

Right ventricular dyssynchrony in pulmonary hypertension: Phase analysis using FDG-PET imaging

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Background. Right ventricular (RV) performance in patients of pulmonary hypertension (PH) requires optimal assessment. The objective of this study is to develop phase analysis using ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging as a feasible tool for evaluation of RV dyssynchrony in PH.

Methods and Results. Fifty-four PH patients with well-characterized hemodynamic parameters were enrolled. All subjects performed FDG-PET imaging for RV phase analysis and RV function evaluation. Two-dimensional echocardiography with speckle tracking analysis was conducted to obtain RV time to peak systolic strain (PSST) as a comparison. The median contraction delay difference between RV middle free wall and septum measured by PET phase analysis (RVPD_{PET}) was 20.12° (interquartile range, 4.99°-30.10°). The median difference of PSST between RV middle free wall and middle septal wall (RVPD_{Echo}) measured by echocardiography was 43.98° (interquartile range, 6.25°-72.00°). RVPD_{PET} was well correlated with RVPD_{Echo} ($r = 0.685$, $P < .001$). RV phase standard deviation (RVSD) and histogram bandwidth (RVBW) derived from PET phase histogram were significantly correlated with cardiac index, RV ejection fraction, 6-minute walking distance, and serum N-terminal pro B-type natriuretic peptide (NT-proBNP) (RVSD: $r = -0.532$, $P < .001$; $r = -0.551$, $P < .001$; $r = -0.544$, $P < .001$; $r = 0.404$, $P < .01$; respectively, RVBW: $r = -0.492$, $P < .001$; $r = -0.466$, $P < .001$; $r = -0.544$, $P < .001$; $r = 0.349$, $P = .01$, respectively), while there were no significant correlations between RVSD and RVBW with hemodynamic parameters (right atrial pressure, right ventricular systolic pressure, right ventricular end-diastolic pressure, mean pulmonary artery pressure, and total pulmonary resistance).

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Conclusions. Contraction delays between RV free wall and septum in PH measured by phase analysis and speckle tracking echocardiography were well correlated. RV dyssynchrony measured by phase analysis of FDG-PET was significantly related to RV dysfunction. Phase analysis of FDG-PET is feasible to evaluate RV mechanical dyssynchrony in patients of PH. (J Nucl Cardiol 2017;24:69–78.)

Key Words: Fluorodeoxyglucose • pulmonary hypertension • right ventricle • dyssynchrony • phase analysis

Abbreviations

PH	Pulmonary hypertension
RV	Right ventricle/ventricular
LV	Left ventricle/ventricular
PET	Positron emission tomography
FDG	Fluorodeoxyglucose
RVPD	Contraction delay difference between RV free wall and septum
RVSD	RV phase standard deviation
RVBW	RV phase histogram bandwidth
PSST	Time to peak systolic strain

See related editorial, pp. 79–82

INTRODUCTION

In pulmonary hypertension (PH), pulmonary vascular proliferation progressively increases pulmonary artery pressure and right ventricular (RV) afterload, subsequently leading to right heart failure.¹ RV function as a major determinant of clinical outcomes in PH patients is of great clinical importance and requires optimal assessment.² To better understand the performance of RV, modern imaging modalities focus on evaluation of not only ventricular systolic function but also right heart metabolism and mechanical synchronicity.

At present, RV mechanical dyssynchrony in PH is predominantly evaluated by echocardiography and has been shown to relate to inefficient RV contraction, impaired left ventricle (LV) diastolic filling, and pump function.³ However, echocardiographic techniques, especially three-dimensional tissue Doppler imaging or speckle tracking, require high standardized expertise for post-processing and optimization of observer variability in clinical practice.⁴ Lately, automated and reproducible phase analysis using ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been suggested as a suitable option for LV dyssynchrony measurement.⁵ Moreover, recent studies employing FDG-PET showed its value for assessment of RV systolic function and myocardial glucose metabolism in PH, suggesting a potential of FDG-PET imaging in comprehensive

evaluation of RV function in PH.⁶ However, the utility of FDG-PET imaging in assessment of RV mechanical synchrony has not been studied. Thus, this study was aimed to validate the feasibility of phase analysis on FDG-PET imaging to evaluate RV mechanical synchrony in patients with PH in a head-to-head comparison with speckle tracking echocardiography and to explore the relationship of RV dyssynchrony and clinical severity.

METHODS

Study Population

A total of fifty-four consecutive patients with PH were enrolled in this study at Fu Wai Hospital from Jan 2011 to Dec 2013. Diagnosis of PH was defined as an increase in mean pulmonary artery pressure (mPAP) \geq 25 mmHg at rest assessed by right heart catheterization according to guidelines for the diagnosis and treatment of PH.⁷ Of the fifty-four patients, twenty-six patients had idiopathic pulmonary arterial hypertension, one had familial pulmonary arterial hypertension, ten had PH associated with congenital heart disease, eight had PH associated with connective tissue disease, six had chronic thromboembolic PH, and three had hereditary hemorrhagic telangiectasia. Patients with diabetes mellitus or glucose intolerance, coronary artery disease, cardiomyopathy, primary valvular disease, or systemic arterial hypertension were excluded. FDG-PET imaging and speckle tracking echocardiography were performed in all subjects at intervals within 3 days. The study was approved by the Institutional Ethics Committee of Fu Wai Hospital. All patients enrolled in the study provided written informed consent.

