



The feasibility of ^{18}F -FDG gated positron emission tomography (PET) for left ventricular dyssynchrony assessment in comparison with $^{99\text{m}}\text{Tc}$ -MIBI gated single-photon emission computed tomography (SPECT) among patients with prior myocardial infarction

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Background: Phase analysis by $^{99\text{m}}\text{Tc}$ -MIBI gated single-photon emission computed tomography (GSPECT) has been considered to be an adequate method in the validation of left ventricular (LV) dyssynchrony. Compared with GSPECT, prior myocardial infarction patients with myocardial perfusion defects but myocardial viability usually show preserved uptake of ^{18}F -FDG, and extensive myocardium is detected by ^{18}F -FDG gated positron emission tomography (GPET). Thus, theoretically, it should be more accurate. The aim of this study was to investigate the feasibility of GPET for LV dyssynchrony assessment in comparison with GSPECT among infarction patients.

Methods: A total of 146 patients with infarction underwent 2 consecutive days of GSPECT and GPET examinations. Quantitative gated SPECT-derived LV phase analysis was applied to GPET and GSPECT data to assess the presence of LV dyssynchrony via histogram bandwidth (BW) and phase standard deviation (SD). The correlation and agreement of BW and SD between GSPECT and GPET were examined. Factors (i.e., total perfusion defect, scar and mismatch) related to the discrepancies of LV dyssynchrony (i.e., BW and SD) in GPET and GSPECT were assessed by univariate and multivariate regression analysis.

Results: A moderate correlation between GPET and GSPECT was found in the measurements of BW ($r=0.554$) and SD ($r=0.537$). Bland–Altman analysis revealed that GPET overestimated both BW and SD (20.5° and 9.5° , respectively). In addition, the BW and SD measured by GPET were still overestimated after subgroup analysis. Between GPET and GSPECT, multivariate regression analysis revealed that total perfusion defects were related to the difference in BW measurement ($P<0.001$), and mismatch was associated with the difference in SD measurement ($P<0.01$).

Conclusions: In patients with infarction, GPET moderately correlated with GSPECT in assessing LV dyssynchrony. GPET overestimated both BW and SD, so these analyses should not be interchangeable in individual patients.

Keywords: Myocardial infarction (MI); ^{18}F -FDG gated positron emission tomography (^{18}F -FDG gated PET);

^{99m}Tc -MIBI gated single-photon emission computed tomography (^{99m}Tc -MIBI gated SPECT); phase analysis; dyssynchrony

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Introduction

Left ventricular (LV) asynchrony is associated with severe heart failure, and cardiac resynchronization therapy (CRT) has proven to be an effective treatment (1-4). However, according to current guidelines, nearly 30% of patients with heart failure have not received good treatment results for CRT (5). Research has shown that LV mechanical dyssynchrony, LV motion patterns, amount of viable myocardium and scar burden are the main factors affecting a patient's response to CRT (6). By evaluating the mechanical dyssynchrony of the left ventricle, it may be helpful to determine which patients will benefit from CRT. Therefore, we selected myocardial infarction (MI) patients with somewhat larger areas of total perfusion defects (TPDs) and scars as the research objects, which is more representative.

Phase analysis of ^{99m}Tc -MIBI gated single-photon emission computed tomography (GSPECT) can evaluate LV dyssynchrony, which has been regarded as a standard reference (7). Compared with ungated acquisition, GSPECT does not increase the risk of additional radiation exposure. Compared with GSPECT, ^{18}F -FDG gated positron emission tomography (GPET) has more advantages. For example, GPET is a routinely performed gated acquisition and has a higher spatial resolution. In addition, the myocardium with impaired but viable blood perfusion often shows reduced uptake of ^{99m}Tc -MIBI and preserved uptake of ^{18}F -FDG. Whether GPET phase analysis is feasible in evaluating LV dyssynchrony depends on the accuracy of its quantitative determination of histogram bandwidth (BW) and phase standard deviation (SD) values. If PET/CT assessment of LV desynchronization is feasible, then a comprehensive assessment of myocardial vitality, infarct location, and LV dyssynchrony in patients with MI in one scan before CRT without additional acquisition will be more effective and beneficial for patients. Current evidence on the role of LV mechanical dyssynchrony evaluation is mainly available for GSPECT, but ^{18}F -FDG GPET is not often used (8). To date, there is a lack of prospective head-to-head studies

to further verify the value of GPET phase analysis on LV dyssynchrony assessment and whether it can be used as a better option. Little information is available on the interchangeability between GSPECT- and GPET-derived LV dyssynchrony.

