ORIGINAL ARTICLE

Can Stress-induced Phase Change Be Observed on ^{99m}Tc Pharmacological Stress Myocardial Perfusion Imaging?

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Received: May 31, 2018/Revised manuscript received: July 15, 2018/Accepted: July 18, 2018
J-STAGE Advance published: August 3, 2018

Abstract

***Background*: Phase analysis of left ventricular contraction has incremental value for facilitating the diagnosis of cardiovascular disease using electrocardiography-gated myocardial perfusion imaging (MPI). However, it is unclear whether phase analysis aids the diagnosis of ischemic heart disease using technetium-99m (^{99m}Tc)-labeled perfusion agents under pharmacological stress. As pharmacological stress does not usually induce "true" ischemia, and ^{99m}Tc MPI is generally performed about one hour after the initiation of stress testing, it is questionable whether phase deterioration can be measured in such conditions.**

***Methods*: We retrospectively analyzed the cases of 61 consecutive patients who underwent adenosine stress/rest MPI using ^{99m}Tc-labeled perfusion agents. Phase parameters [bandwidth, phase standard deviation (PhaseSD), and entropy] were evaluated using automatic analysis software (cardioREPO). All parameters were assessed both under stress and at rest. The changes (delta) in the phase parameters between the stress and resting conditions were also measured.**

***Results*: The patients were separated into those without and with ischemia. Stress bandwidth (46.2 ± 13.0 vs 73.2 ± 41.2, respectively), stress PhaseSD (11.7 ± 3.2 vs 18.2 ± 10.5), stress entropy (0.46 ± 0.06 vs 0.53 ± 0.12), rest PhaseSD (9.4 ± 3.0 vs 12.5 ± 6.4) and rest entropy (0.42 ± 0.07 vs 0.46 ± 0.10) and the delta bandwidth (6.49 ± 11.88 vs 23.58 ± 28.04) and delta PhaseSD (2.29 ± 3.11 vs 5.78 ± 6.89) values exhibited significant differences between the two groups although there were large overlaps between the two groups.**

***Conclusions*: On ^{99m}Tc MPI performed under pharmacological stress, some minor left ventricular contraction phase changes were observed.**

Keywords: ^{99m}Tc labeled perfusion agents, Adenosine, Ischemia, Myocardial perfusion imaging, Phase analysis, Stress test

Ann Nucl Cardiol 2018; 4 (1): 34–41

Cardiovascular disease (CVD) is a major cause of mortality. In 2015, 17.7 million people died from CVD around the world (1). Great effort has been made to search for optimal diagnostic techniques for CVD. Myocardial perfusion imaging (MPI) using a radiopharmaceutical, such as a technetium-99m (^{99m}Tc)-labeled agent [e.g., methoxyisobutylisonitrile (MIBI) or tetrofosmin] or thallium-201, plays a key role in the diagnosis and/or risk stratification of CVD, especially ischemic heart disease. Furthermore, recently developed advanced imaging technologies provide informa-

doi: 10.17996/anc.18-00072

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tion not only about the distribution of the tracer, but also about cardiac motion, function, and synchrony.

Phase (the onset of myocardial contraction) analysis using gated MPI provides information about the synchrony of left ventricular (LV) cardiac contraction (2, 3). It was developed as a technique for measuring LV dyssynchrony based on gated single-photon emission computed tomography (SPECT) MPI (4). It has been shown that quantitative indices derived from phase analysis, such as the phase standard deviation (PhaseSD) and bandwidth, correlate well with LV dyssynchrony, as measured by tissue Doppler imaging (5). Phase analysis can be applied to conventional gated SPECT MPI and is used as a nuclear cardiology technique for assessing various cardiac diseases, such as heart failure, arrhythmia, and coronary artery disease (CAD). Phase analysis has incremental value for evaluating non-ischemic heart disease, such as for predicting the prognosis of heart failure (6), monitoring cardiac resynchronization therapy (7), and differentiating between ischemic and non-ischemic cardiomyopathy (8).

