Slow upsloping ST-segment depression during exercise: Does it really signify a positive stress test?

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Background Slow upsloping ST-segment depression during stress is thought to represent an ischemic response to exercise treadmill testing (ETT).

Aim We used modern single-photon emission computed tomography (SPECT) imaging protocols to determine the incidence of ischemia in patients with slow upsloping ST depression during exercise and whether this response signifies more or less severe coronary artery disease (CAD) and risk in comparison with rapid upsloping ST depression and particularly with horizontal or downsloping ST depression.

Methods We enrolled 33 patients (group 1) with rapid upsloping ST depression (>1 mm extending <0.08 seconds beyond J point), 32 patients (group 2) with slow upsloping depression (>1.5 mm extending >0.08 seconds beyond J point), and 35 patients (group 3) with horizontal or downsloping depression (>1 mm at 0.08 seconds beyond J point). Summed stress score (SSS), summed difference score (SDS), stress extent percent (SE%) and reversible extent percent (RE%) of perfusion abnormalities, lung-heart ratio (LHR), and transient ischemic dilatation (TID) were calculated.

Results The mean SSS, SDS, SE%, RE%, and LHR were similar between groups 1 and 2 but significantly higher in group 3. Incidence of ischemia was similar in groups 1 and 2 (39% and 25%) but significantly higher in group 3 (77%, $P < .001$). Evidence of TID was seen in none of the patients in groups 1, in 3% of patients in group 2, and in 23% of patients in group 3.

Conclusions Slow upsloping ST depression does not signify more severe ischemia, more extensive CAD, or more stress-induced backward left ventricular failure. Thus, it would be reasonable to consider patients with slow upsloping ST depression during exercise as having a very low likelihood of CAD, similar to patients with rapid upsloping ST depression. (Am Heart J 2002;143:482-7.)

It is generally accepted that >1 mm horizontal or downsloping ST-segment depression at 0.08 seconds after the J point (Figure 1, *A*) during exercise treadmill testing (ETT) signifies a positive stress test and predicts ischemia and coronary artery disease (CAD).[1,2] It is also generally accepted that rapid upsloping ST-segment depression (not extending to 0.08 seconds from the J point [Figure 1, *B*]) does not indicate an ischemic response to exercise,[1-4] whereas slow upsloping ST-segment depression (≥1.5 mm extending 0.08 seconds or more from the J point [Figure 1, *C*]) is thought to be indicative of ischemia.[1,2,5-7] However, this latter assumption is based on older and generally retrospective studies, with the reference standard being >50% or 70% coronary artery stenosis by coronary angiography (an anatomic marker of CAD). Only one study has used myocardial perfusion imaging (marker of functional significance of CAD) to assess the ability of slow upsloping ST depression during exercise to predict ischemia and CAD.[8] However, that study used planar imaging technique, not single-photon emission computed tomography (SPECT), thallium-201 without reinjection, and no quantification was performed.

To our knowledge, the presumption that slow upsloping ST-segment depression during exercise signifies ischemia and to what extent has not been addressed with modern SPECT imaging and analytic methods. This is important because patients are frequently referred for imaging studies on the basis of electrocardiographic (ECG) response during standard exercise testing. The aim of this study was to use current imaging protocols, quantitative perfusion assessment, functional parameters, and prognostic adjunctive markers to determine the incidence of ischemia in patients with slow upsloping ST-segment depression during exercise and whether this response signifies more or less severe and extensive

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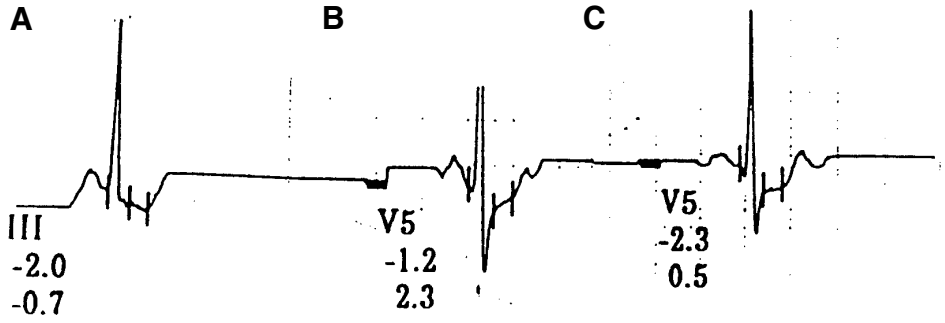
Figure 1



A, >1-mm downsloping ST-segment depression at 0.08 seconds after J point. **B**, >1-mm upsloping ST-segment depression extending <0.08 seconds beyond J point. **C**, >1.5-mm upsloping ST-segment depression extending >0.08 seconds beyond J point.

