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ORIGINAL ARTICLE

Comparison of left ventricular mechanical dyssynchrony parameters between exercise and adenosine triphosphate stress tests using gated single-photon emission computed tomography myocardial perfusion imaging

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KEY WORDS
adenosine triphosphate, exercise stress test, left ventricular mechanical dyssynchrony, myocardial perfusion imaging, single-photon emission computed tomography

ABSTRACT

BACKGROUND Left ventricular mechanical dyssynchrony (LVMD) can be induced after stress test. However, no studies have compared the influence of different stress-inducing methods on LVMD parameters.

AIMS The aim of the study was to determine whether there is a difference between exercise and adenosine triphosphate (ATP) stress tests in terms of changes in LVMD parameters assessed using gated single-photon emission computed tomography myocardial perfusion imaging (GSPECT MPI).

METHODS A total of 190 patients who underwent ^{99m}Tc-sestamibi GSPECT MPI were consecutively enrolled. Treadmill exercise and ATP stress tests were performed in 95 patients each. Normal myocardial perfusion was defined as the summed stress score (SSS) ≤3 and summed rest score (SRS) ≤3, myocardial ischemia as SSS >3 and SRS ≤3, and myocardial infarction as SSS >3 and SRS >3. Parameters of LVMD, including phase standard deviation (PSD), phase bandwidth (PBW), skewness, and kurtosis were compared. Subtraction was made between values during stress and rest phases to acquire ΔPSD, ΔPBW, Δskewness, and Δkurtosis.

RESULTS There were no differences in LVMD parameters between the exercise and ATP groups. The same results were obtained in the normal perfusion, ischemia, and infarction subgroups. Furthermore, no differences were observed in ΔPSD (median [interquartile range, IQR], 0.25 [–2.3 to 3.1] vs 0.42 (–1.7 to 3.1]; $P = 0.73$), ΔPBW (median [IQR], 1 [–7 to 11] vs 1 [–6 to 11]; $P = 0.95$), Δskewness (mean [SD], –0.06 [0.63] vs 0 [0.81]; $P = 0.53$), and Δkurtosis (median [IQR], –0.47 [–4.2 to 4.3] vs –0.42 [–4.8 to 5.2]; $P = 0.73$) between the exercise and ATP stress-inducing methods.

CONCLUSIONS There are no differences between the exercise and ATP stress tests in terms of changes in LVMD parameters. Thus, the 2 methods can be used alternatively.

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INTRODUCTION Left ventricular mechanical dyssynchrony (LVMD) parameters derived from gated single-photon emission computed tomography myocardial perfusion imaging (GSPECT MPI) have been widely used in the diagnosis of various diseases,[1,2] such as coronary artery disease (CAD),[3] end-stage renal disease,[4] dilated cardiomyopathy,[5] and diabetes mellitus,[6] as well as in cardiac resynchronization therapy.[7-10] Different stress-inducing methods have been used to observe changes in LVMD parameters during stress and rest.[11-14] Hida et al[14] and Singh et al[15]

WHAT'S NEW?

Gated single-photon emission computed tomography myocardial perfusion imaging (GSPECT MPI) has been widely used in the diagnosis and prognosis of various diseases, including coronary artery disease, dilated cardiomyopathy, and end-stage renal disease. Left ventricular mechanical dyssynchrony (LVMD) parameters derived from GSPECT MPI can provide quantitative information on the ventricular wall in addition to that on perfusion. Both exercise and pharmacological stress tests are used to induce changes in LVMD parameters through their own mechanisms. This is the first study to compare poststress changes of LVMD parameters between exercise and adenosine triphosphate stress tests using GSPECT MPI. Our study showed no difference between these 2 stress-inducing methods with regard to changes in LVMD parameters.

reported that phase standard deviation (PSD) and phase bandwidth (PBW) were significantly higher after exercise treadmill stress test. Chen et al[16] found that dipyridamole stress test could cause changes in LVMD parameters in the ischemic region.