Phase analysis is also reported to aid the diagnosis of ischemic heart disease, especially in severe cases (5, 9). However, the latter studies involved thallium-201 imaging or exercise-based stress testing. As thallium-gated SPECT MPI data are acquired close to the time of peak stress (within 5 min of the injection), they provide an opportunity to observe stress-induced changes in cardiac function. However, when ^{99m}Tc-labeled perfusion agents are used the images are acquired roughly one hour after the tracer injection, which allows the patient time to recover from the stress. Exercise induces “true” ischemia; i.e., a poor oxygen supply that does not meet the increase in demand caused by exercise. On the other hand, adenosine-induced pharmacological stress does not increase the oxygen demand of the myocardium. This indicates that pharmacological stress does not induce “true” ischemia. Considering recent trends (the reduced use of medical radiation and the increase in the numbers of aged/disabled patients), it is expected that stress/rest ^{99m}Tc MPI will be performed under pharmacological stress in increasing numbers of patients.

In summary, there are two major questions regarding phase analysis after ^{99m}Tc MPI performed under pharmacological stress: 1) As pharmacological stress does not induce “true” ischemia, does it cause phase abnormalities? 2) As stress imaging using a ^{99m}Tc-labeled agent is usually performed about one hour after the initiation of the stress test, can stress-induced phase anomalies be observed on ^{99m}Tc stress MPI?

The purpose of this study is to answer the above mentioned two questions.

Materials and methods

Patients

We conducted a retrospective study of the cases of 61 consecutive patients who underwent pharmacological stress/rest MPI with electrocardiographic (ECG) gating using ^{99m}Tc-labeled perfusion agents (tetrofosmin or sestamibi) between April 2015 and July 2016 at Nagasaki University Hospital. All of the patients who underwent pharmacological stress MPI with ECG gating using ^{99m}Tc-labeled perfusion agents during the relevant period were included in the study. Patients who suffered acute coronary syndrome within the month before the imaging, severe valve disease, left or right bundle branch block, atrial fibrillation or non-ischemic cardiomyopathy/myocarditis were excluded. Patients with large myocardial infarctions [summed rest score (SRS): >10] were also excluded.

34 patients had a history of coronary angiography within three months before/after MPI. The number of vessels which showed significant stenosis (75% or more) was also evaluated.

SPECT MPI protocol

MPI was performed with a stress-first protocol. In the stress imaging, roughly 300-370 MBq of the ^{99m}Tc-labeled perfusion agent were administered in the morning. The rest imaging was performed with 740 MBq of the same ^{99m}Tc perfusion agent roughly 4 hours after the stress injection. Both the stress and rest SPECT imaging were carried out about 60 min after the injection of the ^{99m}Tc-labeled agent. The image acquisition was carried out using a dual-head gamma camera with a low-energy high-resolution collimator, a 180° arc, and a 16 frames/beat acquisition protocol (e.Cam Signature, Siemens Healthcare GmbH, Germany). With this protocol, more than 100 count/pixel both on stress and rest images were maintained. All of the patients were instructed to refrain from eating food (breakfast) before the scans.

Image analysis

All of the images were analyzed using the gated MPI analysis software cardioREPO (FUJIFILM RI Pharma, Tokyo, Japan), which was developed in collaboration with EXINI Diagnostics, Lund, Sweden, and Kanazawa University, Kanazawa, Japan.

The following parameters were analyzed: the summed stress score (SSS), the summed rest score (SRS), the summed difference score (SDS), end diastolic volume (EDV), end systolic volume (ESV), LV ejection fraction (EF), peak of the phase (peakPhase), bandwidth of the phase (bandwidth), standard deviation of the phase (PhaseSD), and the entropy of the phase (entropy). All of these parameters were automatically measured using cardioREPO. The changes between the

stress and rest (delta) conditions were also assessed.

As reported by Nakajima (10), normal values of the phase parameters measured with cardioREPO are following. Bandwidth; 40.3 ± 11.6 (range 17-64), PhaseSD; 10.3 ± 3.2 (range 4-17), entropy (0.430 ± 0.064, range 0.30-0.56).

Statistical analysis

All statistical analyses were performed using the JMP Pro11 software. All continuous parameters are expressed as mean ± SD values. The Student's t-test or chi-square test was used for comparisons between two groups. Correlations between two variables were tested using the Pearson correlation coefficient (r). P-values of < 0.05 were considered to be statistically significant.