CAD, and therefore risk, in comparison with rapid upsloping ST depression and particularly with downsloping or horizontal ST depression.

Methods

Patients

We prospectively enrolled patients with known or suspected CAD, referred for symptom-limited ETT and SPECT myocardial perfusion imaging, only on the basis of the type of ST-segment changes during ETT. Pretest likelihood of CAD was determined in each patient before the stress test on the basis of established guidelines.[9] Before the stress test, a thorough review of the patient's chart was made and a focused history was obtained to collect information regarding symptoms, medications, coronary risk factors, previous cardiac events, and previous coronary interventions. Hypertension was defined as blood pressure (BP) ≥140/90 mm Hg at rest or ongoing treatment with antihypertensive medications. Diabetes mellitus was determined on the basis of history and use of medications. Only patients with normal baseline ECGs were included in the study. Patients were excluded if they had baseline ST-segment abnormalities, ST-segment changes in recovery only, left or right bundle branch block, left ventricular (LV) hypertrophy, implanted pacemaker, recent (<4 weeks) history of coronary intervention, or were being treated with digoxin. They were also excluded if they had motion artifacts that did not allow an adequate reading of the stress ECG or if the scans had excessive extracardiac activity or motion artifacts interfering with assessment of the perfusion. The patients were divided into 3 groups based only on the type of ST-segment depression during ETT.

Group 1 (rapid upsloping). Group 1 consisted of 33 patients who had >1 mm upsloping ST-segment depression extending <0.08 seconds beyond the J point. Twenty-seven patients (82%) had an intermediate likelihood, 4 patients (12%) had a low likelihood, and 2 patients (6%) had a high likelihood of CAD. The demographic data are summarized in Table I.

Group 2 (slow upsloping). Group 2 consisted of 32 patients with >1.5 mm upsloping ST-segment depression extending >0.08 seconds beyond the J point. Twenty-eight patients (88%) had an intermediate likelihood, 3 patients (9%) had a low likelihood, and 1 patient (3%) had a high likelihood of CAD. The demographic data are summarized in Table I.

Table I. Demographic data for patients in the 3 groups

	Group 1 (n = 33)	Group 2 (n = 32)	Group 3 (n = 35)
Mean age (y)	59 (±10)	60 (±11)	61 (±10)
Sex (male)	19	21	23
Hypertension	15 (45%)	16 (50%)	29 (83%)*
Diabetes	5 (15%)	3 (9%)	5 (6%)
Myocardial infarction	1 (3%)	1 (3%)	13 (37%)
Percutaneous coronary intervention	4 (12%)	3 (9%)	10 (39%)
Coronary bypass	4 (12%)	3 (9%)	6 (17%)
β-Blockers	12 (36%)	10 (31%)	24 (69%)*
Mean resting HR (beats/min)	67 (±13)	71 (±13)	66 (±12)
Mean resting BP (mm Hg)	131 (±20)	129 (±16)	132 (±14)

*$P < .05$.

Group 3 (horizontal or downsloping). Group 3 consisted of 35 patients with >1 mm horizontal or downsloping ST depression at 0.08 seconds beyond the J point. Thirty patients (86%) had an intermediate likelihood, 1 patient (3%) had a low likelihood, and 4 patients (11%) had a high likelihood of CAD. The demographic data are summarized in Table I.

Treadmill protocol

After giving informed consent, the patients underwent ETT according to standard Bruce protocol. The patients were advised not to drink anything except water after midnight on the night before the test. The patients continued the use of cardiac medications on the day of the test. Symptoms, ECG, heart rate, rhythm, and BP were recorded in supine and standing positions before the test. Midway through each stage, peak exercise, and at 1, 3, 5, and 8 minutes into recovery, 12-lead

