

Physiological basis for stress-induced myocardial stunning as assessed by gated single-photon emission computed tomography

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Abstract

Background : Postischemic myocardial stunning as assessed by gated single-photon emission computed tomography (SPECT) has been criticized for being a perfusion-associated artifact caused by false endocardial tracking. We hypothesized that if severe perfusion defects all cause false wall motion abnormality, they should be observed regardless of the underlying mechanisms of perfusion abnormality.

Methods and Results : We evaluated 132 patients with stress-induced perfusion defects of moderate severity or more after exercise ($n=84$) or adenosine triphosphate disodium (ATP) stress ($n=48$) were evaluated using gated ^{99m}Tc -sestamibi SPECT. Summed stress and difference scores were similar in the 2 groups. However, the overall incidence of post-stress stunning was 54% in the exercise group, but only 19% in the ATP group ($p<0.0001$). Furthermore, based on the severity of coronary artery stenosis in 43 patients with 1-vessel disease, the prevalence of post-stress stunning was 77% in patients with $\geq 99\%$ coronary stenosis, 67% in those with 90% stenosis, and 29% in those with 75% stenosis after exercise stress, whereas it was 57% in those with $\geq 99\%$ stenosis, 17% in those with 90% stenosis, and 0% in those with 75% stenosis after ATP stress ($p=0.003$).

Conclusion : The predominant mechanism of post-stress wall motion abnormality observed by gated SPECT was thought to be severe myocardial ischemia, but not a perfusion-associated artifact. Thus, this scintigraphic finding was regarded as actual myocardial stunning.

Introduction

Although stress-induced left ventricular (LV) wall motion abnormalities usually disappear rapidly once myocardial ischemia is eliminated, there are a few cases in which LV wall motion abnormalities remain, even > 30 minutes after elimination of the ischemia; myocardial stunning being the apparent mechanism in such cases¹⁻⁴. Using technetium-99m sestamibi, which rarely redistributes⁵, it is possible to assess myocardial ischemia during stress and LV wall motion and function at least 30 minutes after stress using electrocardiogram-gated single photon emission computed tomography

(SPECT)^{6,7}. Although previous studies have reported that post-stress myocardial stunning as assessed by gated SPECT is an important marker of severe coronary artery disease (CAD)⁶⁻⁸, these studies applied various protocols involving different radiotracers such as ^{99m}Tc sestamibi, ^{201}Tl or dual isotopes, and employed different stress methods, either with exercise or pharmacologic loading⁶⁻¹⁵. The occurrence of post-ischemic stunning was also reported to show a wide range from 13% to 46%^{4,6,9,11,14}. As a result, this important scintigraphic finding is criticized as being a perfusion-associated artifact¹⁵⁻¹⁷. We hypothesized that if severe transient perfusion defects unanimously cause false wall motion abnor-

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mality, they should be observed regardless of the underlying mechanisms of perfusion abnormality. However, if the occurrence of post-stress LV wall motion abnormality differs according to the method of stress, not only the severity of perfusion abnormality but also the physiological consequences caused by stress should be taken into consideration as the etiology for this phenomenon. Thus, the aim of this study was to examine post-stress wall motion abnormality using gated SPECT in patients with severe myocardial perfusion defects, comparing exercise and pharmacologic vasodilation with adenosine triphosphate disodium (ATP); the latter usually induces maldistribution of blood flow, but not actual ischemia.