Ethical statement

This study was approved by the ethics committee of Nagasaki University Hospital (16020829).

Results

The patients without large infarctions (SRS: < 11) were selected and categorized into those with (SDS: ≥ 4; the ischemia group) and without significant ischemia (SDS: < 4, the no ischemia group). There were 13 patients in the ischemia group and 57 patients in the no ischemia group.

The patients' characteristics and parameters are listed in Table 1.

There were no differences in age or gender between the two groups.

The ischemia group exhibited slightly lower systolic function (EF, EDV, and ESV) than the no ischemia group. However, these differences were not significant. In addition, none of the resting-phase parameters differed significantly between the two groups. Only the phase parameters measured during stress (except for peakPhase) and the delta values for these parameters (except for peakPhase and entropy) demonstrated significant intergroup differences. Among the parameters that displayed significant intergroup differences, the ischemia group demonstrated larger values than the no ischemia group, which indicates that the phase distribution was wider (which is suggestive of dyssynchrony) in the ischemia group than the no ischemia group.

However, when each data point was plotted on a scatterplot (Fig. 1) extensive overlapping of the data was observed between the ischemia and no ischemia groups, especially for the stress parameters. Two patients who showed large delta bandwidth and delta PhaseSD largely affects statistical difference between two groups (the cases indicated by red and blue circle in Fig. 1). Those patients are the two out of three patients who showed high SDS (SDS＝8 and 7, SRS＝5 for both). There was one more patients who showed SDS＝8 (with SRS＝9) (indicated with black arrow in Fig. 1). However, he did not express high delta bandwidth (＝7) and delta PhaseSD (＝3.973). The two cases which showed highest delta bandwidth in no ischemia group (35 and 32, indicated with red and blue arrow on Fig. 1) showed similar SRS (＝5 for both) and mild SDS (3 and 2, respectively).

Table 2 shows the results of correlation analysis between the phase parameters and SSS, SRS, SDS. The phase parameters showed weak correlation between SSS, SRS and SDS. However, the delta of the phase parameters only showed significant correlation with SDS, not with SSS nor SRS. (Fig. 2)

Previous study on normal database (10) revealed gender differences of the phase. We analyzed gender differences in no ischemia group and whole patients. There is no gender difference except delta PhaseSD in whole patients (M:F＝ 3.7 ± 0.7 : 1.4 ± 0.9, p=0.0451). However, two patients who showed large delta PhaseSD/bandwidth are both male. This may strongly affect the difference. The gender difference in ischemia group was not analyzed because only two females are included in this group.

We also evaluated the relationship between numbers of vessels with significant stenosis and the phase parameters. Any of the phase parameters did not show significant relationship.

Case presentation (Fig. 3)

62-year-old male with hypertension, chronic kidney disease (under hemodialysis). He had stenosis on the right coronary artery (#1＝75%) controlled with optimal medication. He had no clinical history of myocardial infarction. The patient had an angina attack and stress MPI was performed. SSS, SRS and SDS of MPI was 13, 5, and 8, respectively. As shown on the image, significant change of bandwidth and PhaseSD was observed between stress and rest. Ischemia was observed in inferior wall. However, location of phase abnormality was not as clear as perfusion abnormality. This case is indicated with red circles on Fig. 1.

Discussion

In the present study, some minor changes were detected in the cardiac contraction phase on pharmacological stress MPI using ^{99m}Tc-labeled perfusion agents, especially in severely ischemic patients. The phase parameters measured one hour after stress and at rest showed relationship between all the SSS, SRS, and SDS. When we analyze the changes of those phase parameters between stress and rest, only SDS still showed minor relationship. This indicates that phase change after stress may have some relationship with ischemia and it remains even one hour after stress procedure, although the