FDG-PET Imaging

After a minimum 8-hour overnight fast, all patients were given 50 g oral glucose load 30 minutes before the injection of 185 MBq ¹⁸F-FDG. Data were acquired 60 minutes later using PET-CT (Truepoint Biography 64, Siemens Healthcare). CT transmission scanning (140 kV, 35 mA) was performed for attenuation correction. The acquisition time was 10 minutes for emission (three-dimensional mode). The cardiac cycle was divided into eight equal intervals. Attenuation-corrected data were reconstructed using an iterative algorithm (OSEM, 4 iterations, 8 subsets). The matrix was 128 \times 128 pixels and the reconstruction zoom was 2.0. Short-axis slices of 3 mm thickness were obtained in PET images.

Gated ¹⁸F-FDG PET images were used to assess RV function as in our previous study.⁶ The parameters including

right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV), and right ventricular ejection fraction (RVEF) were automatically calculated by QGS (version 3.1, Cedars-Sinai Medical Center, Los Angeles, CA, USA), and manual correction was processed in case of inadequate anatomical delineation.

In PET image processing, reconstructed transaxial images were reoriented into short-axis images using the Emory Cardiac Toolbox (version 3, Emory University, Atlanta, GA, USA). An interactive tool, as illustrated in Figure 1 was used to specify parameters characterizing RV location and size from the short-axis images. These RV parameters were input into a 3D sampling algorithm, which searched the maximal count circumferential profiles for each cardiac frame.⁸ The 3D samples were then processed by a RV phase analysis tool based on the first-harmonic Fourier approximation to calculate the onset of contraction for each sample, which is similar to the LV phase analysis technique published by Chen et al.⁹

The phase values of all RV samples were rendered on the RV polar map, which was then segmented to calculate the regional mean phases in RV middle free wall and RV middle septal wall, respectively. Thereafter, the contraction delay between the middle RV free wall and septal wall was calculated as the difference between their mean phases (RVPD_{PET}). The RV phase standard deviation (RVSD) and histogram bandwidth (RVBW) were measured for assessing the RV dyssynchrony, which is similar to assessment of LV dyssynchrony described previously.⁹

Echocardiographic Examination and Speckle Tracking Analysis

Transthoracic echocardiographic examinations were performed on all subjects using iE33 (S5-1 transducer, Philips Medical Systems, Best, The Netherlands) by experienced cardiologists, blinded to FDG-PET imaging and clinical

details. Two-dimensional grayscale images were acquired from apical four-chamber view in three consecutive cardiac cycles with a frame rate over 70 Hz. Speckle tracking analysis was performed on QLAB Quantification Software 8.1 (Philips Healthcare, Netherlands). Time to peak systolic strain (PSST) was analyzed in RV middle free wall and middle septal wall corresponding to the PET slices. The contraction delay difference between RV free wall and septum was defined as the difference of PSST between RV middle free wall and middle septal wall (RVPD_{Echo}). PSST for each patient was standardized by R-R interval. Average values of three cardiac cycles were used in statistical analysis.

Statistical Analysis

Normally distributed continuous data were expressed as mean ± standard deviation (SD) and non-normally distributed continuous data were expressed as median with the first and the third quartiles. Categorical data were expressed as frequency with percentage (%). Differences between two groups were analyzed by the unpaired Student t test for continuous variables and the Fisher exact test for categorical variables. Correlations between the two parameters were determined by linear regression analysis. All statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

Table 1 shows baseline characteristics of total 54 patients. The mean age was 30.5 ± 9.3 years old. 43 (79.6%) patients were female. Most patients had heart failure with 1.9% (1/54) of patients in New York Heart Association class I, 38.9% in (21/54) class II, 55.6% (30/

