

Isoproterenol stress thallium scintigraphy for detecting coronary artery disease

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Summary

The value of exercise thallium scintigraphy in detecting coronary artery disease is well established. However, there are at times situations in which the exercise test cannot be readily used. Isoproterenol (ISP) stress ECG (ISP-ECG) is reportedly a useful method in diagnosing coronary artery disease. In the present study, we assessed the diagnostic value of ISP thallium scintigraphy, comparing it with those of ISP-ECG and exercise thallium scintigraphy.

The study population consisted of 24 patients who had histories of chest pain without previous myocardial infarction. ISP was given at increasing doses of 0.02, 0.04, 0.08 $\mu\text{g}/\text{kg}/\text{min}$ at 3-minute intervals, and was terminated for any of the following reasons: angina, significant arrhythmia, significant ST segment depression (≥ 0.1 mV) or target heart rate. Thallium scintigrams were obtained immediately after terminating ISP infusion, and after a 3-hour delay, redistribution scans were obtained. Scintigrams were considered positive when a reversible defect was present. In nine patients who underwent exercise tests, exercise thallium scintigraphy was also performed. After the stress tests, coronary angiography was performed. According to the presence or absence of significant coronary artery stenosis ($\geq 75\%$), all subjects were divided into two groups: coronary artery disease (CAD) group ($n=12$) and so-called normal coronary (NC) group ($n=12$).

1. Among 12 patients in the CAD group, ISP induced anginal pain in six (50%), and ISP-ECG and ISP thallium scintigraphy were positive in 10 (83%) and in 11 (92%), compared with four (33%), four (33%) and two (17%) in the NC group. These data indicate that the sensitivity of ISP-ECG was 83%; its specificity, 67% and diagnostic accuracy, 75%; and that those of ISP thallium scintigra-

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phy were 92%, 83% and 88%, respectively.

2. Among nine patients who underwent both ISP thallium scintigraphy and exercise thallium scintigraphy, all but one false negative case in ISP thallium scintigraphy were correctly diagnosed by both tests.

3. No serious complications occurred using the ISP infusion test.

ISP thallium scintigraphy, which can be performed in patients who cannot undergo exercise tests, was considered to be a safe, sensitive and specific method for the diagnosis of coronary artery disease.

Key words

Isoproterenol infusion stress test

Coronary artery disease

Thallium-201 scintigraphy

Introduction

The value of exercise stress testing in detecting coronary artery disease is well established¹, but its application is frequently limited because of concurrent illness, the patient's poor condition and caution in performing vigorous exercise. To evaluate such patients, pharmacological stress tests have become increasingly important. Reportedly, isoproterenol (ISP), a beta-adrenergic stimulating agent with positive chronotropic, positive inotropic, and vasodilating properties², frequently induces ischemic ST segment depression in patients with coronary artery disease³⁻⁵, and the diagnostic accuracy of the ISP stress ECG (ISP-ECG) has been shown to be comparable to that of the exercise ECG⁶⁻¹⁰.

ST segment depression, widely used as an index of myocardial ischemia, is known to be less than accurate as a marker for ischemia¹¹. Myocardial imaging with thallium-201, however, has been used to improve sensitivity and specificity in detecting coronary artery disease^{7,9,12,13}.

The present study assessed whether ISP thallium scintigraphy can detect myocardial ischemia in a group of patients undergoing diagnostic coronary angiography and compared its diagnostic accuracy with that of ISP-ECG and exercise thallium scintigraphy.

Methods

Patients

The study population consisted of 24 patients, 14 men and 10 women, whose average age

was 60 ± 12 years, and who had histories of chest pain without ECG evidence of myocardial infarction. The final clinical diagnoses were effort angina pectoris in 12 patients, chest pain syndrome in eight, valvular heart disease in two, dilated cardiomyopathy in one and variant angina pectoris in one. All patients underwent ISP-ECG and ISP thallium scintigraphy, and exercise thallium scintigraphy was also performed for nine patients who could perform an exercise test. Selective coronary angiography was performed within two weeks after the stress tests, and the diagnostic data of all stress tests were compared. All patients were informed of the nature of this investigation and all consented to participate.