Table II. Mean (±SD) ETT and SPECT myocardial perfusion data for the 3 groups

	Group 1 (n = 33)	Group 2 (n = 32)	Group 3 (n = 35)
ETT time (min)	8.8 (±3)	8.6 (±3)	7.6 (±3)
Achieved peak HR	145 (±20)	149 (±24)	136 (±17)*
Peak BP	182 (±17)	185 (±24)	174 (±24)
SSS	3.5 (±5)	2.6 (±4)	11.4 (±10)†
SRS	1.4 (±3)	0.6 (±2)	6.5 (±8)†
SDS	2.1 (±4)	1.9 (±4)	5.2 (±4)†
SE% (CEqual)	4.9 (±7)	4.1 (±7)	18.3 (±15)†
RE% (CEqual)	2.2 (±5)	1.7 (±5)	7.7 (±9)†
LHR	0.41 (±0.1)	0.39 (±0.1)	0.47 (±0.1)†
Ejection fraction	60 (±10)	63 (±9)	59 (±13)
LV end-diastolic volume (mL)	86 (±30)	81 (±27)	90 (±34)

95% CI for differences of mean between groups 1 and 2 were as follows: SSS (−1.34 to 3.19); SRS (−0.45-1.99); SDS (−1.73-2.04); SE% (−2.65-4.28), RE% (−1.75-2.86) and LHR (−0.03-0.05).
*$P < .05$.
†$P < .001$.

ECG, heart rate, BP, rhythm, and symptoms were recorded. The exercise protocol was symptom limited, and patients were encouraged to stop the exercise at peak symptoms rather than at achievement of age-related target heart rate. The stress test was terminated if there was severe anginal pain, a fall in BP (≥20 mm Hg), significant arrhythmia, or >2 mm horizontal or downsloping ST depression from baseline. The PR segment was considered as the isoelectric line, and the ST-segment depression was measured 0.08 seconds after the J point. Each of the changes had to be detected in 2 or more leads on comparison with the pretest supine ECG to be included in the study. The ST-segment changes in leads aVr and V_1 were not considered for analysis. Peak heart rate (peak HR), percent peak HR ([peak HR/220 – age] × 100), and peak BP were computed in each patient. The monitoring was terminated at 8 minutes in recovery unless warranted by persistent ST-segment changes or symptoms. All the ECG tracings were analyzed in a blinded manner by 3 independent observers at different times (M. Y. D., F. M., and S. C.), without knowledge of the myocardial perfusion results, and differences were resolved by consensus.

SPECT myocardial perfusion imaging

A stress-rest imaging protocol was used. Eight to 10 mCi (based on weight) technetium 99m tetrofosmin was administered at peak stress, and the patient continued to exercise for 1 minute after the injection. Stress imaging was performed 20 to 40 minutes after tracer administration. Three to 4 hours later, 24 to 30 mCi (based on weight) ^{99}Tc tetrofosmin was injected at rest. Rest imaging was performed 20 to 40 minutes after tracer administration.

A 3-headed camera (Prism, Picker Int, Cleveland, Ohio) equipped with low-energy, high-resolution collimators was used. Data were acquired in a 64 × 64 matrix, >180 degrees from LPO 45 to RAO 45, 32 angles, 25 s/angle for the stress study, and 20 s/angle for the rest study. All studies were reconstructed by using filtered back projection (ramp). A low-pass filter was applied (order 0.5 with cutoff 0.33 for rest studies and order 0.5 with cutoff 0.25 for stress studies). Software zoom was subsequently applied, and the data were reformatted to short axis, vertical long axis, and horizontal long axis (6 mm), according to the individually determined anatomic cardiac long axes. The stress and rest studies were carefully aligned and displayed simultaneously on a high-resolution monitor with a standard color table for visual semiquantitative analysis.

Assessment of regional myocardial perfusion

A 20-segment myocardial model was used, and visual summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were calculated with a 5-point scoring system[10] (0 = normal perfusion, 1 = equivocal perfusion, 2 = moderatedly decreased perfusion, 3 = severe perfusion defect, and 4 = no perfusion). The myocardial perfusion results were divided into 4 categories on the basis of the SDS (degree of ischemia): normal (0-3), mildly abnormal (4-8), moderately abnormal (8-13), and severely abnormal (>13). Quantitative analysis of myocardial perfusion was also performed with the CEqual method.[11] With this method the extent (percent of total myocardium) of stress and reversible perfusion abnormalities were computed.