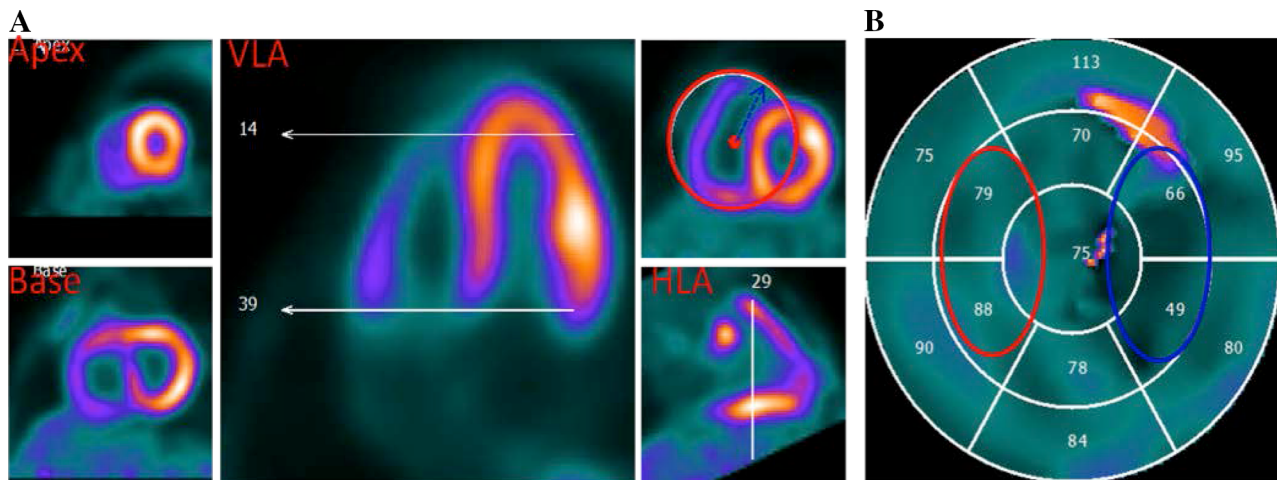


Figure 1. PET image processing. (A) An interactive tool to identify RV parameters, including the apex, base, and circle enclosing the RV myocardium; (B) the phase polar map of the RV. The mean phases in the red and blue regions on (B) were used to calculate contraction delay between RV middle free wall and middle septal wall.

54) in class III, and 3.7% (2/54) in class IV. The mean RVEF was $31.5\% \pm 10.9\%$ and the mean LVEF was $60.6\% \pm 14.5\%$.

The Correlation of FDG-PET and Speckle Tracking Echocardiography in Measurement of Contraction Delay Between RV Free Wall and Septum

The contraction delay between RV free wall and septum measured by FDG-PET imaging and speckle tracking echocardiography were compared to validate the accuracy of phase analysis of FDG-PET images.

In the 54 patients, FDG-PET imaging and echocardiography concordantly found that the contraction onset of the middle RV free wall was later than that of middle RV septal wall in 41 patients; meanwhile, these two methods concordantly found that the contraction onset of the middle RV free wall was earlier than that of middle RV septal wall in nine patients, achieving an overall agreement rate of 92.6% (50/54).

For a clearer comparison, $RVPD_{Echo}$ units of ms were converted to $RVPD_{PET}$ units of degrees using R-R interval. The median $RVPD_{PET}$ was 20.12° (interquartile range, 4.99° - 30.10°) and the median $RVPD_{Echo}$ was 43.98° (interquartile range, 6.25 - 72.00°). $RVPD_{PET}$ was well correlated with $RVPD_{Echo}$ ($r = 0.685$, $P < .001$, Figure 2).

The Correlation of RV Dyssynchrony and Clinical Severity

The quantitative parameters for RV mechanical dyssynchrony, RVSD and RVBW, were derived from the phase histogram. The mean phase RVSD was $39.1^\circ \pm 12.0^\circ$ and the mean phase RVBW was $123.9^\circ \pm 51.1^\circ$.

Figure 3 shows correlations between RVSD, RVBW, and RV systolic function, hemodynamic parameters, 6-minute walking distance (6MWD), and

NT-proBNP. Both RVSD and RVBW had significantly negative correlations with cardiac index, RVEF, and 6MWD (RVSD: $r = -0.532$, $P < .001$; $r = -0.551$, $P < .001$; $r = -0.544$, $P < .001$; respectively, RVBW: $r = -0.492$, $P < .001$; $r = -0.466$, $P < .001$; $r = -0.544$, $P < .001$; respectively), and positively correlated with NT-proBNP (RVSD: $r = 0.404$, $P < .01$, RVBW: $r = 0.349$, $P = .01$).

Table 2 shows correlation coefficients between RV dyssynchrony parameters and hemodynamic parameters. There were no significant correlations between RVSD and RVBW with hemodynamic parameters (right atrial pressure, right ventricular systolic pressure, right ventricular end-diastolic pressure, mean pulmonary artery pressure, and total pulmonary resistance).

Representative images of RV function evaluation, PET phase analysis, and echocardiographic

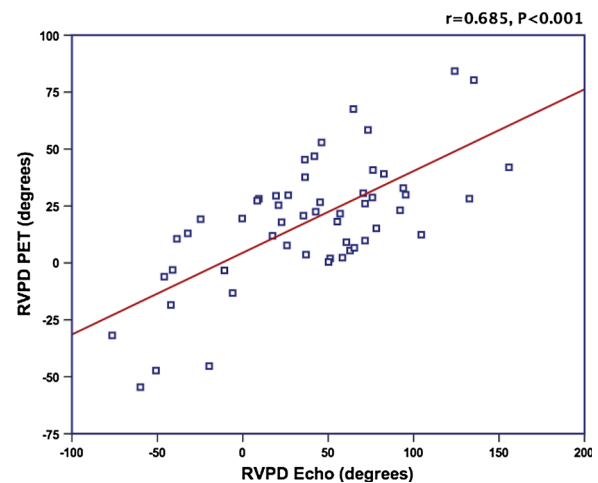


Figure 2. A good correlation between phase analysis of FDG-PET and speckle tracking echocardiography in measuring the contraction delay between RV middle free wall and middle septal wall. ($RVPD_{PET}$ vs $RVPD_{Echo}$, $r = 0.685$, $P < .001$).