Methods

Subjects

Between January 2003 and December 2007, 1697 consecutive patients with suspected or known CAD underwent gated ^{99m}Tc -sestamibi SPECT after stress and at rest. Patients with angiographically documented CAD or previous coronary angioplasty were considered to have known coronary artery disease, while those with clinical risk profiles, symptoms or electrocardiographic abnormalities were considered as having suspected CAD. Among these 1697 patients, 340 patients were retrospectively identified because they underwent coronary angiography within 3 months of the SPECT study. Patients with previous myocardial infarction or those with coronary artery bypass grafts were excluded from this study. In addition, patients in whom automatically derived LV volumes could not be measured were also excluded. Based on these criteria, 163 patients were excluded: 80 with previous myocardial infarction, 23 with coronary artery bypass grafts, 39 with unsuccessful gated SPECT study due to atrial fibrillation or frequent extrasystoles, and 21 patients in whom automatically derived LV volumes could not be measured due to severe perfusion defects or marked tracer uptake in the liver or gallbladder. Among the remaining 177 patients, 132 patients were included in this study because they showed stress-induced perfusion defects of moderate severity or more, as described previously¹⁸⁾. There were 121 men and 11 women, with a mean age of 64 ± 10 years. Concerning the presence of risk factors for CAD, 97 patients (74%) had hypertension, 86 (66%) had hypercholesterolemia and 65 (50%) had diabetes mellitus. At presentation, all patients provided informed consent for the anonymous publication of scientific data. In 2008, formal ethics committee approval was not applicable for this observational study involving only routinely performed work-up procedures in Japan. Furthermore, written informed consent for invasive coronary angiography was obtained from all participants.

Stress technetium-99m sestamibi SPECT

In 84 patients, exercise myocardial perfusion imaging with ^{99m}Tc -sestamibi was performed using the 1-day protocol¹⁹⁾. Symptom-limited multi-step exercise using a bicycle ergometer was performed⁴⁾. ^{99m}Tc -sestamibi (259 MBq) was administered when submaximal heart rate, chest pain, ST-segment depression of ≥ 0.1 mV, or leg fatigue developed. Exercise was then continued for 1 minute at the same level as before. In the remaining 48 patients, ATP (0.16 mg/kg/min) was administered intravenously for 6 minutes⁴⁾, and 3 minutes later, ^{99m}Tc -sestamibi (259 MBq) was given intravenously. In both protocols, electrocardiogram-gated SPECT was acquired 30 minutes after stress²⁰⁾. Four hours later, the patients were given ^{99m}Tc -sestamibi (777 MBq) while at rest. Thirty minutes after that, electrocardiogram-gated SPECT image acquisition was started.

Data was acquired with a 3-detector gamma camera (Prism 3000XP, Picker, Cleveland, OH) over a 360-degree arc (in 20 six-degree-wide directions, for 30 seconds/direction). A low-energy high-resolution parallel multi-hole collimator was used, with a maximum matrix size of 64×64 . When obtaining electrocardiogram-gated images, the R-R interval was divided by the R-wave trigger into 8 equal portions. End-diastolic and end-systolic images were thus obtained. All of the patients were in sinus rhythm during image acquisition. SPECT images were reconstructed from the data using a data Odyssey VP processor (Picker) combined with a Butterworth filter (order 8; cutoff frequency 0.25 cycles/cm) and a ramp filter⁴⁾.

According to a previously reported method²¹⁾, each SPECT image was scored using a 20-segment model. The accumulation of the radioisotope in the myocardium was visually evaluated by 2 cardiologists, without any knowledge of patient information, using a 5-point scoring system: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake) or 4 (absence of radioactive uptake). Disagreements in image interpretation were resolved by consensus. The total of the scores for all of the segments, during exercise and at rest, was designated as the summed stress score (SSS) and the summed rest score (SRS), respectively. The sum of the differences between the SSS and SRS was defined as the summed difference score (SDS) to assess the overall extent and severity of stress-induced myocardial ischemia²²⁾.

Each reconstructed short-axis gated SPECT image was processed by a quantitative gated SPECT program developed by Germano et al (Cedars-Sinai Medical Center, Los Angeles, CA), to calculate the LV end-diastolic volume, LV end-systolic volume and LV ejection fraction²³⁾. In addition, changes in LV volumes with stress were calculated as LV end-diastolic volume after stress minus LV

end-diastolic volume at rest, or LV end-systolic volume after stress minus LV end-systolic volume at rest.

