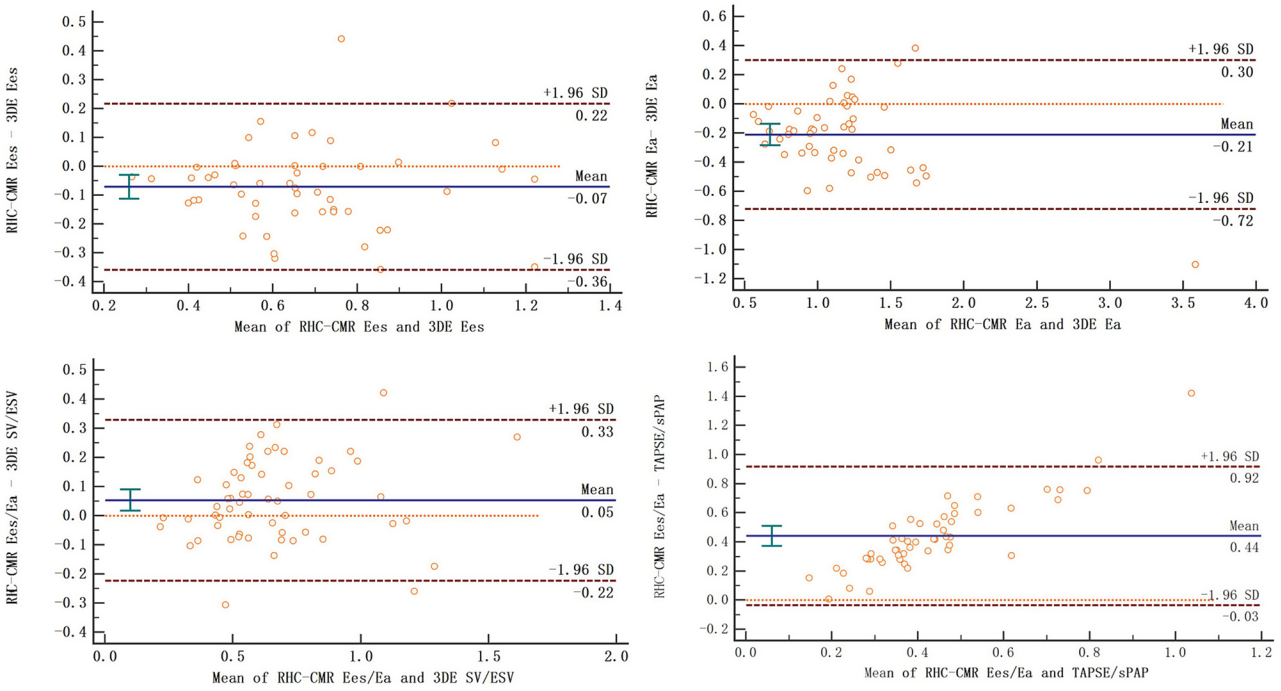

Fig. 3 The consistency of echocardiographic RV-PA coupling parameters with the RHC-CMR coupling standard. The consistency between echocardiographic coupling parameters and the RHC-CMR coupling standard was analyzed using the Bland–Altman test. RHC-CMR Ees/Ea, RHC-MR Ees and RHC-CMR Ea refer to the right ventricular arterial coupling index, right ventricular end-contraction elasticity and pulmonary arterial elasticity derived from right heart catheterization and cardiac magnetic resonance parameters, respectively; 3DE Ees: right ventricular end-contraction elasticity calculated by echocardiographic parameters; 3DE Ea: pulmonary arterial elasticity calculated by echocardiographic parameters; 3DE SV/ESV: three-dimensional echocardiography-derived stroke volume/end-systolic volume; TAPSE/sPAP: the ratio of tricuspid annular plane systolic excursion and systolic pulmonary artery pressure estimated by echocardiography

a more comprehensive assessment of overall RV function. 3DE SV/ESV offers broader applicability, as it is independent of TR and not confined to cardiac surgery. The RV exhibits a strong tolerance to volume load, and significant changes in RV volume and SV often occur before RV function is notably decompensated. This may explain why 3DE SV/ESV is better able to reflect early alterations in RV-PA coupling. Similar findings were reported by Aubert et al., though they noted less satisfactory agreement between 3DE and RHC-CMR parameters, with considerable bias [17]. This discrepancy may be attributed to the heterogeneity of their study cohort. Previous study has suggested that accounting for the effect of pulmonary artery wedge pressure (PAWP) on pulmonary circulation provides a more accurate description of pulmonary effective arterial elastance [18]. Our cohort, however, exclusively included pre-capillary PH patients with PAWP ≤ 15 mm Hg, which contributed to a more homogeneous sample and minimized the potential for confounding factors related to left heart failure or elevated PAWP that could have affected pulmonary circulation and coupling measures.