Table 1 Patients' characteristics and measurement data

		Whole	No ischemia	Ischemia	p-value
Age		69.7 (85-44)	69.8(85-44)	69.9(85-53)	p=0.8455 (n.s.)
Gender (M:F)		41:20	31:18	10:2	p=0.1644 (n.s.)
0/1/2/3 vessel dis.		7/10/9/8	6/7/7/6	1/3/2/2	p=0.8943 (n.s.)
SSS		0-17	0-11	4-17	p=0.025 (<0.01)
SRS		0-10	0-10	0-9	p=0.2546 (n.s.)
SDS		0-8	0-3	4-8	p<0.0001
Medication	Beta-blocker	11	10	1	p=0.2948 (n.s.)
	Ca-channel blocker	28	23	5	p=0.7420 (n.s.)
	ARB	28	21	7	p=0.3354 (n.s.)
	ACE-Inhibitor	4	4	0	p=0.1773 (n.s.)
	Statin	32	25	7	p=0.6486 (n.s.)
	Aspirin	32	23	9	p=0.0747 (n.s.)
	Anti-platelet (clopidogrel, etc)	24	18	6	p=0.4032 (n.s.)
stress	Heart rate	61.8 ± 11.0	62.0 ± 11.0	61.1 ± 11.4	p=0.8064 (n.s.)
	EF	69.7 ± 9.3	70.6 ± 8.7	65.7 ± 10.8	p=0.0965 (n.s.)
	EDV	85.5 ± 30.4	81.18 ± 25.4	103.8 ± 41.9	p=0.0188 (<0.05)
	ESV	27.1 ± 16.9	24.4 ± 13.4	37.8 ± 24.6	p=0.0128 (<0.05)
rest	Heart rate	66.1 ± 10.9	66.0 ± 10.9	66.3 ± 11.3	p=0.9529 (n.s.)
	EF	72.0 ± 8.9	73.2 ± 7.7	67.1 ± 11.3	p=0.0315 (<0.05)
	EDV	85.8 ± 29.1	81.5 ± 23.9	103.3 ± 41.4	p=0.0190 (<0.05)
	ESV	25.0 ± 15.3	22.2 ± 11.0	36.1 ± 24.1	p=0.0041 (<0.01)
stress	peakPhase	130.8 ± 14.8	131.1 ± 14.6	129.8 ± 16.7	p=0.7801 (n.s.)
	Bandwidth	51.5 ± 23.7	46.2 ± 13.0	73.2 ± 41.2	p=0.0002 (<0.01)
	PhaseSD	13.0 ± 6.0	11.7 ± 3.2	18.2 ± 10.5	p=0.0004 (<0.01)
	Entropy	0.48 ± 0.08	0.46 ± 0.06	0.53 ± 0.12	p=0.0047 (<0.01)
rest	peakPhase	130.0 ± 13.9	130.5 ± 13.7	127.8 ± 15.1	p=0.5514 (n.s.)
	Bandwidth	41.7 ± 16.53	39.8 ± 13.5	49.6 ± 24.5	p=0.0636 (n.s.)
	PhaseSD	10.0 ± 4.0	9.4 ± 3.0	12.5 ± 6.4	p=0.0184 (<0.05)
	Entropy	0.43 ± 0.08	0.42 ± 0.07	0.46 ± 0.10	p=0.0463 (<0.05)
Delta EF		-2.30 ± 3.79	-2.51 ± 3.80	-1.42 ± 3.79	p=0.3750 (n.s.)
Delta EDV		-0.24 ± 8.21	-0.43 ± 8.29	0.55 ± 8.21	p=0.7149 (n.s.)
Delta ESV		2.11 ± 4.02	2.20 ± 4.33	1.73 ± 2.45	p=0.7194 (n.s.)
Delta peakPhase		0.84 ± 5.10	0.57 ± 4.92	1.92 ± 5.92	p=0.4177 (n.s.)
Delta Bandwidth		8.85 ± 17.44	6.49 ± 11.88	23.58 ± 28.04	p=0.0017 (<0.01)
Delta PhaseSD		2.98 ± 4.29	2.29 ± 3.11	5.78 ± 6.89	p=0.0103 (<0.05)
Delta Entropy		0.05 ± 0.05	0.05 ± 0.05	0.07 ± 0.05	p=0.2831 (n.s.)

study population is too small to conclude causal relationship.