Table 1. Baseline characteristics of patients with PH

Age (years)	30.5 ± 9.3
Sex (M/F)	11/43
New York Heart Functional class (I/II/III/IV)	1/21/30/2
Left ventricular ejection fraction (%)	60.6 ± 14.5
Right ventricular ejection fraction (%)	31.5 ± 10.9
Right ventricular end-diastolic volume (mL)	115.8 ± 53.5
Right ventricular end-systolic volume (mL)	83.3 ± 47.5
Mean pulmonary artery pressure (mmHg)	61.2 ± 17.8
Total pulmonary resistance (dyn s cm^{-5})	1106.5 ± 553.2
Cardiac index ($\text{L} \cdot \text{minute}^{-1} \cdot \text{m}^{-2}$)	2.95 ± 1.10
6-minute walking distance (m)	395 ± 89
NT-proBNP ($\text{fmol} \cdot \text{mL}^{-1}$)	1406.7 ± 936.4

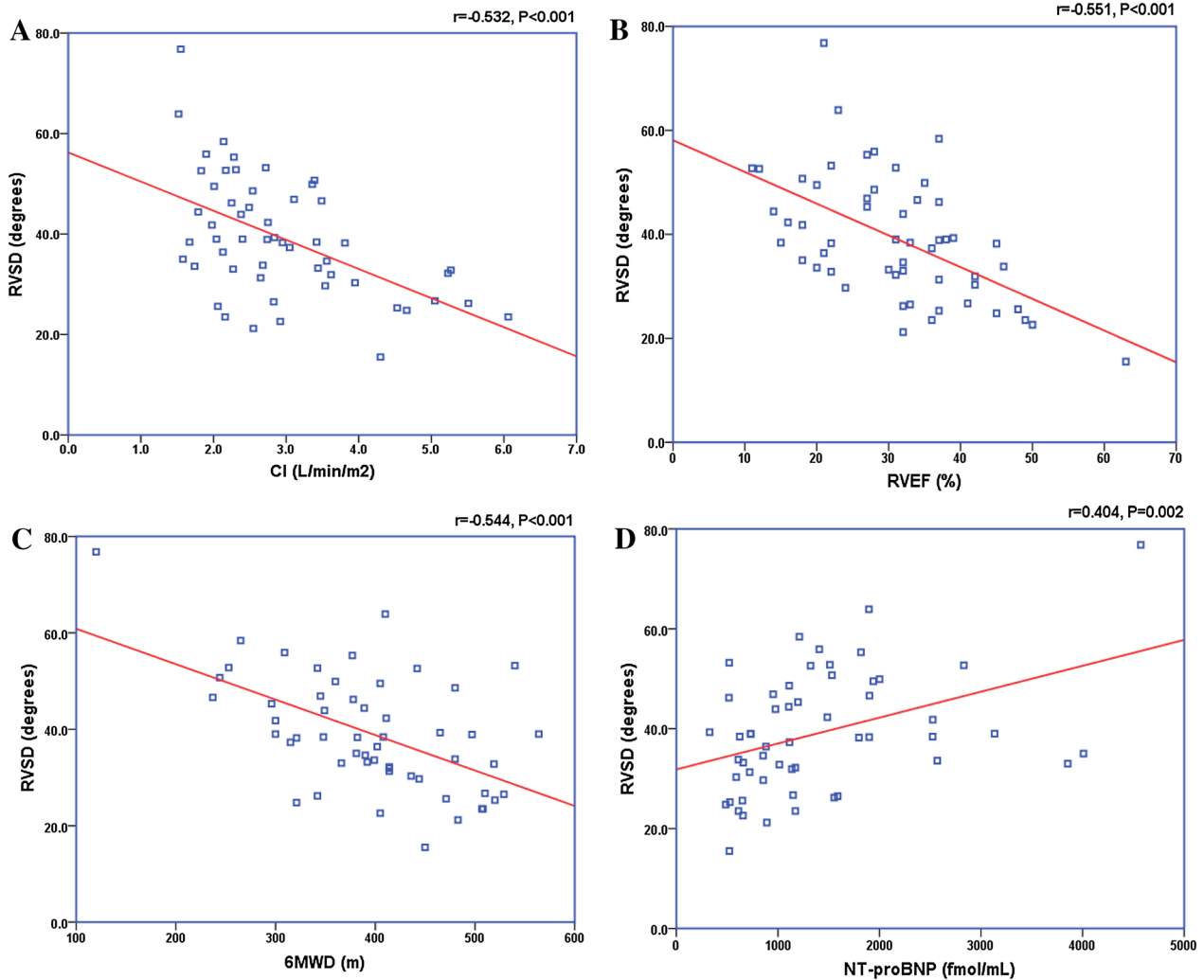


Figure 3. RVSD and RVBW significantly negatively correlated with cardiac index (A, E), RVEF (B, F), and 6MWD (C, G), and positively correlated with serum NT-proBNP (D, H).

speckle tracking analysis of a PH patient was shown in Figure 4.