The aim of this study was to evaluate the feasibility of GPET phase analysis for clinical utilization among MI patients. Furthermore, we evaluated the impacts of viable myocardium, TPDs and scarring on the accuracy of LV mechanical dyssynchrony measured by GPET and used GSPECT phase analysis as the reference standard. We present the following article in accordance with the STARD reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-21-822/rc>).

Methods

Study population

We prospectively studied 196 consecutive patients with prior MI who underwent GSPECT and GPET viable myocardial examination at Fu Wai Hospital from July 2016 to October 2017. The 2-day protocol was used to assess myocardial viability. That is, ^{99m}Tc -MIBI resting myocardial perfusion imaging was performed on the first day, and ^{18}F -FDG myocardial metabolism imaging was performed on the second day. According to the diagnostic criteria of the European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation (WHF) expert consensus, the diagnosis of prior MI was confirmed by increased levels of biomarkers of myocardial necrosis, electrocardiographic (ECG) changes, pathological examination and imaging (9). After excluding patients with left bundle branch block, severe arrhythmia (ventricular tachycardia, or ventricular fibrillation), pregnancy, low GSPECT or GPET imaging quality and inaccurate detection of LV contour, 146 patients were included in this study. Before the start of the study, the first author evaluated all subjects and screened their research eligibility. The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Fu Wai Hospital and Cardiovascular Institute. Informed consent was obtained from all patients.

Resting GSPECT

The resting GSPECT image began approximately 60–90 min after intravenous administration of 925 MBq $^{99\text{m}}\text{Tc}$ -sestamibi. The imaging acquisition was performed with a dual-head SPECT system (e.cam, Siemens Medical Systems), which is carried out in a zoom factor of 1.45, a 128×128 matrix and a total of 32 views at 30 s per view. With a 20% window centered, the cardiac cycle was divided into eight equal fixed intervals over the 140 keV photopeak, and the Butterworth-filtered back-projection method (10) (order 5; cutoff frequency 0.40) was used to reconstruct the cardiac gated transaxial images. GSPECT images were displayed as short-axis slices, vertical long-axis slices and horizontal long-axis slices.

GPET

Under fasting conditions, the patients received a glucose load. After 40 min, regular short-acting insulin was injected intravenously according to their serum glucose level. After the serum glucose level reached the target, 148 MBq ^{18}F -FDG (Chinese Atomic Energy Institute, Beijing, China) was administered intravenously. Imaging acquisition was performed for 10 min after 1 hour. The ^{18}F -FDG myocardial images were obtained by a high spatial resolution PET scanner (Truepoint Biography 64, Siemens Healthcare, Knoxville, TN, USA). With a zoom factor of 2.0, the cardiac cycle was divided into 8 equal intervals and formatted into a 128×128 matrix.

Analysis of GSPECT and GPET images

After gated image acquisition was completed, the gated and nongated datasets of SPECT and PET were transferred to the Siemens e.soft workstation. Quantitative gated SPECT (QGS) (version 3.1, Cedars-Sinai Medical Center, Los Angeles, CA, USA) algorithms were used to analyze SPECT and PET images with the same functional parameters. LV parameters, such as BW, SD, mismatch, scar scores and TPD, were analyzed by QGS and quantitative perfusion SPECT (QPS) (version 3.1, Cedars-Sinai Medical Center, Los Angeles, CA, USA). For patients with a large TPD and

inaccurate delineation of the endocardium and epicardium, both PET and SPECT images needed to be corrected manually. The manual correction rate was 8.2%. All data analyses were performed by a senior nuclear medicine doctor who was blinded to the patient data.

Statistical analysis

SPSS v22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Continuous data are expressed as the mean \pm SD. For nonnormal distributions, disagreements were analyzed by the Wilcoxon nonparametric test (11), and the strength of agreement was tested using Spearman correlation. The degree of agreement between GPET and GSPECT was evaluated by Bland-Altman analysis (12,13). The agreement limits were evaluated by the mean difference ± 1.96 SD of differences. Factors (such as mismatch, scarring and TPD) related to the difference in LV dyssynchrony parameters (BW and SD) between GPET and GSPECT were assessed by linear regression analysis. Only variables with statistical significance in univariate analysis were further included in multivariate analysis. A P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics and phase analysis

The clinical characteristics of the patients are shown in *Table 1*. One hundred and thirty-one men and 15 women were included. All patients had a history of prior MI. The mean values of BW and SD from GPET were 154° and 46° , respectively, and those from GSPECT were 133° and 36° , respectively.