The stress-inducing methods differ in terms of the underlying mechanisms. Exercise stress test simulates physiological load, which reflects real cardiac demand and induces myocardial ischemia. Pharmacological stress tests, such as dipyridamole and adenosine triphosphate (ATP) tests, directly dilate coronary arteries and increase myocardial blood flow. Prior studies have compared different stress-inducing methods for CAD diagnosis and the results showed high concordance.[17,18] However, no studies have compared the influence of different stress-inducing methods on LVMD parameters. This study aims to determine whether there is a difference between exercise and ATP stress tests in terms of changes in LVMD parameters assessed using GSPECT MPI.

METHODS This retrospective study was approved by the Institutional Ethical Committee of the First Affiliated Hospital of Nanjing Medical University. Patients diagnosed with or suspected of CAD who underwent both stress and rest ^{99m}Tc-sestamibi GSPECT MPI in our center were consecutively enrolled from September 2008 to November 2017. Patients who underwent an ATP stress test were enrolled first. Then, a group of patients matched for age, sex, and QRS wave duration who underwent an exercise stress test over the same period were selected. Patients with bundle branch block, permanent pacemaker implantation, or acute coronary syndrome, as well as those who did not reach at least 85% of the predicted maximum heart rate during the exercise test were excluded.

In this study, hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg, or the use of antihypertensive drugs. Diabetes was defined as fasting blood glucose level greater than or equal to 7 mmol/l or the use of antidiabetic medicines. Smoking was defined as regular consumption of at least 1 cigarette per day.

Acquisition and processing of gated single-photon emission computed tomography myocardial perfusion imaging GSPECT MPI was performed using a 2-day stress-rest protocol. β-Blockers, calcium channel antagonists, and nitrates were stopped 2 days before the test. In the exercise stress test, the patients underwent symptom-limited multistep exercise following the standard Bruce protocol. ^{99m}Tc-sestamibi (20–30 mCi) was administered intravenously at 85% of the expected peak heart rate, or when symptoms such as chest pain or an ST-segment depression of 0.1 mV or greater occurred. In the ATP stress test, the patients were administered with ATP at the dosage of 140 µg/kg/min for 5 minutes and ^{99m}Tc-sestamibi was given 3 minutes after the beginning of ATP administration.[19,20] Acquisition of both stress and rest images was commenced 30 to 60 minutes after ^{99m}Tc-sestamibi injection.

A Philips CardioMD system (Philips Medical Systems, Milpitas, California, United States) was used to acquire scans with 20% energy windows around 140 keV. A total of 64 projections (24 s/projection; total acquisition time, 14 min) were obtained over a 180° circular orbit. The GSPECT data were acquired as 8 frames per cardiac cycle and stored in a 64–64 matrix with 6.4 mm/pixel. They were reconstructed using a manufacturer-provided filtered back-projection program with a Butterworth filter (order, 5; cutoff frequency, 0.66; AutoSPECTPlus, Philips Medical Systems). No attenuation correction was applied.

Quantitative analysis of gated single-photon emission computed tomography myocardial perfusion imaging The total myocardial perfusion scores during stress and rest were designated as the summed stress score (SSS) and the summed rest score (SRS). The sum of the differences between SSS and SRS was defined as the summed difference score (SDS).[21] The final results were visually inspected by 2 experienced readers. Only the consensus readings were reported and scores were manually corrected if necessary. Normal myocardial perfusion was defined as SSS ≤3 and SRS ≤3, myocardial ischemia was recognized as SSS >3 and SRS ≤3, and myocardial infarction was deemed as SSS >3 and SRS >3. Left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), and end-systolic volume (ESV) were acquired. All reconstructed data were reoriented to generate

TABLE 1 Baseline patient characteristics

Variable	EXE (n = 95)	ATP (n = 95)	*P* value
Age, y, mean (SD)	60 (6)	60 (7)	0.51
Male sex, n (%)	57 (60)	49 (51.6)	0.31
Hypertension, n (%)	66 (69.5)	60 (63.2)	0.44
Diabetes, n (%)	22 (23.2)	20 (21.1)	0.86
Smoking, n (%)	32 (33.7)	31 (32.6)	0.88
PCI / CABG, n (%)	30 (31.6)	22 (23.2)	0.26
SSS, median (IQR)	4 (2–7)	4 (2–7)	0.54
SRS, median (IQR)	0 (0–2)	0 (0–1)	0.57
SDS, median (IQR)	3 (1–5)	3 (1–5)	0.81
Rest LVEF, %, mean (SD)	67.2 (9.1)	66.9 (8.3)	0.36
QRS, ms, median (IQR)	80 (80–90)	85 (80–90)	0.8