The simultaneously obtained 3-dimensional electrocardiogram-gated images of the LV myocardium (the end-diastolic peripheral image of the LV tunica intima overlapped the end-systolic image), were displayed in 2 directions. One approximately corresponded to the right anterior oblique 30-degree left ventriculography, the other to the left anterior oblique 60-degree imaging. For the images thus obtained, the periphery of the LV tunica intima was divided into 7 areas, according to the American Heart Association's classification of left ventriculograms²⁴. Five areas (anterobasal, anterior, apical, inferior and inferobasal) were derived in the right anterior oblique view, and 2 areas (septal and posterolateral) in the left anterior oblique view (Fig. 1). The regional wall motion of each area was visually rated by 2 cardiologists, who were blinded to patient information, with a 4-point scoring system: 0 (normal), 1 (mild hypokinesia), 2 (moderate to severe hypokinesia), 3 (akinesia or dyskinesia). The global wall motion score was calculated by totaling the regional wall motion scores for all 7 areas. The changes in global wall motion score with stress, defined as a wall motion difference score (WMDS), were obtained by subtracting the wall motion score at rest from the score >30 minutes after stress. We defined a definite stress-induced wall motion change as a WMDS ≥ 3 documented after stress⁴. When this stress-

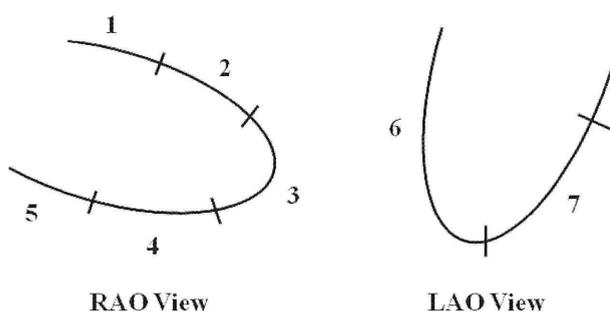


Fig. 1 Assignment of left ventricular (LV) regional wall motion for scoring of quantitative gated SPECT images. The periphery of the LV tunica intima was divided into 7 areas according to the American Heart Association's classification of left ventriculograms. Four areas (anterobasal, anterior, apical, and septal) corresponded to the areas perfused by the left anterior descending coronary artery. Two areas (inferior and inferobasal) corresponded to the areas perfused by the right coronary artery, and the posterolateral area corresponded to the areas perfused by the left circumflex coronary artery. A 4-point scoring system graded wall motion on each segment, where 0 represented normal, 1 represented mild hypokinesia, 2 represented moderate to severe hypokinesia, 3 represented akinesia or dyskinesia. LAO, left anterior oblique; RAO, right anterior oblique.

induced wall motion change was observed >30 minutes after stress, the development of myocardial stunning was considered²³. This definition of myocardial stunning indicates that in patients with a culprit LAD stenosis for example, exercise-induced apical moderate hypokinesia and anterior mild hypokinesia resolve completely at rest. More severe and extensive exercise-induced wall motion abnormalities were also included, but milder abnormalities were not considered to be myocardial stunning.

Coronary angiography

All of the patients underwent coronary angiography within 3 months of gated SPECT. Multi-directional coronary angiography was performed according to the Judkins method. Angiographic diameter narrowing of >50% was considered to represent significant stenosis, in accordance with the American Heart Association's classification²⁴.

Statistical analysis

Results are presented as mean values \pm SD, or percentages. Student's unpaired *t*-test and the Mann-Whitney *U*-test was used to compare the means of the continuous variables, and contingency tables were analyzed using a chi-square test. Spearman's correlation coefficient was used to estimate the correlation between SDS and WMDS. A general linear model was used to demonstrate that the exercise and ATP groups were independently related to the prevalence of myocardial stunning in patients with 1-vessel CAD. A *p* value of <0.05 was considered to indicate a statistically significant difference. Analyses were performed using the SPSS-PC+ computer program (version 11.0, SPSS Inc., Chicago, IL).