With regard to BW and SD, the correlation between GPET and GSPECT was moderate ($r=0.554$ and 0.537 , respectively; both $P<0.001$) (*Figure 1A,1B*). Through Bland-Altman analysis, GPET overestimated both BW and SD (20.5° and 9.5° , respectively). The overestimation of GPET had an increasing trend with increasing magnitudes of BW and SD (*Figure 1C,1D*) compared to GSPECT.

Influence of the correlation factor on the discrepancies between GPET and GSPECT

According to the TPD scores, patients were divided into two groups. A score $\leq 20\%$ was Group 1, with 22 (15%) patients, and $>20\%$ was Group 2, with 124 (85%) patients.

Table 1 Clinical characteristics (n=146)

Characteristic	Values
Male sex	131 [90]
Age (years)	58±11
Body mass index (kg/m ²)	25.1±3.4
Diabetes	56 [38]
Hypertension	91 [62]
Hyperlipidemia	115 [79]
PCI or CABG	65 [45]
Coronary angiography	n=96
Three-vessel disease	57 [59]
Two-vessel disease	25 [26]
One-vessel disease	14 [15]
New York Heart Association class III–IV	44 [30]
TPD (%)	36±15
Mismatch (%)	17±12
Scar (%)	16±11
EF (%; echo)	39±10

Data are number (with percentage in parentheses) or mean ± SD. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TPD, total perfusion defect; EF, ejection fraction; SD, standard deviation.

Table 2 summarizes the mean values of BW and SD for these patients. The correlation between GPET and GSPECT was moderate with respect to BW and SD ($r=0.445-0.561$) between the two groups. In comparison with GSPECT, the values of BW and SD were overestimated by GPET in the two groups. $P<0.001$ when the TPD scores were greater than 20%, and $P<0.05$ when the TPD scores were less than or equal to 20%.

In addition, according to the mismatch scores, the patients were divided into three groups. A score $<10\%$ was assigned to Group 1, which had 57 (39%) patients. A score of 10–19% was assigned to Group 2, which had 49 patients (34%). A score $\geq 20\%$ was assigned to Group 3, which had 40 (27%) patients. *Table 3* summarizes the mean values of BW and SD for these patients. According to the QGS results, the correlation between GPET and GSPECT was moderate for BW and SD ($r=0.518-0.612$). Compared with GSPECT, GPET overestimated the values of BW and SD in the three groups ($P<0.001$).

Finally, according to the perfusion/metabolic match,

the patients were divided into three groups. Those with perfusion/metabolic match (scar) were assigned to Group 1, which had 21 (14%) patients. Those with perfusion/metabolic partial mismatch (partially viable) were assigned to Group 2, which had 105 (72%) patients. Those with perfusion/metabolic mismatch (viable) were assigned to Group 3, which had 20 (14%) patients. *Table 4* summarizes the mean values of BW and SD for these patients. The correlation between GPET and GSPECT was moderate for BW and SD ($r=0.504-0.656$), as indicated by QGS analysis. Compared with GSPECT, GPET overestimated the values of BW and SD in the three groups ($P<0.05$).

Univariate and multivariate regression analysis

Table 5 shows the corresponding factors related to BW and SD measurements. The results of univariate regression analysis demonstrated that several factors were significantly related to the discrepancy in BW and SD measurements between GPET and GSPECT. Furthermore, according to the results of multivariate regression analysis, TPD was related to the difference in BW measurement ($P<0.01$), and mismatch was associated with the discrepancy in SD measurement ($P<0.01$) between GPET and SPECT.

Discussion

In this study, our main findings were as follows: (I) The correlation between GPET and GSPECT was moderate for BW and SD in patients with MI. GPET overestimated both BW and SD. The mean differences in BW and SD were 21° and 10°, respectively. (II) Subgroup analysis showed that BW and SD measured by GPET were overestimated (3). Between GPET and GSPECT, TPD was correlated with the difference in BW measurement, and mismatch was related to the difference in SD measurement.