Abbreviations: ATP, adenosine triphosphate; CABG, coronary artery bypass graft; EXE, exercise; IQR, interquartile range; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score

gated short-axis images and then submitted to phase analysis to calculate LVMD parameters including PSD, PBW, skewness, and kurtosis (Emory Cardiac Toolbox, Atlanta, Georgia, United States).[1,19] Values obtained during the rest phase were subtracted from values obtained during the stress phase to acquire changes in those parameters, which were defined as ΔPSD, ΔPBW, Δskewness, Δkurtosis, ΔLVEF, ΔEDV, and ΔESV.

Coronary angiography A total of 62 patients underwent coronary angiography within 3 months after GSPECT MPI. At least 2 orthogonal views were obtained and the projection showing the most severe stenosis was used for quantitative coronary measurements. Considering the mean proximal and distal reference diameters, the percentage lumen reduction was calculated offline by 2 experienced investigators. Multivessel CAD was defined as 2 or more main coronary arteries presenting with stenosis of more than 70%, and single-vessel CAD was defined as only 1 main coronary artery presenting with stenosis of more than 70%.

Statistical analysis Statistical analysis was performed with the IBM SPSS Statistics software, version 18.0 (SPSS Inc., Chicago, Illinois, United States). Normality of distribution was assessed by the Kolmogorov–Smirnov test. Continuous data were expressed as mean (SD) in case of normal distribution or as median with interquartile range (IQR) if nonnormally distributed. Categorical data were expressed as number and percentage. Normally distributed continuous variables were compared by the unpaired *t* test and nonnormally distributed data were compared by the Mann–Whitney test. Dichotomous data were analyzed by the χ^2 test or the Fisher exact test when the total number was less than 40. All tests were 2-tailed and a *P* value of less than 0.05 was considered significant.

RESULTS

Baseline characteristics Overall, 95 patients who underwent a treadmill exercise stress test and 95 patients who had an ATP stress test were enrolled. Among them, 80 patients (42%) had normal myocardial perfusion (40 patients in each group), 80 (42%) had myocardial ischemia (40 patients in each group) and 30 (16%) had myocardial infarction (15 patients in each group). The baseline characteristics were comparable between the 2 groups (TABLE 1). In the subgroups of normal perfusion, ischemia, and infarction, the baseline characteristics were comparable as well (Supplementary material, *Table S1–S3*).

Comparison of left ventricular mechanical dyssynchrony parameters All LVMD parameters at rest and after stress were comparable between the exercise and ATP groups (FIGURE 1 and 2). In total, no differences between the 2 groups were observed in ΔPSD (median [IQR], 0.25 [–2.3 to 3.1] vs 0.42 [–1.7 to 3.1], respectively; *P* = 0.73), ΔPBW (median [IQR], 1 [–7 to 11] vs 1 [–6 to 11], respectively; *P* = 0.95), Δskewness (mean [SD], –0.06 [0.63] vs 0 [0.81], respectively; *P* = 0.53), and Δkurtosis (median [IQR], –0.47 [–4.2 to 4.3] vs –0.42 [–4.8 to 5.2], respectively; *P* = 0.73). In a subgroup analysis of patients with normal perfusion, ischemia, and infarction, there were also no differences in the above-mentioned parameters (TABLE 2).