Results

Clinical characteristics of patients

Prolonged LV wall motion abnormalities >30 minutes after the cessation of exercise or ATP stress, which was defined as post-stress myocardial stunning, were observed in 54 patients (41%). Clinical and angiographic characteristics of 132 patients were compared based on the stress methods used during the SPECT study, and these data were similar in those who underwent exercise or ATP stress SPECT (Table 1). In 43 patients with 1-vessel CAD, $\geq 99\%$ coronary stenosis was found in 13 (50%) patients, 90% stenosis in 6 (23%) and 75% stenosis in 7 (27%) after exercise stress, whereas $\geq 99\%$ coronary stenosis was found in 7 (41%) patients, 90% stenosis in 6 (35%) and 75% stenosis in 4 (24%) after ATP stress (*p*=0.837).

Findings of perfusion and volumetric analyses

Among 84 patients who underwent exercise stress, significant ST-segment depression on electrocardiography was observed in 51 cases (61%), whereas ST-segment

Table 1 Clinical characteristics of 132 patients

	Exercise stress (<i>n</i> =84)	ATP stress (<i>n</i> =48)	<i>p</i> Value
Age (years)	63 ± 10	65 ± 10	0.323
Gender (male/female)	79/5	42/6	0.236
Height (cm)	165 ± 6	163 ± 8	0.245
Body weight (kg)	67 ± 11	65 ± 10	0.316
Body mass index	24.5 ± 2.9	24.3 ± 2.6	0.657
Coronary risk factors			
Hypertension	58 (70%)	39 (81%)	0.139
Dyslipidemia	58 (70%)	28 (58%)	0.193
Diabetes mellitus	36 (43%)	29 (60%)	0.061
Smoking	35 (42%)	26 (54%)	0.208
Angiographic findings			0.781
Insignificant lesion	7 (8%)	4 (8%)	
1-vessel disease	26 (31%)	17 (36%)	
2-vessel disease	28 (33%)	14 (29%)	
3-vessel disease	23 (28%)	13 (27%)	

ATP, adenosine triphosphate.

depression was observed in only 1 of the 48 patients undergoing ATP stress. The averages of SSS, SRS and SDS in all patients were 14.7±5.9 (range 9 to 33), 6.6±4.1 (range 0 to 23) and 8.1±4.2 (range 0 to 24), respectively. No significant differences between the 2 groups were observed in SSS, SRS and SDS. The changes in global wall motion scores with stress, defined as a WMDS, were greater in the exercise than in the ATP group (2.5±1.8 vs 1.4±1.2; $p<0.0001$). Post-stress myocardial stunning was observed in 45 patients (54%) in the exercise group, but only in 9 patients (19%) in the ATP group ($p<0.0001$) (Table 2).

In volumetric and functional analyses, LV end-diastolic volume, LV end-systolic volume and LV ejection fraction were similar in the exercise and ATP groups, both at rest and after stress (Table 2). When comparing the change in LV function with stress (stress - rest), LV end-diastolic volume was greater in the ATP than the exercise stress group, while LV end-systolic volume and LV ejection fraction were similar (Table 2).

The relation between myocardial stunning and severity of coronary artery stenosis

In the exercise group, both the SSS ($r=0.32$, $p=0.005$) and SDS ($r=0.40$, $p<0.0001$) correlated significantly with the WMDS. In the ATP group, however, no significant correlation was observed between the WMDS and SSS ($r=-0.01$, $p=0.952$), or SDS ($r=0.21$, $p=0.157$) (Fig. 2).