ISP stress test protocol

ISP stress test was performed in the supine position. In each patient, intravenous flow was established via an antecubital vein. Isoproterenol (ISP) was administered using an infusion pump at increasing doses of 0.02, 0.04 and 0.08 $\mu\text{g}/\text{kg}/\text{min}$ at 3-min intervals. ISP infusion was terminated for any of the following reasons: (1) angina; (2) significant arrhythmia; (3) significant ST segment depression; and (4) target heart rate. An ischemic response was defined as a horizontal or downsloping ST segment depression of 0.1 mV of 0.08 sec duration or greater. Single-channel ECG was monitored continuously during and after ISP infusion to observe any arrhythmias. Twelve-lead electrocardiograms were recorded every minute before and during ISP infusions and until five min after the ISP infusions were completed. Blood pressure was measured with a cuff

sphygmomanometer every minute throughout the test.

Exercise protocol

Nine patients who underwent the exercise tests were subjected to graded bicycle exercise testing, beginning with 1.0 watt/kg/min. Half of the initial load was added every three min. Reasons for discontinuing the exercise tests were the same as those for the ISP test. The protocol for monitoring or recording the ECG, blood pressure and heart rate was the same as that for the ISP test.

Thallium scintigraphy

Two mCi thallium-201 were injected intravenously at the termination of the ISP infusion, or one min before terminating the exercise. Planar images or SPECT images were obtained immediately after completing the exercise or ISP infusion. Planar images were obtained using an LEM scintillation camera (Siemens) with an HRC collimator. For SPECT images, we used an RC-150DT scintillation camera (HITACHI) with an LEHR collimator for data acquisition and an RP-200 (HARP-II) for data processing. Standard views obtained were the anterior projection, 45-degree left anterior oblique projection and left lateral projection in the planar images, and the short-axis view, horizontal long-axis view and vertical long-axis view for SPECT images. After a 3-hour delay, redistribution scans were obtained using similar views. Thallium scintigrams were interpreted by physicians specializing in nuclear medicine who had no knowledge of the patients' clinical histories or coronary angiograms. Tests were considered positive when a reversible defect was present during ISP infusion or during an exercise test. Since SPECT images were not obtained in some patients, planar images were used for data analysis.

Coronary angiography and data analysis

Selective coronary angiography was performed employing the Judkins or Sones technique within two weeks after the stress tests. A patient was considered to have significant coronary stenosis if there was 75% or more decrease in diameter in one or more coronary

arteries or their major branches. All subjects were categorized in two groups: the coronary artery disease group (CAD group) ($n=12$), and the so-called normal coronary group (NC group) ($n=12$). The final clinical diagnosis of all 12 patients in the CAD group was effort angina pectoris. The diagnostic values of the two tests were compared. The Student's *t*-test was used to evaluate the statistical significance of the results. A probability (*p*) value <0.05 was considered significant. Values were expressed as means \pm standard deviations.

Results

1. Results of ISP stress tests

By ISP stress, the heart rate (HR) increased from 68.6 ± 12.7 /min at rest to 110.1 ± 17.2 /min ($p < 0.001$) at the end of the ISP infusion in the CAD group, and from 76.7 ± 12.1 /min to 124.3 ± 16.7 /min ($p < 0.001$) in the NC group. Systolic blood pressure (S-BP) in both groups (from 136.7 ± 12.7 mmHg to 137.2 ± 20.4 mmHg in the CAD group and from 135.6 ± 14.8 mmHg to 144.6 ± 19.2 mmHg in the NC group) did not change significantly. Diastolic blood pressure (D-BP) in the NC group (from 83.2 ± 11.8 mmHg to 77.8 ± 18.7 mmHg) did not change significantly; however, it decreased from 80.7 ± 12 mmHg to 66.7 ± 16.1 mmHg ($p < 0.05$) in the CAD group.

Among the 12 patients in the CAD group, ISP infusion induced anginal pain in six patients (50%). ISP-ECG was positive in 10 patients (83%) and ISP thallium scintigraphy was positive in 11 patients (92%), while in the 12 patients of the NC group, chest pain was induced in four (33%), with positive ISP-ECG in four (33%) and positive ISP thallium scintigraphy in two patients (17%) (Table 1). These data indicate that the sensitivity of ISP thallium scintigraphy was 92%, its specificity 83%, and the diagnostic accuracy 88%, being superior to those of ISP-ECG (83%, 67% and 75%, respectively) (Table 2).