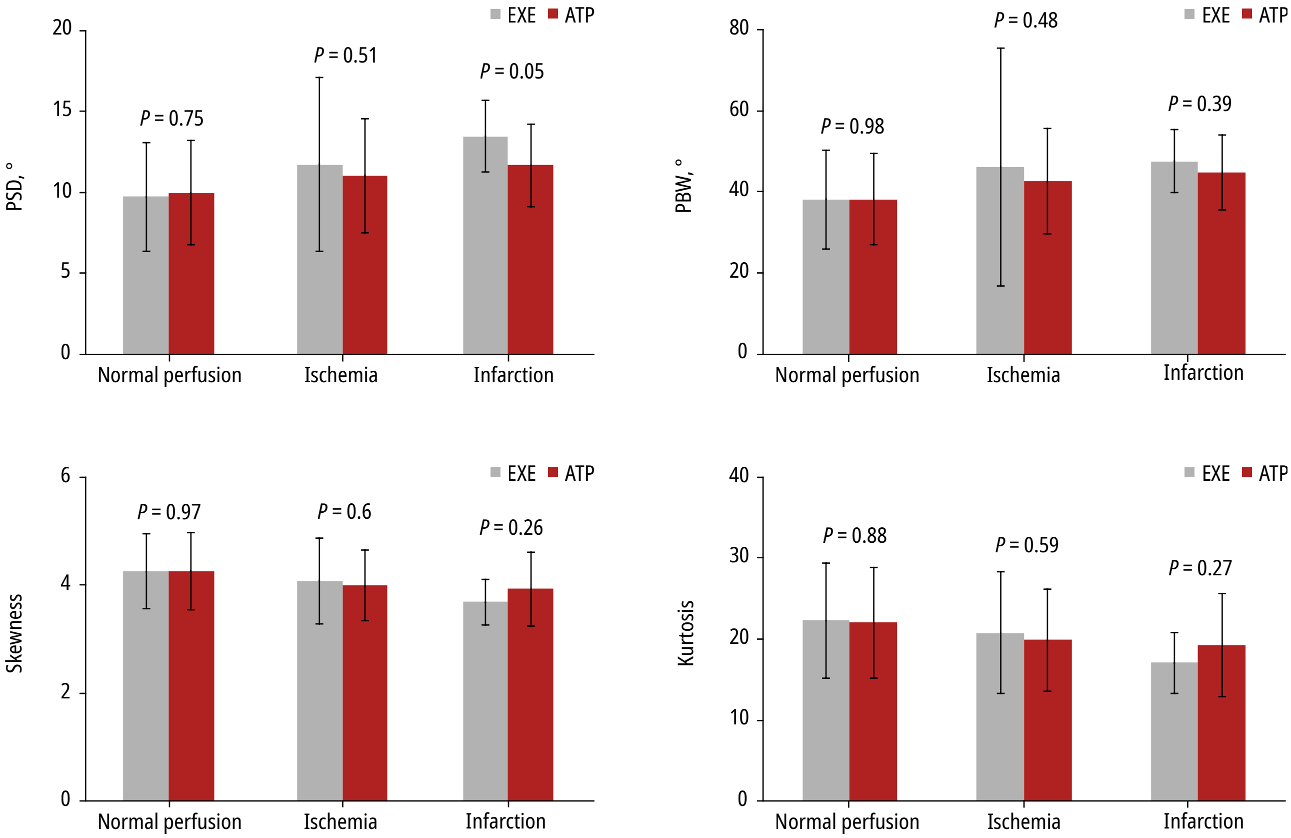

FIGURE 1 Comparison of rest left ventricular mechanical dyssynchrony parameters between the exercise (EXE) and adenosine triphosphate (ATP) groups
Abbreviations: PBW, phase bandwidth; PSD, phase standard deviation