Based on the severity of coronary artery stenosis in 43 patients with 1-vessel CAD, the SSS values were similar in the ≥99% coronary stenosis group (18.5±8.0 vs. 18.0±5.9; $p=0.895$), in the 90% stenosis group (12.8±3.5 vs. 12.7±3.3; $p=0.934$) and in the 75% stenosis

group (10.9±2.4 vs. 11.5±3.1; $p=0.709$) (Fig. 3). Among this particular group of patients, the prevalence of post-stress stunning was 10 of 13 (77%) patients with ≥99% coronary stenosis, 4 of 6 (67%) with 90% stenosis, and 2 of 7 (29%) with 75% stenosis after exercise stress, whereas it was 4 of 7 (57%) with ≥99% stenosis, 1 of 6 (17%) with 90% stenosis, and 0 of 4 (0%) with 75% stenosis after ATP stress ($p=0.03$) (Fig. 4).

Discussion

Although post-stress LV wall motion abnormality as assessed by gated SPECT, also known as post-ischemic myocardial stunning, has been regarded an important marker of severe CAD, the mechanism of this phenomenon is controversial⁶⁻¹¹. Previous studies reported that inaccurate endocardial tracking using gated SPECT in perfusion defects of moderate severity or more resulted in false wall motion abnormality¹⁶⁾¹⁷⁾. If stress-induced perfusion defects disappear at rest, the aforementioned false wall motion abnormality induced by stress will normalize because of accurate tracking in the area of normal perfusion. Based on these observations, post-ischemic LV wall motion abnormality was believed to not be true myocardial stunning¹⁶⁾¹⁷⁾.

In an attempt to evaluate the mechanism of post-ischemic LV wall motion abnormality as assessed by gated SPECT, scintigraphic and angiographic findings in 132 CAD patients with stress-induced perfusion defects of moderate severity or more (an average SSS of 14.7; range 9 to 33) were compared based on the method of stress utilized, either exercise or ATP. In contrast to exercise stress, which causes demand ischemia physio-

Table 2 Comparison of scintigraphic findings between exercise and ATP SPECT

	Exercise stress (n=84)	ATP stress (n=48)	p Value
Peak heart rate achieved (beats/min)	129 ± 17	—	
ST-segment depression	51 (61%)	1 (2%)	<0.0001
Summed scores			
Summed stress score	14.4 ± 5.8	15.2 ± 6.0	0.452
Summed rest score	6.6 ± 4.3	6.6 ± 3.6	0.968
Summed difference score	7.8 ± 3.8	8.6 ± 4.8	0.307
LV function at rest			
LV end-diastolic volume (ml)	101 ± 32	103 ± 46	0.715
LV end-systolic volume (ml)	44 ± 25	48 ± 34	0.477
LV ejection fraction (%)	58 ± 9	57 ± 13	0.605
LV function after stress			
LV end-diastolic volume (ml)	103 ± 33	111 ± 48	0.293
LV end-systolic volume (ml)	49 ± 27	56 ± 34	0.238
LV ejection fraction (%)	54 ± 10	52 ± 11	0.286
Changes in LV function with stress (stress-rest)			
LV end-diastolic volume (ml)	2.0 ± 9.9	7.5 ± 9.7	0.002
LV end-systolic volume (ml)	5.1 ± 8.8	7.8 ± 7.6	0.073
LV ejection fraction (%)	-4.0 ± 5.2	-4.9 ± 5.2	0.376
Wall motion difference score	2.5 ± 1.8	1.4 ± 1.2	<0.0001
Post-stress myocardial stunning*	45 (54%)	9 (19%)	<0.0001

*Post-stress myocardial stunning was defined if a wall motion difference score of ≥ 3 was documented after stress. ATP, adenosine triphosphate; LV, left ventricular.