Previous study demonstrated that the TAPSE/sPAP had the strongest correlation with the Ees/Ea [19]. However, our study revealed that while TAPSE/sPAP is moderately correlated with the RHC-CMR coupling standard, the consistency was suboptimal. This could be due to the limitations of TAPSE as an angle-dependent, one-dimensional measure, which may not fully capture RV contractility or afterload, particularly in severe PH. Additionally, the use of TR to estimate sPAP can be affected by several factors [20], including the absence of TR or issues with TR quantification, which can compromise the accuracy of TAPSE/sPAP as a surrogate for RV-PA coupling. In some cases, such as secondary PH due to heart failure with reduced ejection fraction, TAPSE/sPAP may obscure RV dysfunction, as both parameters are influenced by changes in RV function and afterload [21]. Therefore, TAPSE/sPAP cannot fully represent the RV-PA coupling under certain circumstances.

Our findings further explored the role of echocardiographic coupling parameters in assessing the RV-PA coupling status before and after PEA in CTEPH patients. Although TAPSE/sPAP was able to reflect disease severity before surgery, it failed to accurately represent RV-PA coupling after surgery. Due to intraoperative RV ischemia or postoperative stunning, TAPSE decreases significantly after cardiac surgery [22–24], and it takes 2 to 3 years to recover [25]. The significant increase in tricuspid valve tent height, volume, and area after PEA could reduce

Table 3 Key results before and after PEA

Variables	Before PEA	After PEA	*P*
Echocardiography			
RA area (cm^2)	29.0 ± 13.6	21.1 ± 8.0	<0.001
RV basal diameter (mm)	47.7 ± 7.5	39.6 ± 5.3	<0.001
RV/LV basal diameter	1.4 ± 0.5	1.0 ± 0.2	<0.001
TAPSE (mm)	16.5 ± 3.7	11.8 ± 2.0	<0.001
S' (cm/sec)	10.9 ± 2.8	9.1 ± 2.0	0.025
FAC (%)	25.8 ± 8.7	36.8 ± 6.0	<0.001
3DE RV SV mL/m^2	36.9 ± 10.0	28.0 ± 9.5	0.004
3DE RV ESV mL/m^2	81.4 ± 29.6	40.6 ± 21.0	<0.001
3DE RV EDV mL/m^2	118.3 ± 36.7	69.0 ± 29.0	<0.001
3DE RVEF(%)	32.2 ± 7.0	42.6 ± 7.9	<0.001
3DE SV/ESV	0.44 ± 0.12	0.71 ± 0.24	<0.001
TAPSE/sPAP	0.20 ± 0.10	0.30 ± 0.08	0.006
Right heart catheterization			
PVR(Wood Units)	13.7 ± 7.0	7.0 ± 3.2	0.001
mPAP (mmHg)	47.1 ± 10.5	29.1 ± 8.7	0.004

Changes in right heart catheterization and echocardiographic parameters before and after PEA were analyzed using paired t tests

RA area: right atrium area; RV/LV basal diameter: ratio of right ventricular and left ventricular basal diameter; TAPSE: tricuspid annular plane systolic excursion; S': systolic velocity of the tricuspid lateral annulus; FAC: fractional area change; 3DE: three-dimensional echocardiography; RV EDV: right ventricular end-diastolic volume; RV ESV: right ventricular end-systolic volume; RV SV: right ventricular stroke volume; RV EF: right ventricular ejection fraction; SV/ESV: storke volume/end-systolic volume; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance

Table 4 The correlation between echocardiographic RV-PA coupling parameters and RHC hemodynamic parameters before and after PEA