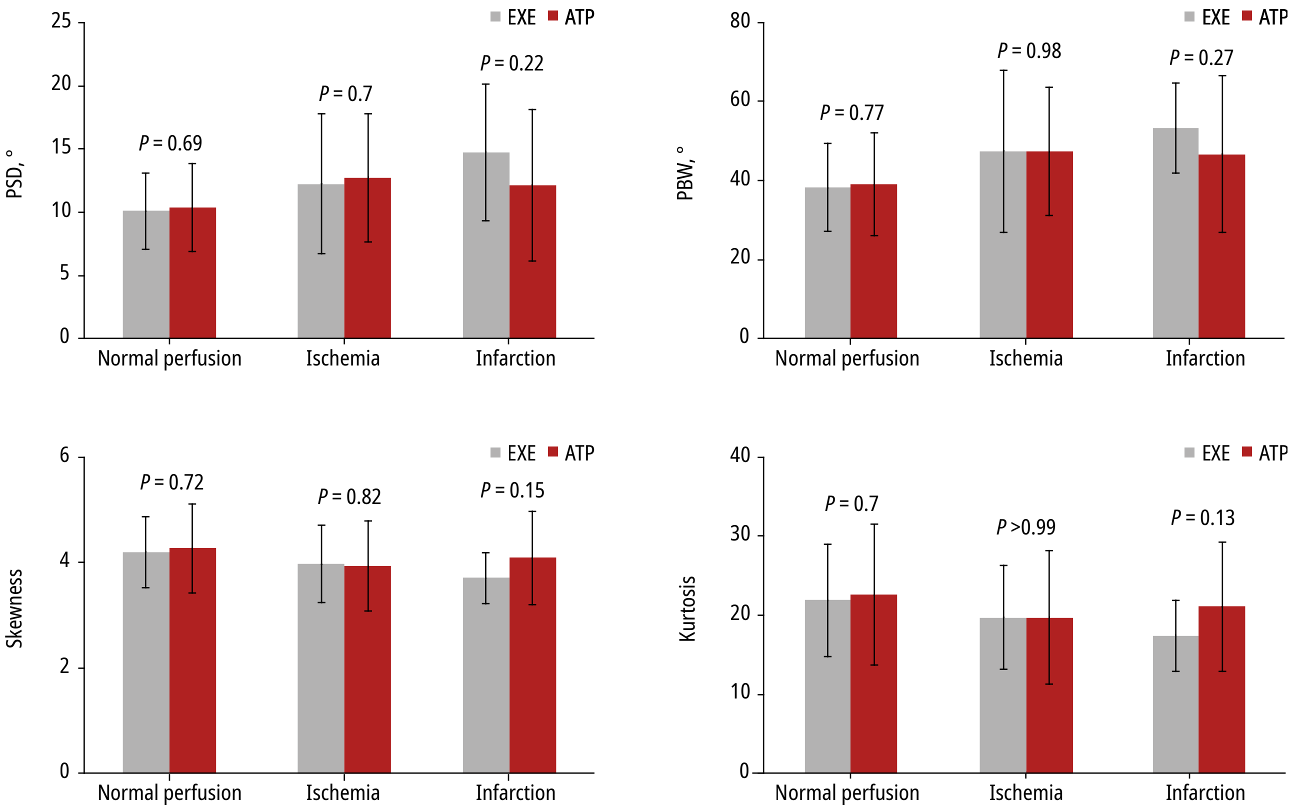

FIGURE 2 Comparison of stress left ventricular mechanical dyssynchrony parameters between the exercise (EXE) and adenosine triphosphate (ATP) groups
Abbreviations: see FIGURE 1

TABLE 2 Changes in left ventricular mechanical dyssynchrony parameters between the exercise and adenosine triphosphate groups

Variable	EXE (n = 95)	ATP (n = 95)	*P* value
Normal perfusion group (n = 80)			
ΔPSD, °, mean (SD)	0.35 (3.53)	0.41 (3.02)	0.94
ΔPBW, °, median (IQR)	1 (–8.8 to 7.5)	–2.5 (–6 to 6)	0.84
Δskewness, mean (SD)	–0.05 (0.65)	0.01 (0.85)	0.74
Δkurtosis, mean (SD)	–0.39 (6.89)	0.54 (8.93)	0.6
Ischemia group (n = 80)			
ΔPSD, °, mean (SD)	0.53 (5.26)	1.66 (4.67)	0.31
ΔPBW, °, median (IQR)	1.5 (–8.5 to 19)	4.5 (–4 to 15)	0.77
Δskewness, mean (SD)	–0.11 (0.68)	–0.06 (0.74)	0.78
Δkurtosis, mean (SD)	–1.04 (6.45)	–0.2 (7.43)	0.59
Infarction group (n = 30)			
ΔPSD, °, median (IQR)	0.04 (–2.3 to 3.6)	–0.8 (–2.7 to 3.7)	0.55
ΔPBW, °, mean (SD)	5.67 (9.82)	1.8 (19.13)	0.49
Δskewness, mean (SD)	0.02 (0.44)	0.17 (0.91)	0.58
Δkurtosis, mean (SD)	0.32 (3.73)	1.86 (8.73)	0.54

Abbreviations: Δ, subtraction of values obtained at rest from values obtained during stress; others, see TABLE 1 and FIGURE 1

TABLE 3 Comparison of left ventricular mechanical dyssynchrony parameters in different stages of coronary artery disease