2. ISP thallium scintigraphy vs exercise thallium scintigraphy

Both ISP thallium scintigraphy and exercise

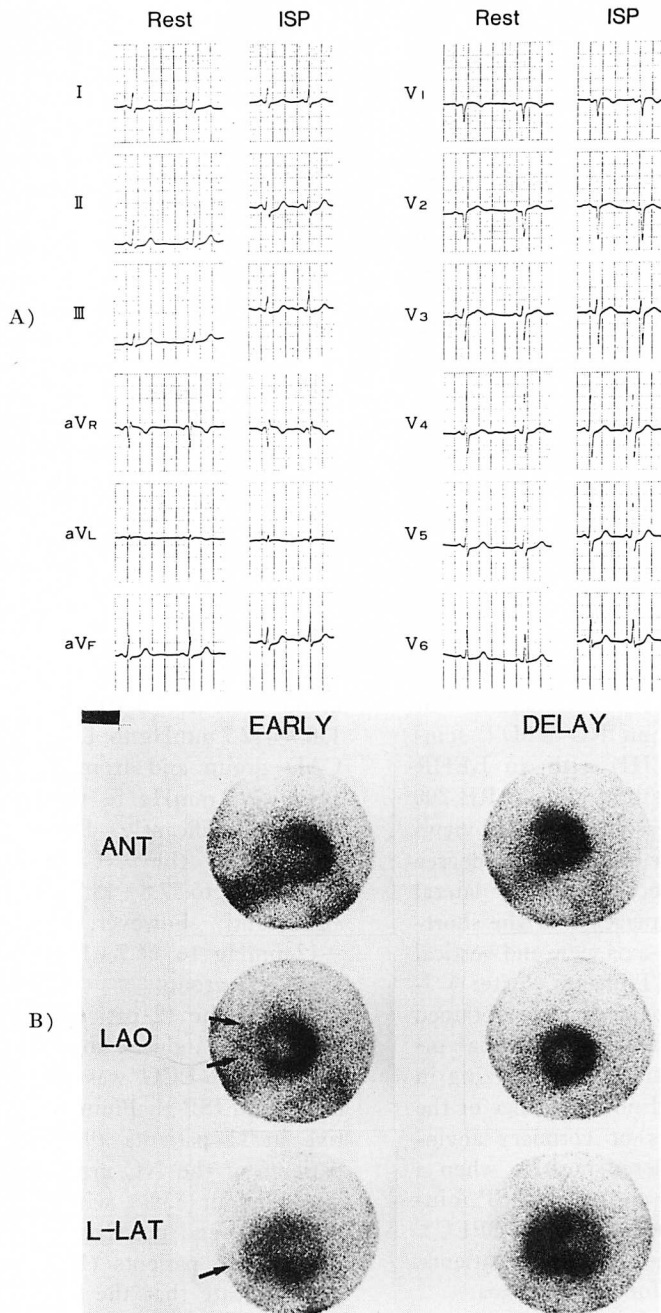


Fig. 1. ISP-ECG (A) and ISP thallium scintigraphy (B) of a 67-year-old man with angina pectoris.

ISP-ECG showed slight ST depression, which was not significant, indicating a negative test. ISP thallium scintigraphy showed reversible defects (arrows) involving the septal wall and apex, indicating a positive test. Coronary angiography revealed 90% stenosis of the proximal portion of the left anterior descending artery in this patient.

ISP=isoproterenol; ANT=anterior; LAO=left anterior oblique; L-LAT=left lateral.