Before PEA			After PEA		
Variables	***r***	***P***	**Variables**	***r***	***P***
3DE SV/ESV vs. mPAP	-0.57	**0.004**	3DE SV/ESV2 vs. mPAP2	-0.61	**0.003**
3DE SV/ESV vs. PVR	-0.61	**0.001**	3DE SV/ESV2 vs. PVR2	-0.66	**0.001**
TAPSE/sPAP vs. mPAP	-0.76	**0.001**	TAPSE/sPAP2 vs. mPAP2	-0.32	0.270
TAPSE/sPAP vs. PVR	-0.61	**.002**	TAPSE/sPAP2 vs. PVR2	-0.47	0.076

Pearson's test was used to analyze the relationships between 3DE SV/ESV or TAPSE/sPAP and hemodynamic indices before and after PEA. Statistical significance was set at $p < 0.05$ (shown in bold). r: correlation coefficient; 3DE: three-dimensional echocardiography; SV/ESV: stroke volume/end-systolic volume; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance

or eliminate TR [26], which complicates the estimation of sPAP. Consequently, 3DE SV/ESV, which relies solely on volume measurements and better reflects overall RV function, emerged as a more reliable and accurate parameter for evaluating postoperative RV-PA coupling. 3DE SV/ESV showed a significant improvement 3 months after PEA and maintained good correlation with mPAP and PVR, suggesting its superiority in assessing postoperative RV-PA coupling. These findings are consistent with previous research indicating that CMR-derived SV/ESV increases from baseline to 12 months post-PEA [27], further supporting the potential of 3DE SV/ESV as a noninvasive surrogate for RV-PA coupling in CTEPH patients.

Regarding prognostic assessment, TAPSE/sPAP is widely used as a marker of disease severity and clinical outcomes in PH patients [28, 29]. Our study confirmed that TAPSE/sPAP was an independent predictor of prognostic risk stratification in pre-capillary PH patients. As PH progresses, TAPSE decreases and sPAP increases, leading to a marked decrease in the TAPSE/sPAP ratio. Additionally, SV/ESV measured by CMR was shown to predict survival in PAH patients [30], and the 3DE SV/ESV was also found to predict adverse clinical events in pediatric PH patients [31]. However, while 3DE SV/ESV is also correlated with disease severity, its correlation with prognosis was less pronounced compared to TAPSE/sPAP in this study. This may be due to the compensatory mechanisms in the RV that help maintain RV-PA coupling in PH [32], as well as limitations imposed by the pericardium. As a result, both SV and ESV do not exhibit significant changes during the early and advanced stages of PH, meaning that SV/ESV does not decrease as markedly as TAPSE/sPAP with disease progression. Despite this, 3DE SV/ESV better reflects the pathophysiology of RV-PA uncoupling, which progresses with disease severity, and thus provides a reliable measure of RV function.

Study limitations

The study has several limitations. First, we lacked the gold standard RV-PA coupling measured by RV conductance and pressure wire catheterization. Previous research has shown that the single-beat method based on a pressure–volume loop is the best surrogate for assessing RV-PA coupling [33], so we used a surrogate based on CMR and RHC measurements. The SV/ESV assumes that the RV volume at zero filling pressure is equal to zero, which is unrealistic, and the SV/ESV will underestimate the true Ees/Ea [33]. Second, the RHC, CMR and echocardiography were not performed on the same day, with an average interval of 3 days between exams. Although all patients' vital signs were stable during the examinations, this temporal difference may introduce some variability. Third, the study was a single-center, retrospective analysis with a relatively small sample size, and the majority of patients had CTEPH, leading to potential selection bias. To enhance the generalizability of the findings, further studies involving larger, multicenter cohorts are needed.

Table 5 Associations between echocardiographic parameters and prognostic risk stratification