DISCUSSION

To our knowledge, this is the first study to evaluate RV dyssynchrony of PH using FDG-PET imaging and explore the relationship between the RV dyssynchrony parameters measured by phase analysis of FDG-PET and speckle tracking echocardiographic measurement as well as clinical severity.

The phase analysis technique has been well established to measure LV mechanical dyssynchrony from gated SPECT myocardial perfusion imaging (MPI).⁹ It has been demonstrated to show good temporal resolution,¹⁰ high reproducibility,¹¹ and good robustness with camera types,¹² tracer dose,¹³ heart rate,¹⁴ and perfusion

defects.¹⁵ The LV dyssynchrony parameters have been shown to correlate well with those measured by echocardiography.^{16,17} In a clinical study with 30 heart failure patients, there was a significant correlation of the parameters measured from FDG-PET and SPECT MPI (bandwidth: $r = 0.88$, $P < .001$; phase SD: $r = 0.88$, $P < .001$), resulting in an excellent clinical agreement of 93% to measure LV mechanical dyssynchrony.⁵ Nevertheless, there is no study to measure RV mechanical dyssynchrony from gated SPECT MPI or FDG-PET, mainly because RV in general has low counts and phase analysis is a count-based method. This study included FDG-PET images of patients with PH, where RV has comparable count levels to LV due to increased after-load and hypertrophic myocardium; therefore, the phase analysis technique developed for LV dyssynchrony measurement can be extended to RV dyssynchrony

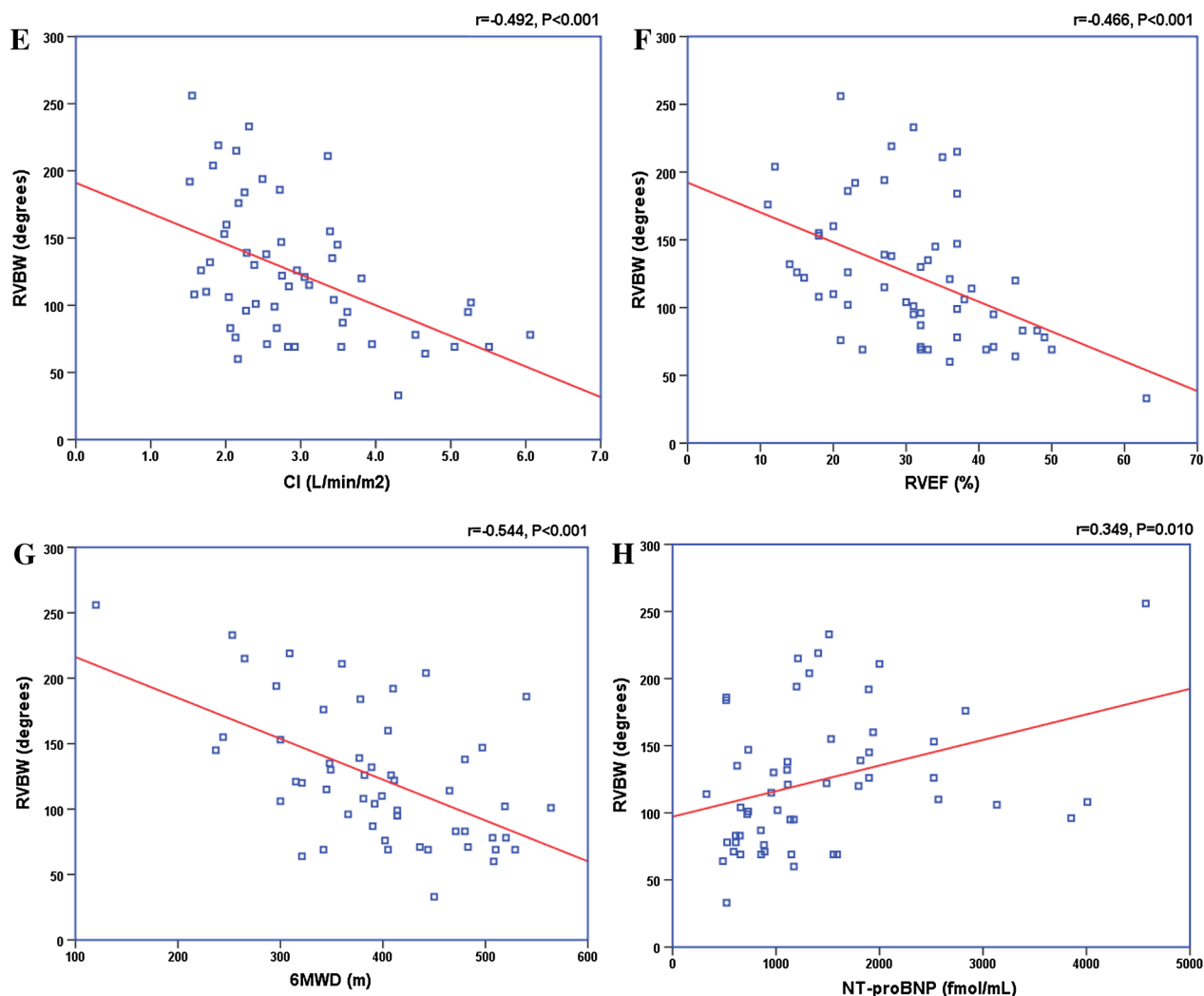


Figure 3. continued.