Evaluation of global LV function and volumes

The rest SPECT acquisition was gated to the R wave, and the cardiac cycle was divided into 8 frames, with an acceptance window of ±20% around the mean R-R interval during 1 minute before the study. The LV ejection fraction and LV end-diastolic volume (in milliliters) were calculated with the commercially available QGS software (Los Angeles, Calif).[12]

Lung-heart ratio

The stress lung-heart ratio (LHR) was determined by measuring the mean counts in a 4 × 4 pixel ROI over the region of the heart with the highest tracer uptake in the anterior view, and over the pulmonary area just above the heart. Lung uptake was considered abnormal when the ratio was ≥0.45.[13-15]

Assessment of stress/rest LV cavity-size ratio

Nongated LV volumes were determined from the rest and stress study by using the QGS software. A stress/rest volume ratio was calculated. A volume ratio >1.21 was considered abnormal.[16]

Statistical analysis

All values are given as mean ±1 SD. Comparison between groups was performed by analysis of variance. The χ^2 test and Fisher exact test were used for comparison of proportions. A P value <.05 was considered significant.

Results

The ETT data from the 3 groups are summarized in Table II. Mean achieved peak heart rate was similar in groups 1 and 2 but significantly lower in group 3 (Table II). Twenty-six patients (79%) in group 1, 28 patients (87%) in group 2, and 22 patients (62%) in group 3 ($P < .05$) achieved 85% of age-related maximal heart rate. Six patients (18%) in group 1, 5 patients (16%) in group 2, and 12 patients (34%) in group 3 ($P < .05$) had typical anginal chest pain symptoms during

Table III. Incidence of ischemia in the 3 groups

	Group 1 (n = 33)	Group 2 (n = 32)	Group 3 (n = 35)
Ischemia			
None	61%	75%	23%*
Mild	24%	13%	34%
Moderate to severe	15%	12%	43%
TID of LV cavity	0%	3%	23%
Abnormal LHR	15%	15%	51%†

*$P < .05$;
†$P < .001$.

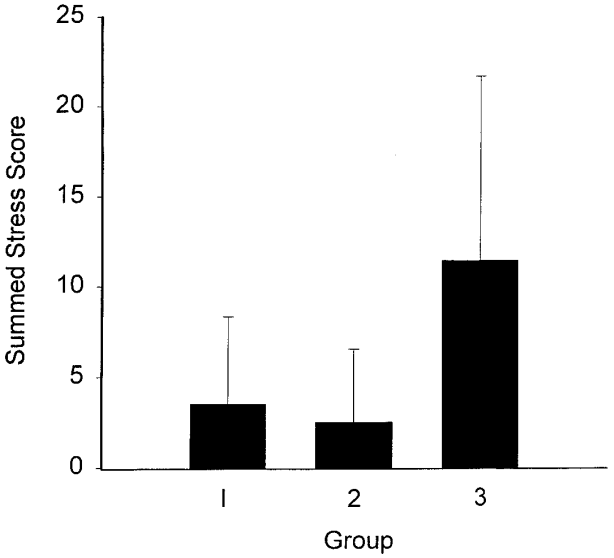
exercise. The rest of the patients in all groups stopped the exercise because of fatigue.

The mean SPECT perfusion and quantification scores are summarized in Table II. The severity of ischemia (mean SSS, SDS, RE% by CEqual) was similar in groups 1 and 2 but significantly higher in group 3 (Table III and Figure 2). The incidence of normal perfusion scans was similar among patients in groups 1 and 2 but significantly lower in patients in group 3 (Table III). Evidence of ischemia was seen in 39% of patients in group 1, 25% of patients in group 2, and 77% of patients in group 3.

There was no significant difference in mean global systolic LV function or LV volumes between the 3 groups (Table II). However, none of the patients in group 1, 3% of patients in group 2, and 23% of patients in group 3 had evidence of transient ischemic dilatation (TID) of LV cavity with stress (Table III).

Similarly, mean LHR was significantly greater in group 3 than in groups 1 and 2 (Table II). Also, the incidence of abnormal LHR was significantly lower in groups 1 and 2 as compared with group 3 (Table III).

Figure 2



Mean and SD bars of SSS in 3 groups. Group 1, 3.5 (±5); group 2, 2.6 (±4); group 3, 11.4 (±10). $P < .001$.