Dyssynchrony indicates an inability to perform uniform LV contractions, which results in poor LV function. This phenomenon can be assessed by measuring the discordance in the myocardial contraction phase. This technique is called phase analysis (4). Previous studies (11) have shown that phase analysis is a valuable tool for patient management and diagnosis, especially in cases of heart failure. Another study demonstrated that phase analysis also has incremental value for evaluating ischemic heart disease using thallium-based exercise-induced stress MPI (5). However, it is unclear whether phase analysis has incremental value for diagnosing ischemia using ^{99m}Tc-labeled perfusion agents under pharmacological stress. In a previous study, phase changes were observed on ^{99m}Tc MIBI SPECT performed under ATP-induced stress (8). However, the patient population in the latter study was composed of heart failure patients with LVEF of <40%, whereas our study included patients whose cardiac functions had largely been maintained. Hida et al. studied CAD with ^{99m}Tc sestamibi and found that phase analysis has incremental value for diagnosing multivessel disease. However, their study involved an exercise stress test. Tanaka et al.

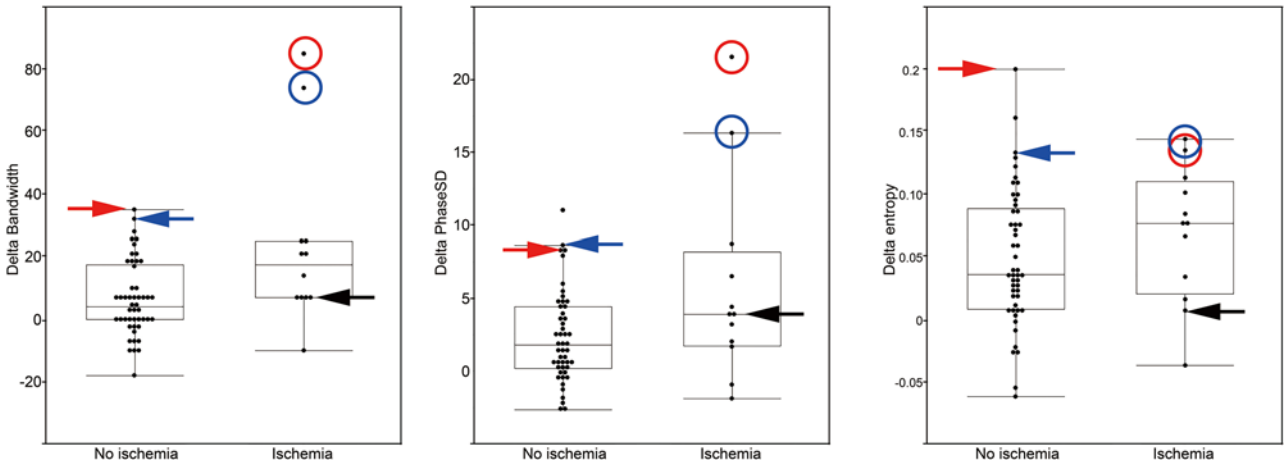


Fig. 1 Plots of delta phase parameters. Case with red circle is presented in "Case presentation".

Table 2 Results of correlation analysis between the phase parameters and SSS, SRS, SDS

		Stress			Rest			Delta		
		Bandwidth	PhaseSD	Entropy	Bandwidth	PhaseSD	Entropy	Bandwidth	PhaseSD	Entropy
SSS	slope	3.09	0.76	0.0096	2.07	0.54	0.0097	1.02	0.22	0.0027
	intercept	38.11	9.7	0.4367	32.68	7.7	0.3834	5.43	2	0.0474
	R-square	0.29	0.27	0.27	0.27	0.3	0.28	0.06	0.05	0.01
	p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0604	0.0937	0.4421
SRS	slope	2.15	0.56	0.0084	1.93	0.51	0.0096	0.22	0.05	0.0001
	intercept	44.36	11.12	0.4499	35.24	8.32	0.3934	9.12	2.8	0.0533
	R-square	0.08	0.09	0.12	0.13	0.15	0.15	<0.01	<0.01	<0.01
	p-value	0.0277	0.0217	0.0063	0.0039	0.0017	0.0018	0.7635	0.7678	0.9339
SDS	slope	7.2	1.76	0.0193	3.66	0.99	0.0166	3.54	0.77	0.0011
	intercept	37.39	9.53	0.4401	34.48	8.07	0.3927	2.9	1.46	0.0565
	R-square	0.38	0.36	0.27	0.2	0.25	0.2	0.17	0.13	<0.01
	p-value	<0.0001	<0.0001	<0.0001	0.0003	<0.0001	0.0003	0.001	0.0038	0.6213