Table 2. Correlation coefficients between RV dyssynchrony parameters and RV hemodynamic parameters

	RAP	RVSP	RVEDP	mPAP	TPR
RVSD	$r = 0.164$ $P = .236$	$r = -0.274$ $P = .075$	$r = 0.044$ $P = .754$	$r = -0.284$ $P = .058$	$r = 0.111$ $P = .425$
RVBW	$r = 0.191$ $P = .168$	$r = -0.318$ $P = .119$	$r = 0.039$ $P = .778$	$r = -0.330$ $P = .115$	$r = 0.083$ $P = .552$

RAP, Right atrial pressure; RVSP, right ventricular systolic pressure; RVEDP, right ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; TPR, total pulmonary resistance; RVSD, right ventricular phase standard deviation; RVBW, right ventricular phase histogram bandwidth.

measurement. Echocardiography has been used to evaluate RV dyssynchrony in clinical practice¹⁸⁻²¹; however, there are limitations due to its reproducibility. Therefore, as an alternative technique, RV phase analysis

using FDG-PET may add clinical values to the management of patients with PH.

We compared RV mechanical dyssynchrony measured from gated FDG-PET with that measured from

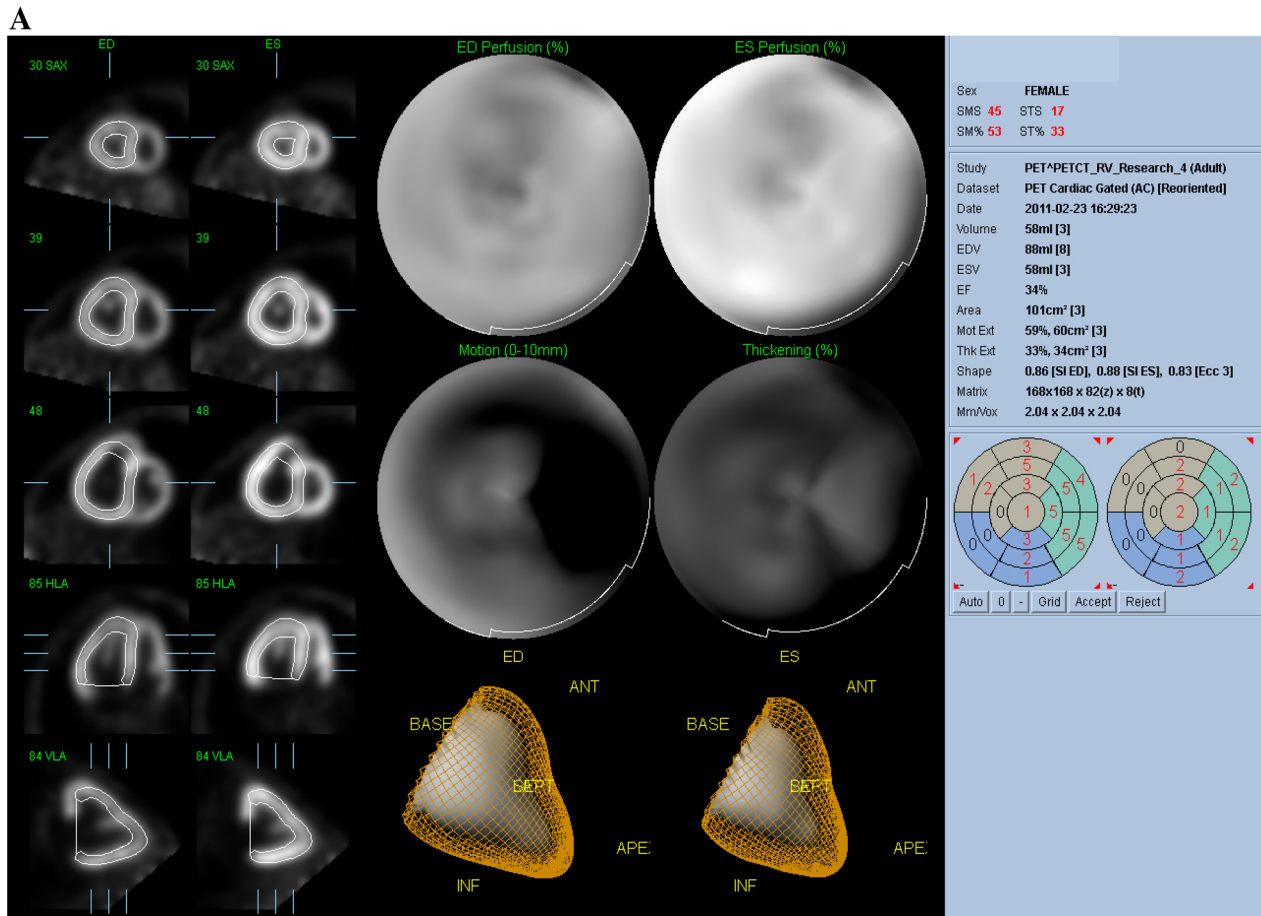


Figure 4. Representative images of RV function evaluation (A) and phase analysis (B) on FDG-PET and echocardiographic speckle tracking analysis (C) of a 31-year-old female patient with PH. RV dysfunction (RVEF = 34%) and RV dyssynchrony (RVSD = 21.2°, RVBW = 71°) were shown. The phase analysis and speckle tracking analysis concordantly found that contraction onset of the middle RV free wall (MAL, indicated by the red arrow) was later than that of middle RV septal wall (MIS, indicated by the blue arrow), RVPD_{PET} was 22.5° and RVPD_{Echo} was 42.7°.

speckle tracking echocardiography. Noteworthy, both speckle tracking and tissue Doppler echocardiography techniques are being clinically used to measure mechanical dyssynchrony; however, compared to tissue Doppler technique, speckle tracking has superior reproducibility,²² and it can measure the strain pattern caused by active wall thickening/thinning.²² In order to compare LV mechanical dyssynchrony measured by phase analysis from gated SPECT with that by speckle tracking echocardiography in,²² the middle LV wall was divided into six segments; it was found that the phase standard deviation (SD) correlated well with the SD of the times to peak systolic radial strains of two opposing LV walls measured by speckle tracking ($r > 0.7$, $P < .001$). In our study, the difference between mean phases of middle RV free wall and middle RV septum (RVPD_{PET}) was validated by the difference between the times to peak systolic strains of middle RV free wall and middle RV

septum (RVPD_{Echo}), and a correlation of 0.685 was achieved ($P < .001$), indicating a good correlation to measure RV mechanical dyssynchrony by phase analysis and speckle tracking.

We further compared RV mechanical dyssynchrony with clinical severity indices to explore the clinical relevance of RV dyssynchrony in PH patients. Our data showed that RV mechanical dyssynchrony seemed to be more related to RV function in comparison to pulmonary vascular hemodynamics. Patients with worse RV systolic function, cardiac index may be related to worse RV systolic synchronicity. Noteworthy, RVSD and RVBW were well correlated with NT-proBNP and 6MWD, two well-studied RV dysfunction markers in PH. In response to ventricular pressure and volume overload,²³ NT-proBNP can be used to detect RV systolic dysfunction in PH,²⁴ while 6MWD reflecting exercise capacity has a strong and independent