The two-day protocol of gated ^{99m}Tc-MIBI SPECT combined with ¹⁸F-FDG PET can simultaneously evaluate myocardial ischemia, viability, LV function parameters and dyssynchrony (14–18). Current evidence on the role of LV mechanical dyssynchrony evaluation is mainly available for GSPECT, and the feasibility of ¹⁸F-FDG GPET is uncertain. Compared with GSPECT, GPET has a higher temporal and spatial resolution, so it should be more accurate in theory. In addition, gated acquisition of GPET is routinely performed. Whether GPET phase analysis is feasible in evaluating LV dyssynchrony depends on the accuracy of its quantitative determination of BW and SD

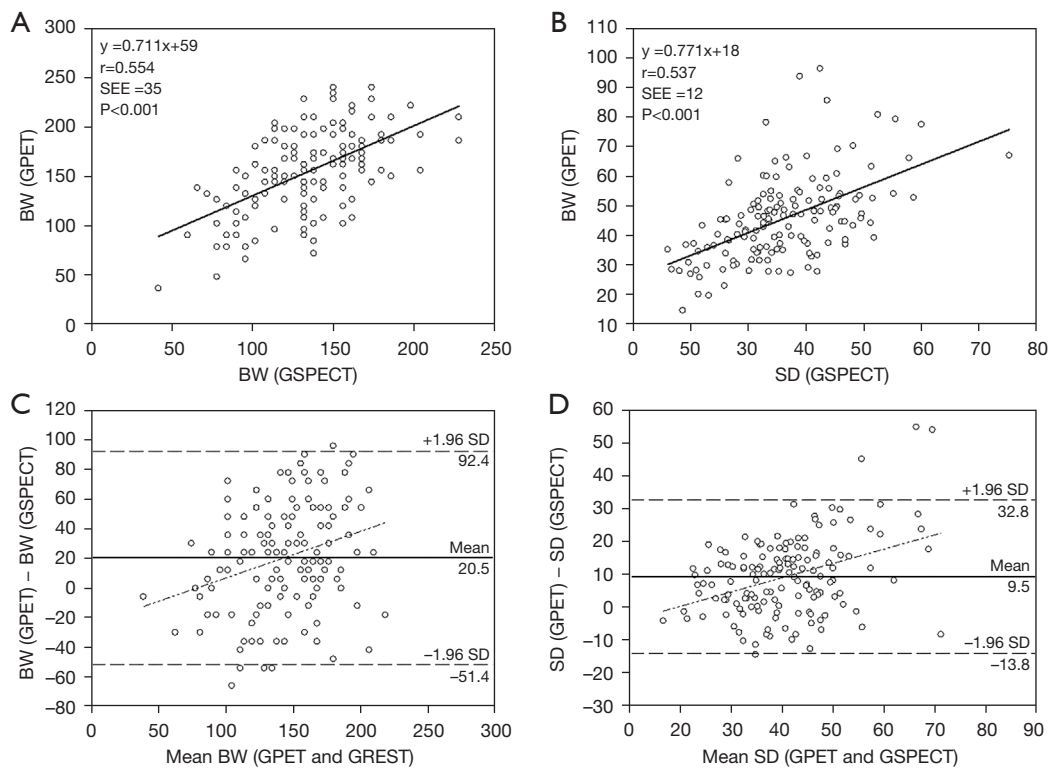


Figure 1 Phase analysis between GPET and GSPECT. Correlation analysis (A,B) and Bland-Altman plots (C,D) of BW and SD from GPET and GSPECT. BW, histogram bandwidth; SD, standard deviation; GPET, ^{18}F -FDG gated positron emission tomography; GSPECT, $^{99\text{m}}\text{Tc}$ -MIBI gated single photon emission computed tomography; SEE, standard error of estimate.

Table 2 Comparisons of BW and SD between GPET and GSPECT in patients with different TPD scores (n=146)

Groups	N	Parameter	GPET	GSPECT	R	P value
Group 1	22	BW	142	112	0.561	0.007
		SD	42	30	0.445	0.038
Group 2	124	BW	156	137	0.545	<0.001
		SD	46	37	0.536	<0.001

TPD scores $\leq 20\%$, Group 1; TPD scores $>20\%$, Group 2. P value, between GSPECT and GPET; R, intraclass correlation coefficient between GSPECT and GPET. BW, histogram bandwidth; SD, standard deviation; GPET, ^{18}F -FDG gated positron emission tomography; GSPECT, $^{99\text{m}}\text{Tc}$ -MIBI gated single-photon emission computed tomography; TPD, total perfusion defect.

values.