SDS: summed difference score, SRS: summed rest score, SSS: summed stress score.

also studied the phase changes after pharmacological stress MPI using ^{99m}Tc-labeled agents (12). They found clear incremental value of the phase analysis for detecting multivessel disease. Our results are much weaker than their study. There is a difference in the study protocol between the two studies. In study by Tanaka, the interval between stress and image acquisition was 30 min which is shorter than 60 min used in our study. This difference should have a significant effect on the difference between studies. Another difference is the study population. In our study, maximum SDS was 8 which was much smaller than the study by Tanaka.

A study by Aljaroudi et al. also evaluated a similar group of patients to our study with ^{99m}Tc-labeled agents (13). They concluded that the use of ^{99m}Tc-labeled perfusion agents did not result in alterations in phase analysis parameters, which disagrees with our results and the results of Tanaka (12). In Aljaroudi's study, the phase parameters are almost identical between at stress and at rest regardless of ischemia. Many ischemic patients (more than one third) in their study showed negative delta phase parameters (rest＞stress). On the other hand, in Tanaka's study, phase parameters are larger at stress than at rest regardless of severity of coronary stenosis. In our study, only minor number of ischemia cases showed negative delta phase parameters. There are several possible explanations for this. One is the difference between the analysis software used. There are several pieces of software that can be used for phase analysis. Nakajima compared the phase parameter data obtained using four pieces of software (QGS; Emory cardiac tool box; Heart function view-F; and cardioREPO) and found significant differences between the four programs (10). The dose of the tracers used in Aljaroudi's study was also different from our and Tanaka's studies. In Aljaroudi's study, they used roughly double dose of our and Tanaka's study. This may influence on the count density of acquired images. Low count density in our and Tanaka's study may lead noisy phase distribution which leads to wider phase