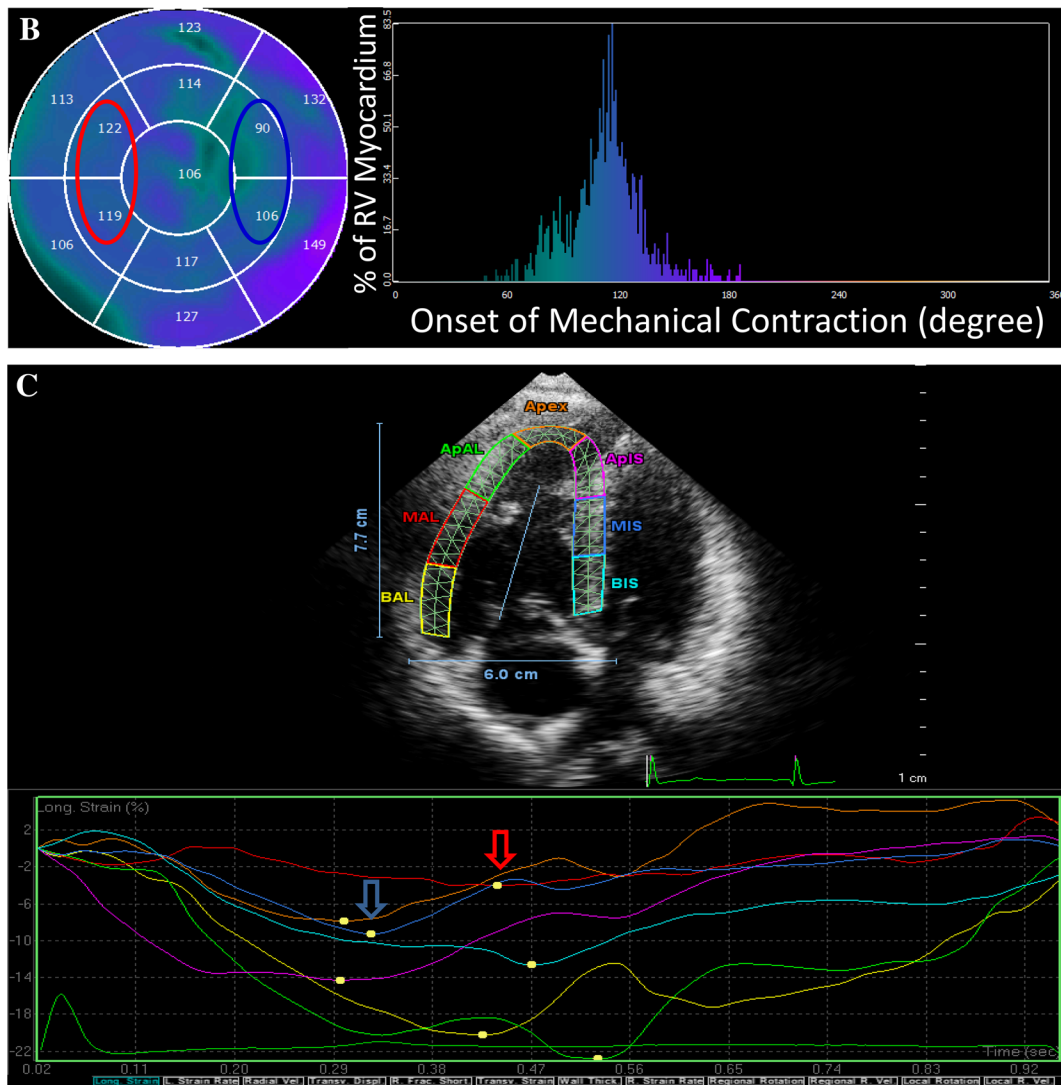


Figure 4. continued.

association with mortality.²⁵ Although the underlying mechanism of RV mechanical dyssynchrony remains not fully elucidated, previous studies have showed that chronic RV pressure overload would cause RV dilation and increased RV wall stress, leading to prolonged contraction duration and RV dyssynchrony.^{26,27} RV dyssynchrony impairs RV performance, leads to a paradoxical septum shift, and subsequently influences LV filling. Therefore, RV dyssynchrony can be interpreted as a sign of RV failure³ and its correlations with RV functional parameters, NT-proBNP and 6MWD can be explained.

Although the relationships between RV dyssynchrony and pulmonary vascular hemodynamics were not significant in current study, several reasons possibly explained this discrepancy from other reports.^{28,29}

Firstly, subjects enrolled in this study included PH patients with heterogeneous etiology who may present different RV compensatory capability. Patients with higher pulmonary artery pressure may be more capable to cope with the increased RV afterload and develop less severe RV failure compared to patients with lower pulmonary artery pressure. Moreover, approximately 70.4% patients in current study had moderate to severe tricuspid regurgitation, which would compromise RV afterload to a certain extent. In these cases, RV function as well as RV dyssynchrony may not necessarily link to pulmonary vascular pressure.

Additionally, applicability of FDG-PET imaging in PH has been increasingly explored. FDG-PET imaging can quantify RV myocardial glucose metabolism in PH. Several studies have reported that PH patients had an

increased glucose uptake in the RV and it correlated with the severity of RV pressure overload and RV systolic dysfunction^{30,31} and may be a predictor for clinical worsening.³² Moreover, data from our previous study showed RV volume and ejection fraction assessed by FDG-PET imaging were in moderate to high correlation with cardiac magnetic resonance imaging, suggesting FDG-PET imaging can be an available method for measurement of RV volume and function.⁶ This study showed the feasibility of FDG-PET imaging to evaluate RV mechanical dyssynchrony. Therefore, employing FDG-PET imaging in PH patients allows for the simultaneous assessment of RV function, glucose metabolism, and mechanical dyssynchrony without additional acquisition. This enables comprehensive evaluation of RV performance and indicates a potential usefulness of FDG-PET imaging as a biomarker in PH patients.