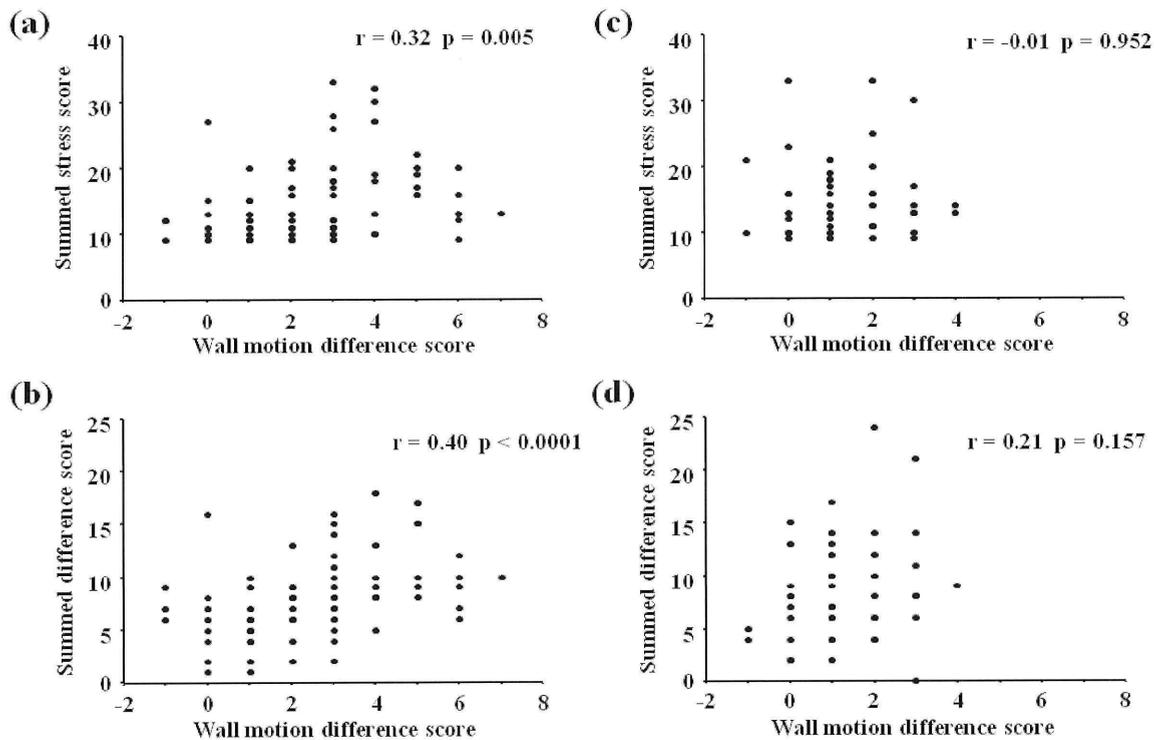


Fig. 2 Relationship between the severity of perfusion abnormalities and wall motion difference score. Correlation between the wall motion difference score and summed stress score (a), and summed difference score (b) in the exercise stress group. Correlation between the wall motion difference score and summed stress score (c), and summed difference score (d) in the ATP stress group.

extent of perfusion defects in each grade of coronary artery stenosis was similar in patients who underwent exercise stress and those who underwent ATP stress (Fig. 3). In this group of patients, the incidence of post-ischemic myocardial stunning was higher after exercise than after ATP stress (Fig. 4). Furthermore, a significant positive relationship between the severity of coronary artery stenosis and the occurrence of myocardial stunning was observed after exercise stress, whereas the incidence of myocardial stunning was rare in patients with 75% or 90% coronary stenosis after ATP stress. However, the fact that a considerable number of patients with 99% stenosis developed myocardial stunning even after ATP loading indicated that myocardial ischemia may be provoked with ATP through collateral steal^{25,26}. These findings underscore the importance of exercise-induced myocardial ischemia in the etiology of post-stress myocardial stunning as assessed by gated SPECT^{4,6-8}.