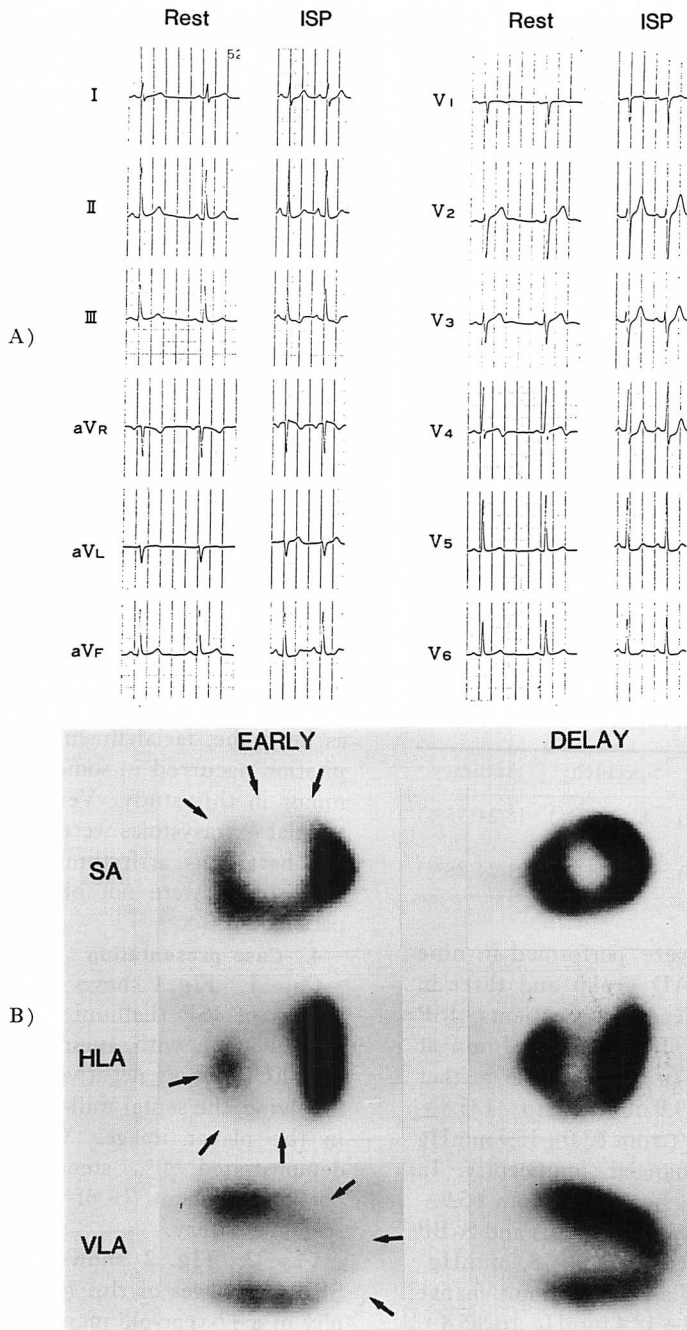


Fig. 2. ISP-ECG (A) and ISP thallium scintigraphy (B) of a 47-year-old man with angina pectoris.

Significant ST depression was shown in V₄ and V₅, and reversible defects (arrows) were seen in the anteroseptal wall and apex, indicating positive ISP-ECG and positive ISP thallium scintigraphy. Coronary angiography demonstrated 99% stenosis of the proximal portion of the left anterior descending artery in this patient.

SA=short axis; HLA=horizontal long axis; VLA=vertical long axis.

Table 1. Results of ISP stress tests

| | CAD group (n=12) | NC group (n=12) |
|--|---------------------|--------------------|
| Age | 61±14 | 59±9 |
| Sex (M:F) | 10:2 | 4:8 |
| Chest pain | | |
| Yes | 6(50%) | 4(33%) |
| No | 6(50%) | 8(67%) |
| ST depression | | |
| Yes | 10(83%) | 4(33%) |
| No | 2(17%) | 8(67%) |
| Reversible defect in thallium scintigraphy | | |
| Yes | 11(92%) | 2(17%) |
| No | 1(8%) | 10(83%) |

CAD=coronary artery disease; NC=normal coronary.

Table 2. Diagnostic values of ISP-ECG and ISP thallium scintigraphy

| | Sensitivity | Specificity | Accuracy |
|---------------------------|-------------|-------------|------------|
| ISP-ECG | 10/12(83%) | 8/12(67%) | 18/24(75%) |
| ISP thallium scintigraphy | 11/12(92%) | 10/12(83%) | 21/24(88%) |

thallium scintigraphy were performed in nine patients (six in the CAD group and three in the NC group). In these nine patients, ISP infusion increased HR from 63.6 ± 6.4 /min at rest to 112.0 ± 17.0 /min ($p < 0.01$), while neither S-BP (from 139.3 ± 9.9 mmHg to 135.8 ± 22.1 mmHg) nor D-BP (from 83.0 ± 15.7 mmHg to 73.8 ± 22.9 mmHg) changed significantly. In the exercise stress test, both HR (from 65.9 ± 6.6 /min to 106.0 ± 18.8 /min; $p < 0.001$) and S-BP (from 139.0 ± 13.6 mmHg to 173.0 ± 18.6 mmHg; $p < 0.001$) increased, while D-BP did not change significantly (from 84.3 ± 12.4 mmHg to 85.4 ± 38.6 mmHg). The increase of S-BP was significantly greater in exercise than during ISP stress ($p < 0.01$), while changes of both HR and D-BP did not differ significantly between the two stress tests.