LIMITATIONS

Firstly, no control group was included in this study because of low counts in the thin RV wall in normal subjects. Secondly, the current findings were based on a relatively small subset of PH patients with heterogeneous etiology. Given the lack of a standardization of imaging techniques to evaluate ventricular dyssynchrony, employing two-dimensional speckle tracking echocardiography as reference may not be optimal. Data to be collected in a large cohort of patients at baseline and during follow-up would further examine the feasibility and applicability of RV dyssynchrony evaluation on FDG-PET imaging, and a subgroup comparison of different PH patients can be analyzed to determine the clinical relevance.

NEW KNOWLEDGE GAINED

This study to our knowledge firstly studied the feasibility of applying phase analysis on FDG-PET imaging to RV mechanical dyssynchrony measurement. In patients with PH, RV mechanical dyssynchrony evaluated by phase analysis on FDG-PET was well correlated with echocardiographic dyssynchrony parameters and was significantly related to RV dysfunction.

CONCLUSIONS

In patients with PH, phase analysis on gated FDG-PET imaging could effectively evaluate RV mechanical dyssynchrony and has good correlation with speckle tracking echocardiography. The RV dyssynchrony parameters measured by phase analysis correlated well with RV functional and clinical parameters, but not with

pulmonary vascular hemodynamics. With the new phase analysis tool, FDG-PET imaging can provide a method for the comprehensive assessment of RV function, glucose metabolism, and mechanical dyssynchrony for patients with PH.

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Disclosures

Drs Chen and Garcia receive royalties from the sales of Emory Cardiac Toolbox. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict-of-interest practice. Drs Wang, Zhou, Liang, Yang, and Fang declare that he/she has no conflict of interest.

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