Variable	Single-vessel disease (n = 30)			Multivessel disease (n = 32)		
	EXE (n = 15)	ATP (n = 15)	*P* value	EXE (n = 19)	ATP (n = 13)	*P* value
Rest dyssynchrony parameters						
PSD, °, mean (SD)	10.4 (4)	10.1 (3.6)	0.8	12.8 (6.3)	12 (3)	0.69
PBW, °, mean (SD)	41.5 (15.7)	39.5 (14.5)	0.72	52.1 (39.6)	46.6 (8.7)	0.63
Skewness, mean (SD)	4.2 (0.7)	4.3 (0.7)	0.57	4.1 (0.7)	3.8 (0.5)	0.19
Kurtosis, mean (SD)	21.9 (6.6)	23.3 (7.1)	0.57	20.4 (6.7)	17.9 (4.7)	0.25
Stress dyssynchrony parameters						
PSD, °, mean (SD)	12.8 (6.6)	11.1 (3.7)	0.38	14.1 (5.8)	13.9 (6.1)	0.94
PBW, °, mean (SD)	49 (23.9)	42.3 (13.3)	0.35	51.3 (17.5)	49.6 (17.3)	0.83
Skewness, mean (SD)	4 (0.6)	4.1 (0.7)	0.66	3.9 (0.8)	3.7 (0.8)	0.47
Kurtosis, mean (SD)	20.1 (5.8)	21.2 (6.9)	0.63	18.9 (6.9)	17 (6.6)	0.44

Abbreviations: see TABLE 1 and 2

Among 62 patients who had coronary angiography, 30 had a single diseased vessel and 32 had multiple diseased vessels. In patients with single-vessel CAD, LVMD parameters showed no differences between the exercise and ATP groups. (TABLE 3). The same was observed for patients with multivessel CAD (TABLE 3).

Comparison of other left ventricular functional parameters Both rest and stress EDV, ESV, and LVEF were comparable between the exercise and ATP groups (TABLE 4). Overall, there were no differences in ΔLVEF (median [IQR], –2 [–5 to 1] vs –1 [–5 to 1], respectively; *P* = 0.7), ΔEDV (median [IQR], 1 [–3 to 6] vs. 2 [–3 to 7], respectively; *P* = 0.34), and ΔESV (median [IQR], 1 [–1 to 4] vs 2 [–1 to 4], respectively; *P* = 0.61). The subgroup analysis also revealed no differences in ΔLVEF, ΔEDV, and ΔESV between the normal perfusion, ischemia, and infarction groups.

TABLE 4 Comparison of other left ventricular functional parameters

Variable	EXE (n = 95)	ATP (n = 95)	*P* value
Normal perfusion group (n = 80)			
Rest LVEF, %, median (IQR)	66 (63–76)	67 (62.3–72)	0.39
Rest EDV, ml, median (IQR)	78 (66.8–98.5)	80 (65.3–103)	0.96
Rest ESV, ml, median (IQR)	27.5 (16.5–35)	25 (18.3–37.8)	0.53
Stress LVEF, %, mean (SD)	67.2 (9)	65.6 (7.1)	0.36
Stress EDV, ml, mean (SD)	82.5 (23.5)	86 (26.1)	0.53
Stress ESV, ml, median (IQR)	28 (18–35.8)	28.5 (21–37.8)	0.52
Ischemia group (n = 80)			
Rest LVEF, %, mean (SD)	67.6 (8.9)	68.1 (8.8)	0.79
Rest EDV, ml, median (IQR)	75 (62.3–90)	68 (58.3–92.5)	0.35
Rest ESV, ml, median (IQR)	24.5 (17.3–32)	23.5 (15.5–32.5)	0.69
Stress LVEF, %, mean (SD)	65.3 (8.2)	66.2 (9.4)	0.65
Stress EDV, ml, mean (SD)	78.3 (19.2)	77.1 (25.8)	0.81
Stress ESV, ml, median (IQR)	27.5 (19.3–33)	24.5 (15.3–35.5)	0.54
Infarction group (n = 30)			
Rest LVEF, %, mean (SD)	62.7 (10.7)	64.8 (10.7)	0.6
Rest EDV, ml, mean (SD)	89 (23)	73.5 (23.9)	0.08
Rest ESV, ml, mean (SD)	34.8 (16.8)	27.9 (15.5)	0.25
Stress LVEF, %, mean (SD)	62.5 (10.9)	63.5 (10.5)	0.81
Stress EDV, ml, mean (SD)	89.1 (25.4)	78.8 (28.7)	0.31
Stress ESV, ml, mean (SD)	35.4 (19)	30.9 (18.5)	0.51