Table 3 shows the results of the ISP thal-

Table 3. Results of ISP thallium scintigraphy and exercise thallium scintigraphy in 9 patients who underwent both tests

| | CAD group (n=6) | NC group (n=3) |
|---|--------------------|-------------------|
| Reversible defect in ISP thallium scintigraphy | | |
| Positive | 5 | 0 |
| Negative | 1 | 3 |
| Reversible defect in exercise thallium scintigraphy | | |
| Positive | 6 | 0 |
| Negative | 0 | 3 |

lium scintigraphy and the exercise thallium scintigraphy. All but one false negative case in the ISP thallium scintigraphy were correctly diagnosed by both tests.

3. Safety of ISP stress test

During or after ISP infusion, side effects such as headache, facial flushing or a sense of palpitation occurred in some cases, but they were minor in this study. Ventricular or supraventricular extrasystoles were sometimes observed, but hazardous arrhythmias such as short run or R on T were not observed in any of the patients.

4. Case presentation

Case 1. **Fig. 1** shows ISP-ECG and planar images of ISP thallium scintigraphy of a 67-year-old man with angina pectoris. Although ISP-ECG was negative, reversible defects involving the septal wall and apex were present in the planar images. Coronary angiography demonstrated 90% stenosis of the proximal portion (segment 7) of the left anterior descending artery.

Case 2. **Fig. 2** shows the ISP-ECG and SPECT images of the ISP thallium scintigraphy of a 47-year-old man with angina pectoris. The ISP-ECG shows significant ST segment depression in leads $V_4 \sim V_5$, and ISP thallium scintigraphy shows reversible defects in the anteroseptal wall and apex, indicating positive ISP-ECG and positive ISP thallium scintigraphy. Exercise thallium scintigraphy showed

the same results. Coronary angiography revealed 99% stenosis of the proximal portion (segment 7) of the left anterior descending artery.

Discussion

The exercise stress test has been widely applied as a means of evaluating coronary artery disease¹¹. However, there are occasions when the exercise test cannot be readily used; for example, in patients with intermittent claudication, chronic lung disease, or other physical or psychological limitations which prohibit adequate exercise. The use of drugs such as epinephrine¹⁴, ergonovine¹⁵ and dopamine¹⁶ has been described as useful in diagnosing ischemic heart disease; however, none of these agents has gained widespread popularity, probably because of side effects and slow reversibility.

The ISP infusion test is reportedly a safe and useful means of diagnosing coronary artery disease³⁻⁵. ISP is a beta-adrenergic stimulating agent with positive chronotropic and positive inotropic properties, which increases the myocardial oxygen demand by enhancing both heart rate and myocardial contractility². Moreover, ISP has vasodilating properties and it has been suggested that ISP may induce a maldistribution of coronary blood flow (coronary steal)¹⁷⁻¹⁹ in patients with coronary artery disease, like other pharmacologic coronary vasodilators such as dipyridamole²⁰. Therefore, ISP infusion may provoke similar hemodynamic changes as do exercise tests and stress tests using vasodilating agents. Wexler et al.³ have described, in a preliminary report, the use of ISP as a method of stress testing. Combs et al.⁴ showed that ISP-ECG test correctly predicted 71% of patients with angiographically-documented coronary artery disease, the result of which was comparable to that of the treadmill exercise test (68%). Kuramoto et al.⁵ reported that the ISP-ECG test is a safe and useful method of the assessing elderly patients with ischemic heart disease, and they showed that its sensitivity and specificity were 72% and 71%, respectively. In this study, the sensitivity, speci-

ficity and accuracy of ISP-ECG were 83%, 67% and 75%, respectively and they compared favorably with those in these reports. The sensitivity of ISP-ECG in this study is higher than the reported sensitivity levels of 58 to 74% in the exercise ECG⁶⁻¹⁰ and dipyridamole stress ECG²¹. However, ISP-ECG had relatively frequent false positive tests despite high sensitivity, because ST segment depression can result from causes other than coronary atherosclerosis, such as anemia, valvular heart disease, hypertension, left ventricular hypertrophy and some metabolic conditions.