Variables	Low risk ($n=16$)	Intermediate risk ($n=32$)	High risk ($n=11$)	Univariable analysis		Multivariable analysis	
				P	OR (95% CI)	*P*	OR (95% CI)
RA area (cm^2)	18.36 ± 4.15	26.78 ± 6.97	28.04 ± 8.05	**0.001**	1.16(1.07, 1.26)		
RV basal diameter (mm)	42.67 ± 6.02	48.88 ± 5.75	51.55 ± 6.96	**0.001**	1.18(1.08, 1.29)		
Basal RV/LV ratio	1.07 ± 0.21	1.46 ± 0.42	1.65 ± 0.44	**0.001**	1.027(1.026, 1.029)		
TAPSE (mm)	19.02 ± 2.43	15.53 ± 3.68	13.79 ± 2.70	**0.001**	0.73(0.62,0.85)		
S' (cm/s)	12.0 ± 3.20	9.97 ± 2.43	9.60 ± 0.78	**0.016**	0.78(0.64, 0.95)		
FAC(%)	35.73 ± 8.2	26.96 ± 7.88	23.3 ± 7.66	**0.001**	0.88(0.82,0.95)		
sPAP (mmHg)	65.04 ± 12.41	84.18 ± 21.98	90.68 ± 11.28	**0.002**	1.044(1.02, 1.07)		
TAPSE/sPAP (mm/mmHg)	0.30 ± 0.06	0.20 ± 0.08	0.16 ± 0.04	**0.001**	0.16(0.06, 0.40)	**0.015**	0.16(0.04, 0.70)
3DE SV/ESV	0.75 ± 0.23	0.58 ± 0.22	0.46 ± 0.15	**0.001**	0.95(0.92, 0.98)		

Associations between echocardiographic parameters and prognostic risk stratification were evaluated using multivariate regression analysis. Statistical significance was set at $p<0.05$ (shown in bold)

RA area: right atrium area; RV basal diameter: right ventricular basal diameter; Basal RV/LV ratio: right ventricular and left ventricular basal diameter; TAPSE: tricuspid annular plane systolic excursion; S': systolic velocity of the tricuspid lateral annulus; FAC: fractional area change; sPAP: systolic pulmonary artery pressure; SV/ESV: stroke volume/end-systolic volume

Conclusions

3DE-derived coupling parameters offer a noninvasive and reliable approach for assessing RV-PA coupling in patients with pre-capillary PH, especially for patients who cannot accurately estimate pulmonary artery pressure or have undergone cardiac surgery. 3DE SV/ESV is superior to TAPSE/sPAP for assessing postoperative RV-PA coupling in CTEPH patients, TAPSE/sPAP remains a valuable parameter for prognostic risk stratification in pre-capillary PH patients. Echocardiography can provide valuable information for assessing RV-PA coupling and prognosis in patients with pre-capillary PH. However, the application of echocardiographic coupling parameters should be determined based on the specific clinical context.

Abbreviations

RV-PA coupling	Right ventricle–to–pulmonary artery coupling
TAPSE	Tricuspid annular plane systolic excursion
sPAP	Pulmonary artery systolic pressure
PEA	Pulmonary endarterectomy
3DE	Three-dimensional echocardiography
PH	Pulmonary hypertension
CTEPH	Chronic thromboembolic pulmonary hypertension
RHC	Right heart catheterization
PAH	Pulmonary artery hypertension
CMR	Cardiac magnetic resonance imaging
Ees	Right ventricular end-systolic maximum elasticity
Ea	Pulmonary artery effective elasticity
SV/ESV	Stroke volume/end-systolic volume
TR	Tricuspid regurgitation
TR PG	TR pressure gradient
TR-mPG	TR mean pressure gradient
mPAP	Mean pulmonary artery pressure
RA	Right atrium area
RV	Right ventricle
S'	Systolic annular tissue velocity of the lateral tricuspid annulus
FAC	RV Fractional area change
IVC	Inferior vena cava
RVOT-act	RV outflow tract acceleration time
RV GLS	Global longitudinal strain of RV
RV EF	Right ventricular ejection fraction
PAWP	Pulmonary artery wedge pressure
RAP	Right atrial pressure
CO	Cardiac output
PVR	Pulmonary vascular resistance
RV EDV	Right ventricular end-diastolic volume

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Author contributions

All authors have participated sufficiently in this submission to take public responsibility for its content. AL.L. proposed research ideas, collected echocardiographic data, revised the paper, and reviewed it academically. YN.Z measured and collected echocardiographic data. L.L. collected echocardiographic data. GJ.L. was responsible for literature review, echocardiographic data measurement, data analysis and writing the manuscript. M.D. measured CMR data. XT.C. performed right heart catheterization. Q.G, WM.X. and ZG.Z. collected the clinical data. JP.L. gave guidance on the statistics.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki. Ethical approval number was 2020-95-K59. The protocol was approved by the Ethic Committee of China-Japan Friendship Hospital. The institutional review board of the China-Japan Friendship Hospital waived the need for written patient informed consent as this study involved the retrospective analysis of clinically acquired data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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