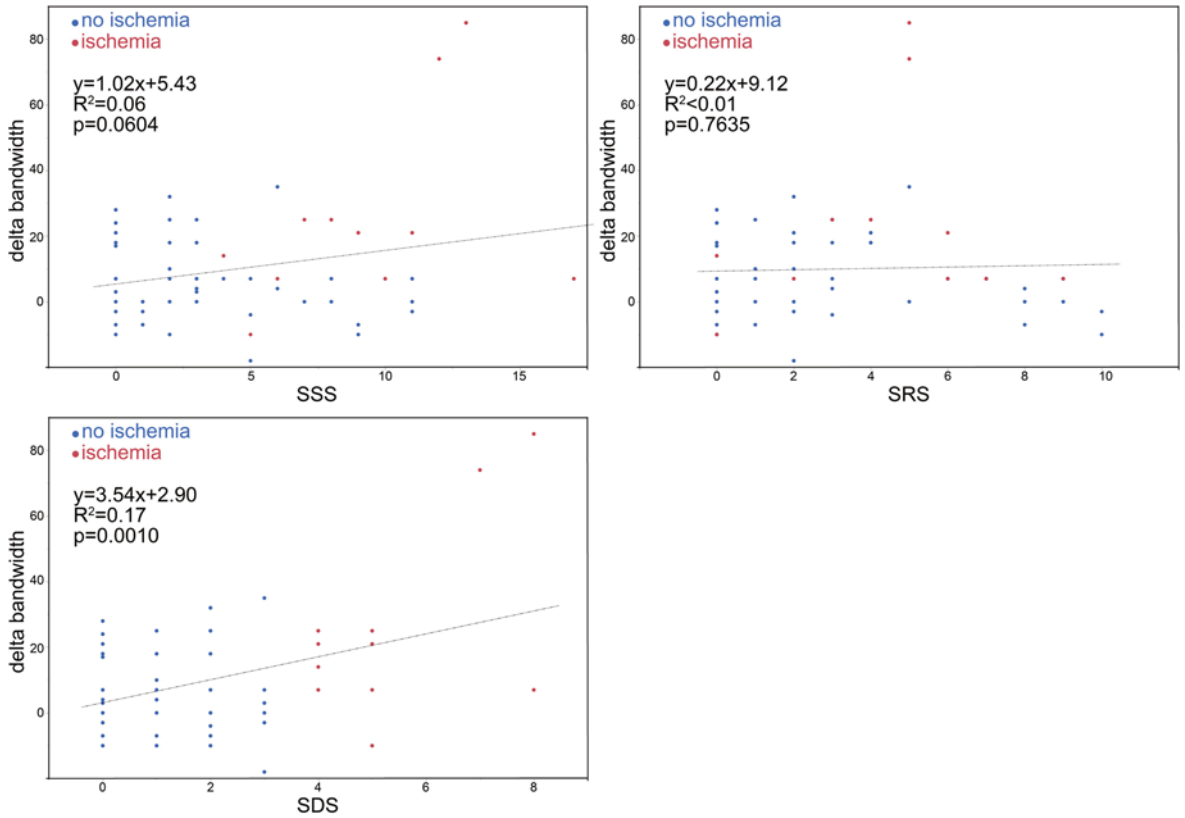


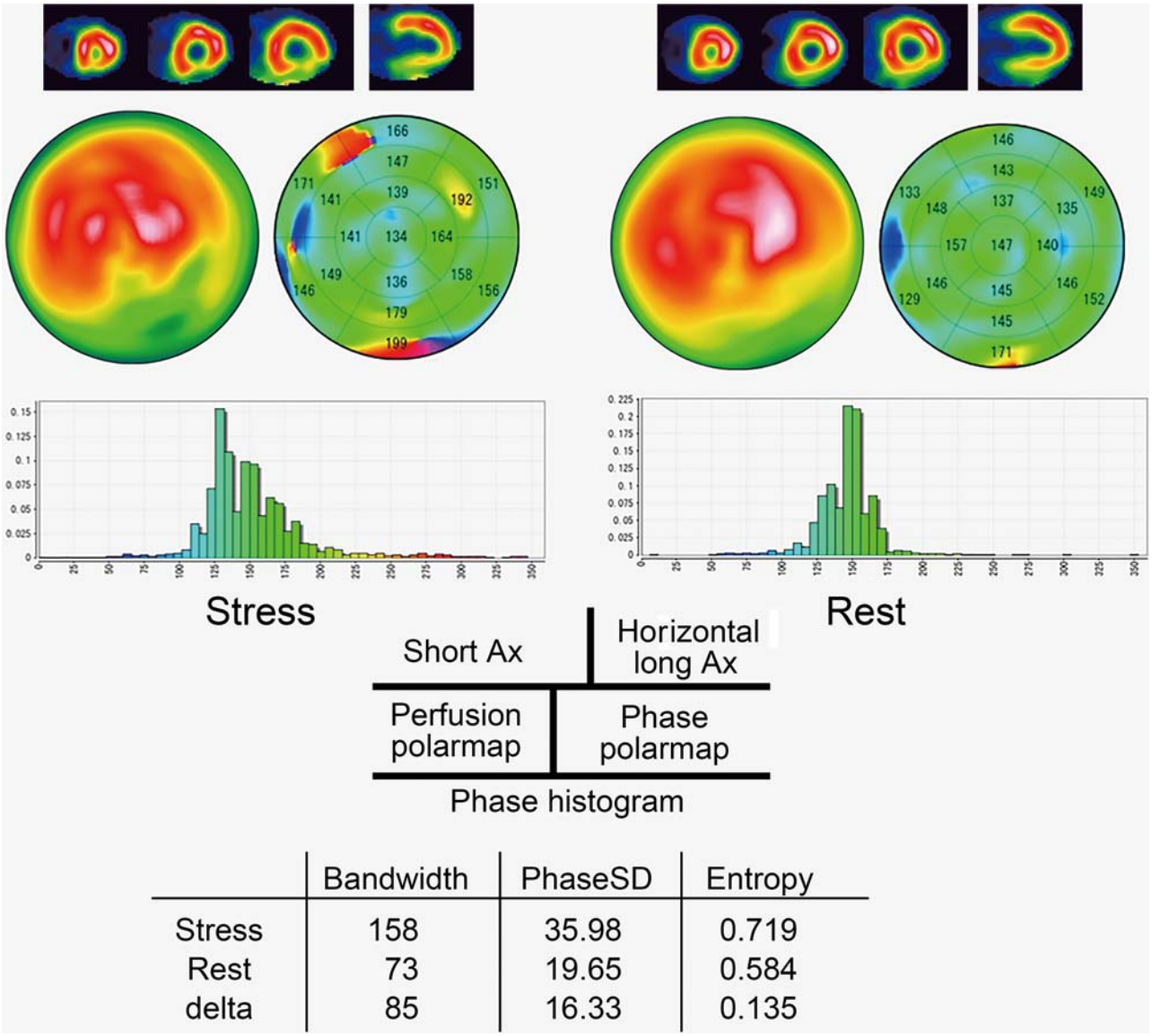
Fig. 2 Scatter plot of SSS/SRS/SDS and delta bandwidth.