Thallium-201, because of its low energy of emission and high degree of concentration in the myocardium, appears to be one of the best suited agents for cardiac imaging²²⁻²⁴. It is believed that the distribution of this tracer represents the regional distribution of blood flow, and myocardial imaging with thallium is expected to improve the diagnostic accuracy of coronary artery disease. Several investigators have examined the diagnostic accuracy of exercise myocardial scintigraphy using thallium-201. They have reported improved sensitivity levels of 75 to 94% as well as improved specificity levels of 68 to 93%^{7,9,12,13} compared with those of the exercise ECG. However, few studies concerning ISP thallium scintigraphy have been previously reported. In the present study, in a group of patients undergoing diagnostic coronary angiography, the high sensitivity (92%) and specificity (83%) of ISP thallium scintigraphy similar to those of exercise thallium scintigraphy were demonstrated. In this study, nine patients underwent both ISP thallium scintigraphy and exercise thallium scintigraphy. All these patients were correctly diagnosed by both tests with the exception of one false negative case in ISP thallium scintigraphy. The diagnostic values in these patients were similar to or slightly greater than those previously reported for dipyridamole thallium scintigraphy (sensitivity 85 to 88%, specificity 64 to 65%)^{12,25}.

In one patient with variant angina pectoris in the NC group, the ISP test was not positive, probably because beta-stimulation can suppress

coronary spasm. ISP stress thallium scintigraphy may be useful in detecting fixed coronary stenosis.

The ISP test could be performed easily and no serious complications occurred. As a result of administering ISP, chest pain, ventricular extrasystoles or supraventricular extrasystoles were noted, but severe chest pain or dangerous arrhythmias were not encountered. Moreover, ISP-induced chest pain or arrhythmias resolved within a few minutes after terminating the ISP infusion, and chest pain was controlled by the sublingual administration of nitroglycerin.

Clinical implications

Our findings revealed the usefulness and some advantages of thallium-201 myocardial perfusion scintigraphy with ISP infusion. This technique is highly sensitive and specific for coronary artery disease, similar to exercise thallium scintigraphy. It has the advantage that performing exercise is not required; thus, patients with problems precluding exercise can be tested. No major side effects were observed. In conclusion, ISP thallium scintigraphy proved to be a safe, sensitive and specific method for diagnosing coronary artery disease.

要 約

イソプロテレノール負荷心筋シンチグラフィによる冠動脈疾患の診断

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運動負荷心筋シンチグラフィ(心筋シンチ)は, 冠動脈疾患の診断上有用であることが報告されているが, 十分な運動負荷を施行することが困難な例が少なくない。このような運動負荷施行困難例に対する冠動脈疾患の診断法として, イソプロテレノール(ISP)負荷心電図の有用性が報告されている。今回我々は ISP 負荷心筋シンチの有用性につき, その診断精度を, ISP 負荷心電図お

よび運動負荷心筋シンチと対比検討した。

対象は胸痛を有する非梗塞患者 24 例。ISP 負荷は ISP を 0.02 $\mu\text{g}/\text{kg}/\text{分}$ にて静注, 3 分毎に増量し, 胸痛, 不整脈, ST 降下, 目標心拍数のいずれかにて中止した。Tl²⁰¹-心筋シンチは負荷直後および 3 時間後に撮像し, 一過性の低灌流所見を心筋虚血とした。運動負荷が可能な 9 例については運動負荷心筋シンチも施行した。負荷試験終了後, 冠動脈造影を施行し冠動脈の有意($\geq 75\%$)狭窄の有無により冠動脈疾患(CAD)群 12 例と“正常”冠動脈(NC)群 12 例に分類した。

1. ISP 静注により CAD 群 12 例中, 胸痛を 6 例(50%), 有意($\geq 0.1\text{ mV}$)の ST 降下を 10 例(83%), シンチ上の虚血所見を 11 例(92%)に認めた。一方, NC 群 12 例中, 胸痛を 4 例(33%), ST 降下を 4 例(33%), 虚血所見を 2 例(17%)に認めた。以上より, ISP 負荷による CAD の診断は, 心電図では感度 84%, 特異性 67%, 診断精度 75% であり, 心筋シンチでは, それぞれ 92%, 83%, 88% であった。

2. ISP 負荷心筋シンチおよび運動負荷心筋シンチを施行した 9 例では, ISP 負荷心筋シンチにおいて偽陰性だった 1 例を除き, 両負荷とも正確に冠動脈疾患を診断し得た。

3. ISP 静注による重大な合併症はみられなかった。

ISP 負荷心筋シンチは, 冠動脈疾患診断上, 診断精度が高くかつ安全であり, また運動負荷施行困難例にも施行でき, 臨床上有用であると考えられた。

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