However, GPET moderately correlated with GSPECT in assessing LV dyssynchrony in this study. The results here are generally similar to those of previous work. Wang *et al.* reported that GPET and GSPECT were moderately correlated in the evaluation of LV dyssynchrony in patients with coronary artery disease (CAD) ($r_{\text{BW}}=0.58$ and $r_{\text{SD}}=0.60$) (19). The results of Tian *et al.* showed that there was a moderate correlation for BW ($r=0.65$) and SD ($r=0.63$)

between GSPECT and GPET in patients with ischemic cardiomyopathy (20). However, there are also some results with high correlations. For example, Shao *et al.* (6) found that BW and SD obtained in GPET and GSPECT showed a good correlation in pigs with MI ($r_{\text{BW}}=0.74$ and $r_{\text{SD}}=0.84$). The reasons for the small difference may be that the parameters of the experimental animal pigs were measured under anesthesia and the blood glucose was not strictly regulated, which could have affected the results

Table 3 Comparisons of BW and SD between GSPECT and GPET with different extents of viable myocardium (n=146)

Groups	N	Parameter	GPET	GSPECT	R	P value
Group 1	57	BW	150	127	0.537	<0.001
		SD	46	34	0.519	<0.001
Group 2	49	BW	154	131	0.518	<0.001
		SD	44	35	0.532	<0.001
Group 3	40	BW	160	146	0.612	<0.001
		SD	48	40	0.558	<0.001

Mismatch scores <10%, Group 1; 10%≤ mismatch scores <20%, Group 2; mismatch scores ≥20%, Group 3. P value, between GSPECT and GPET; R, intraclass correlation coefficient between GSPECT and GPET. BW, histogram bandwidth; SD, standard deviation; GPET, ¹⁸F-FDG gated positron emission tomography; GSPECT, ^{99m}Tc-MIBI gated single-photon emission computed tomography.

Table 4 Comparisons of BW and SD between GSPECT and GPET with different extents of perfusion/metabolic mismatch (n=146)

Groups	N	Parameter	GPET	GSPECT	R	P value
Group 1	21	BW	152	140	0.643	0.002
		SD	47	38	0.589	0.005
Group 2	105	BW	160	134	0.526	<0.001
		SD	47	36	0.531	<0.001
Group 3	20	BW	125	125	0.656	0.002
		SD	38	34	0.504	0.023

Perfusion/metabolic match (scar), Group 1; perfusion/metabolic partial mismatch (partially viable), Group 2; perfusion/metabolic mismatch (viable), Group 3. P value, between GSPECT and GPET; R, intraclass correlation coefficient between GSPECT and GPET. BW, histogram bandwidth; SD, standard deviation; GPET, ¹⁸F-FDG gated positron emission tomography; GSPECT, ^{99m}Tc-MIBI gated single-photon emission computed tomography.

Table 5 Variables related to the differences in BW and SD measurements between GSPECT and GPET (n=146)

Variables	Univariate analysis		Multivariate analysis		
	Correlation coefficient	P value	Coefficient	Standard error beta	P value
Variables related to the differences in BW (Δ BW)			-0.254	0.260	0.001
TPD	-0.254	0.001			
Mismatch	-0.160	0.038			
Scar	-0.179	0.021			
Variables related to the differences in SD (Δ SD)			-0.210	0.117	0.006
TPD	-0.202	0.009			
Mismatch	-0.210	0.006			
Scar	-0.084	0.281			

BW, histogram bandwidth; SD, standard deviation; GPET, ¹⁸F-FDG gated positron emission tomography; GSPECT, ^{99m}Tc-MIBI gated single-photon emission computed tomography; TPD, total perfusion defect.