Abbreviations: EDV, end-diastolic volume; ESV, end-systolic volume; others, see TABLE 1

DISCUSSION This is the first study to compare poststress changes in LVMD parameters between exercise and ATP stress tests assessed using GSPECT MPI. The main finding of our study is that there are no significant differences between the 2 stress-inducing methods for inducing changes in LVMD parameters. The potential explanation is that the exercise treadmill test causes increase of oxygen demand in the ischemic region and therefore leads to ventricular contractile dysfunction,[22] whereas the ATP stress test induces changes in blood flow distribution between normal and stenosed coronary arteries, which increases the demand for oxygen in the artery with severe stenosis.[13] This phenomenon of "blood steal" results in subendocardial hypoperfusion, which shares the same mechanism as the exercise treadmill stress.[23,24] As another global parameter of LV function, LVMD deteriorates following myocardial ischemia during both exercise and ATP stress tests.[15,16,25]

Changes in LVMD parameters are associated with myocardial stunning, which lasts from minutes to days and depends on the duration and severity of ischemia.[26] Therefore, the acquisition time potentially has an impact on LVMD parameters. The effect of acquisition time on LVMD parameters has been studied by Emer et al.[27] In their study, PSD and PBW tended to increase over time (from 15 to 45 min) in the conditions of an exercise stress test. Different results were observed for the exercise stress test and the dipyridamole stress test using Thallium-201 GSPECT MPI, in which the images are acquired 10 minutes after stress. In a study by Singh et al,[15] all the groups showed lower postexercise PSD and PBW values. On the contrary, Chen et al,[16] reported in their study that in the ischemia group, PSD and PBW values were significantly higher during dipyridamole stress than at rest. In this study, stress image was acquired 30 to 60 minutes after ^{99m}Tc-sestamibi injection, and LVMD parameters tended to be unchanged between stress and rest phases in the ischemia group. Furthermore, LVMD parameters were not different for the 2 stress-inducing methods. Whether the same results could be achieved using early stress GSPECE MPI data requires further study.

Some researchers have compared LV functional parameters obtained during exercise and pharmacology stress tests using GSPECT MPI.

Demir et al[20] compared LVEF in dipyridamole and exercise stress tests in 439 patients. In their study, there was no significant difference between the 2 methods in terms of ΔLVEF in both normal perfusion and ischemia groups. Ohtaki et al[28] assessed the effects of exercise and ATP stress tests on ΔESV, ΔEDV, and ΔLVEF in patients with normal scintigraphic findings. No significant differences in ΔESV and ΔLVEF were found between the 2 groups. In this study, the same results of ΔESV, ΔEDV, and ΔLVEF were observed not only in the normal perfusion and ischemia groups, but also in the infarction group. The homogeneity of LV functional parameters in exercise and ATP stress tests further supports our findings on LVMD parameters.

Cardiac magnetic resonance (CMR) imaging is the gold standard in the detection and evaluation of myocardial scar extent when using late gadolinium enhancement. Recent studies indicate that CMR can detect ischemia in patients with CAD as well as GSPECT MPI.[29] Meanwhile, in a meta-analysis by Lipinski et al[30] there was no significant difference between vasodilator and dobutamine stress CMR, which is in line with our results. However, no study has yet compared these 2 noninvasive imaging tests after stress. In our opinion, further studies are needed to better assess associations between these 2 functional cardiac imaging tests.

Limitations There are several limitations to our study. Firstly, data collected retrospectively were used, which could lead to selection bias. Secondly, only exercise and ATP stress tests were compared. Although the underlying mechanism of the ATP and dipyridamole stress tests is the same, it is unclear whether the latter would yield the same results. The same question applies to the dobutamine stress test, which has a different mechanism compared with the ATP stress-inducing method.

In conclusion, we found no difference between the exercise and ATP stress tests regarding changes in LVMD parameters, which indicates that the 2 methods can be used alternatively.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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