In the present study, we also examined the degree to which global cardiac function was affected by exercise or ATP stress. Although stress-induced LV wall motion abnormality occurred more frequently after exercise, changes in LV ejection fraction with ATP stress were similar. Changes in LV end-diastolic volume were even greater after ATP loading than after exercise stress. These observations may be explained not only by the inclusion of patients without transient LV wall motion abnormalities in each group, but also by the greater volumetric increase induced by ATP, compared with exercise³⁰. In the detection of post-stress LV wall motion abnormality using electrocardiogram-gated SPECT, therefore, the evaluation of LV segmental wall motion applied in this study may be more sensitive and important, compared with the assessment of global cardiac function, and should be fully utilized to detect post-ischemic myocardial stunning.

Study limitations

The present study has several limitations that are common to any study relying on retrospective data collection. Although patient characteristics and the extent of perfusion defects on myocardial SPECT were similar between patients with exercise and ATP stress, an unidentified confounder was likely to exist. However, it seems appropriate to evaluate, at least, the effects of perfusion defects induced either by exercise or by APT stress, on the occurrence of transient LV wall motion abnormality with this study design. Therefore, the reliability of the conclusions reached on the basis of these data seems sufficient, although a prospective study is necessary.

Conclusions

The predominant mechanism of post-stress wall motion abnormality observed by gated SPECT was thought to be severe myocardial ischemia, but not a per-

fusion-associated artifact. Thus, this scintigraphic finding was regarded as actual myocardial stunning.

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心電図同期心筋 SPECT 検査によって評価された 負荷後心筋スタニングに関する検討

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【背景】 99mTc-sestamibi を用いた心電図同期心筋 SPECT (gated SPECT) の QGS 解析により評価される運動負荷後の一過性壁運動障害、いわゆる心筋スタニングは、重症冠動脈疾患の存在を示唆することが知られている。しかしながら、心筋スタニングは灌流低下部位に見られることから、不正確な画像解析により生じたアーチファクトにすぎないとの反論がある。

【目的】 Gated SPECT の QGS 解析における左室壁運動・心機能について運動負荷(心筋虚血を誘発)と薬剤負荷(血流分布異常の誘発)を比較することにより、心筋スタニングが心筋虚血によるものか、あるいは灌流低下によるアーチファクトによるものかを検討した。

【方法】 病歴より冠動脈疾患が既存、或いは疑われ、^{99m}Tc-sestamibi を用いた負荷 gated SPECT 検査が施行された症例のうち、負荷時に中等度～高度灌流低下を認めた症例 132 名(運動負荷 84 名, 薬剤: ATP 負荷 48 名)を対象とした。全例で冠動脈造影検査が施行された。

【結果】 SPECT で評価した両群間の虚血重症度スコアに有意差は認めなかったが、運動負荷群で 54%、ATP 負荷群で 19% に心筋スタニングを認めた ($p < 0.0001$)。運動負荷群で虚血スコアと壁運動異常スコアに有意な相関を認めしたが、ATP 負荷群では有意な相関は認めなかった。冠動脈造影検査で一枝病変を認めた 43 名において、狭窄度と心筋スタニングの関係をみたところ、いずれの狭窄度においても、運動負荷群において心筋スタニングの出現頻度が有意に高かった。一方 ATP 負荷群でも一部の症例で心筋スタニングが出現したが、その多くは 90% 以上の高度狭窄症例であった。

【結語】 99mTc-sestamibi を用いた運動負荷 gated SPECT 検査ではしばしば負荷後に心筋スタニングを認め、虚血の重症度と有意に相関した。一方、薬剤負荷では血流の分布異常の誘発が主体であり、同様の灌流欠損の重症度であるにもかかわらず、心筋スタニングの出現は有意に少なかった。このことから、QGS で評価された心筋スタニングは心筋虚血を反映しているものであり、不正確な画像解析によるアーチファクトの可能性は低いと考えられた。

〈キーワード〉 冠動脈疾患、心筋スタニング、心電図同期心筋 SPECT、運動負荷、ATP 負荷