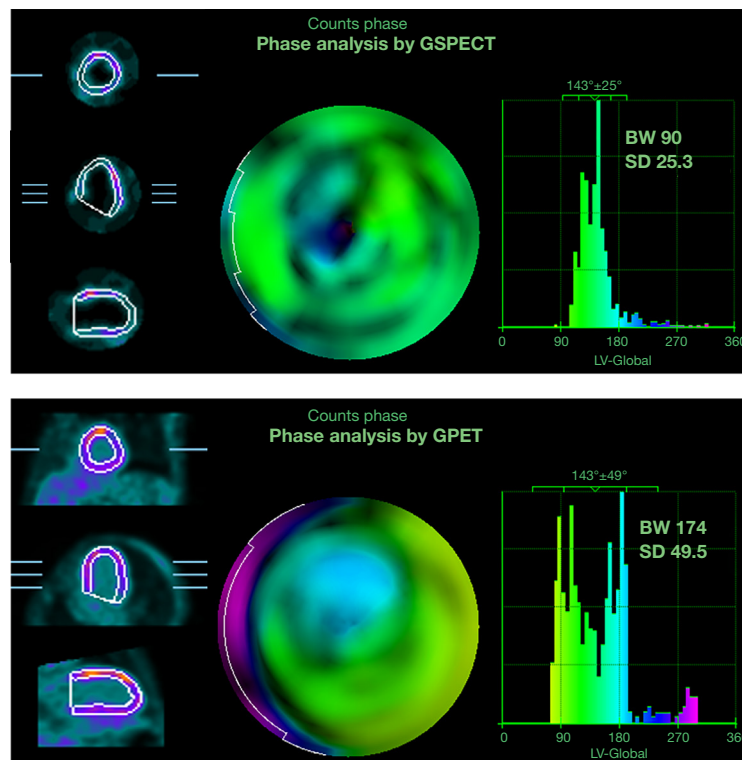


Figure 2 GPET overestimated the BW and SD values in an MI patient with large perfusion defects but viable myocardium. BW, histogram bandwidth; SD, standard deviation; GPET, ^{18}F -FDG gated positron emission tomography; GSPECT, $^{99\text{m}}\text{Tc}$ -MIBI gated single photon emission computed tomography; MI, myocardial infarction; LV, left ventricular.

of dyssynchrony. Ali *et al.* also confirmed that there was a statistically significant difference in SD and BW between resting and stress states (21). In addition, the value of phase analysis may vary depending on the software program, even when using the same software (22,23). Additionally, the phase parameter has great variability because the phase histogram is affected by many factors, such as sex, cardiovascular risk factors, including hypertension, diabetes, and kidney disease, and imaging protocol (7,24,25).

The patients were further divided into different subgroups according to TPD scores, viable myocardial range and perfusion metabolism matching degree. The results showed that GPET overestimated the values of BW and SD in the different subgroups. In an MI patient with large perfusion defects but viable myocardium, the myocardial area detected by GPET was larger than that detected by GSPECT, and GPET overestimated the BW and SD values (*Figure 2*). In addition, according to the results of multivariate regression analysis, TPD was related to the difference in BW measurement, and the extent of viable myocardium was related to the difference in SD

measurement between GPET and GSPECT. Similarly, Wang *et al.* reported that the degree of myocardial perfusion defect is an independent predictor of LV systolic dyssynchrony (26). They suggested that for coronary heart disease patients with obvious LV remodeling, poor myocardial ^{18}F -FDG uptake or severe functional impairment, gated GPET phase analysis should be carefully applied. However, although most LV mechanical dyssynchrony is currently evaluated by GSPECT, its accuracy still needs to be further studied. MI patients with viable myocardium in the myocardial perfusion defect site usually show preserved uptake of ^{18}F -FDG. Compared with SPECT perfusion imaging, PET detects a larger area of myocardium. In this study, we selected MI patients with a larger TPD score and scar area as the research objects, which is more representative. Taken together, in patients with MI, BW and SD measured by GPET differ from those determined by GSPECT, and thus, these results should not be interchanged in individual patients. Therefore, whether GPET can be used to evaluate LV mechanical dyssynchrony in patients with MI still needs further investigation in large-

scale studies.

This study has several limitations. First, GSPECT does not perform attenuation correction, so it may underestimate the extent of viable myocardium, especially in the posterior and inferior walls of mild perfusion defects. Second, for patients with a large area of myocardial perfusion defects, the accuracy of the software to detect the boundaries of the outer and inner membranes will be reduced. In addition, the QGS algorithm is mainly designed for GSPECT research, and for PET imaging, a more suitable algorithm should be used for analysis to obtain more accurate results. Another limitation to consider is that the study was a single center study. Possible future work in a multicenter study to evaluate the accuracy of PET phase analysis through the results of clinical cardiac resynchronization therapy could confirm our findings. Since entropy and machine-learning approaches may help improve the estimation of CRT candidates, they can be introduced later.

Conclusions

In conclusion, there was a certain deviation between BW and SD measured by GPET and GSPECT in MI patients, and thus, they should not be interchangeable in individual patients.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-21-822/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-21-822/coif>). The authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Fu Wai Hospital and Cardiovascular Institute. Written informed consent was obtained from the patient.

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