parameters. Another possible explanation is the differences between the acquisition methods. In Aljaroudi's study, data that were obtained using 8 and 16 frames/cycle were combined. In our study, all of the scans involved 16 frames/cycle. In Tanaka's study, 8 frames/cycle was used. Such differences in the acquisition protocol can influence the outcomes of phase analysis. For example, it is known that the acquisition orbit can affect phase analysis (14). Most important difference between Aljaroudi's study and Tanaka's study should be the short interval between stress and image acquisition. In Tanaka's study, interval was 30 min which is shorter than usually recommended 45-60 min interval which was mentioned in Aljaroudi's study. It must be kept in mind that phase analysis is not a mature method, especially under pharmacological stress.

Those conflicting results raise the controversy regarding the incremental value of phase analysis on pharmacological stress MPI using ^{99m}Tc-labeled agents. Hida et al. proved that there is clear incremental value when the stress is performed with exercise (9). For pharmacological stress, specific protocol may be required, such as shorter intervals between stress and image acquisition, less than 30 min as studied by Tanaka (12). Further study should be required.

Despite the fact that perfusion defects that arise during periods of adenosine-induced stress usually represent heterogeneity in the distribution of coronary perfusion, rather than "true" ischemia, we found that adenosine-induced stress may have some effects on the results of phase analysis. "True" ischemia induced by pharmacological stress is usually considered to be due to the steal phenomenon, which is not common, but can occur in cases of severe ischemia. It can occur not only in the circumferential and longitudinal directions (i.e., inter-coronary steal) (15, 16), but also in the vertical direction (i.e., transmural steal), which can lead to myocardial dysfunction (17, 18). In our study, patients with severest ischemia exhibited phase changes between the stress and resting conditions. The steal phenomenon might explain why such changes were observed in our study.

This study had several limitations. The major limitation of this study was the small number of patients. Specifically, our study population only included patients with relatively minor ischemia (SDS: <9). This was partly due to the fact that we removed patients with high SRS values of >10 to avoid the effects of large infarctions on the cardiac contraction phase. Our preliminary findings should be confirmed in a larger study that includes patients with more severe ischemia. Another limitation is that the analysis was conducted with automatic software. We scored perfusion automatically without any modification to avoid any subjective effects caused by the skill of the observer. However, it is well known that automatic scoring is not perfect, and in fact it is less accurate than the data produced by experienced observers. Thus, the classification of the patients into the ischemia and no ischemia groups might have been influenced by such inaccuracies. Our



	Bandwidth	PhaseSD	Entropy
Stress	158	35.98	0.719
Rest	73	19.65	0.584
delta	85	16.33	0.135

Fig. 3　Images of the patient who showed largest delta bandwidth and delta PhaseSD in ischemia group.

population includes relatively large SRS group. That is another limitation. The two cases which showed large delta phase parameters showed moderate SRS (= 5). Thus, the changes of phase parameters can be influenced not only with ischemia but also with low perfusion at rest.

Conclusion

In severely ischemic patients, phase changes can be observed with pharmacological stress MPI performed using ^{99m}Tc-labeled perfusion agents one hour after stress procedure. However, the incidence of these phase disturbances was low. Further studies are required to clarify the value of such imaging techniques for clinical diagnosis.

Acknowledgments

None.

Sources of funding

This study was supported by JSPS KAKENHI grant number JP26461857.

Conflicts of interest

None.

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