Discussion

Identification of patients with severe ischemia and extensive CAD is a major objective of noninvasive cardiac testing. Once identified, these patients are often considered candidates for more aggressive treatment or intervention. Such an approach makes it vital to have accurate diagnostic and prognostic data. It is widely believed that slow upsloping ST-segment depression during exercise carries a worse prognosis because it predicts more ischemia and extensive CAD.[1,2,5-7] A major shortcoming of this assumption is that it is based on older, retrospective studies that have used a reference of >50% to 70% coronary artery stenosis on coronary angiography (an anatomic marker of CAD). Also, angiographically defined CAD does not take into consideration the functional significance of a coronary artery lesion or the presence of small-vessel CAD and their contribution to an ischemic response during exercise or the degree of collateral circulation.

We conducted this study to determine whether patients with slow upsloping ST-segment depression have significant ischemia or extensive CAD by using functional markers of CAD. We also enrolled patients who had rapid upsloping ST-segment depression (nonischemic response to exercise) and horizontal or downsloping ST-segment depression (ischemic response to exercise) for comparison. The patients were enrolled only on the basis of the types of ST-segment changes during exercise.

This study confirms prior observations that patients with horizontal or downsloping ST-segment depression have a greater extent and severity of ischemia on myocardial perfusion images.[1,2] It also confirms that patients with rapid upsloping ST-segment depression during exercise should be considered at low risk for CAD.[1-4]

In the present study, the extent and severity of myocardial ischemia (with the use of qualitative and quantitative SPECT techniques) in patients with slow upsloping ST changes during exercise was very similar to patients with rapid upsloping ST-segment changes and significantly less than patients with horizontal or downsloping ST changes (Table III and Figure 2). In fact, 75% of patients with slow upsloping ST changes (compared with 23% with horizontal or downsloping ST changes) had entirely normal myocardial perfusion images, and only 12% of patients (compared with 43% with horizontal or downsloping ST changes) had evidence of moderate or severe ischemia.

Increased tracer uptake in the lung has been shown to reflect stress-induced LV dysfunction and is considered a bad prognostic sign.[13-15] It is most likely the result of augmented pulmonary transit time, with enhancement of extraction and increases in interstitial water or pulmonary permeability. In the present study, there was no difference in the mean LHR between patients in groups 1 and 2, but patients in group 3 had a significantly higher ratio (Table III). There was also no difference in the incidence of an abnormal uptake between groups 1 and 2 (15% and 15%), but there was a significantly higher incidence in group 3 (51%).

TID of the LV cavity during stress is also considered a poor prognostic sign because it may indicate extensive CAD.[16] In fact, patients with extensive CAD who have an abnormal cavity dilatation with stress have a worse outcome than those with no cavitary dilatation. In the present study, TID of the LV cavity during stress was noted in 3% of patients in group 2 and 23% of patients in group 3. Although statistical analysis was not possible because of the very low number of patients in groups 1 and 2 (0 and 1, respectively), a trend toward a low incidence of cavitary dilatation with stress among patients with slow upsloping ST depression was evident, similar to that among patients with rapid upsloping ST depression.

On the basis of the present study, it can be inferred that patients with slow upsloping ST-segment depression during exercise have a low incidence of ischemia (on the basis of both qualitative and quantitative SPECT criteria). They also have a low incidence of backward LV failure. Hence, these patients should be considered as having a very low likelihood of CAD.

Although this study was not powered to determine sensitivity or specificity of slow upsloping ST-segment changes during exercise, it can be indirectly inferred that considering this finding as a "positive" response to exercise might increase the sensitivity but significantly reduce the specificity and positive predictive value of exercise stress testing with significant economic consequences.

Limitations of this study

We excluded patients who had baseline ECG abnormalities such as nonspecific STT changes, bundle branch blocks, pacemaker, and patients who had LV hypertrophy or were being treated with digoxin. One can argue that this was a selected group not representative of all the CAD patients undergoing ETT. However, we deliberately used these strict selection criteria to avoid the effects of resting ECG changes and drug therapy on the interpretation of ETT. There was a trend (statistical analysis of all the demographic data was not feasible because of less incidence in groups 1 and 2) toward a higher incidence of hypertension, myocardial infarction, and β-blocker usage in group 3, but that was expected because these patients had more extensive CAD retrospectively. In our opinion, it was not a confounding factor because the patients had similar pretest likelihood of CAD and were divided into 3 groups only on the basis of ST-segment changes during exercise. Correlation with angiography was not the aim of the study, and a statistical analysis was not feasible because only a few patients in the study underwent coronary angiography. For the purposes of analysis, a normal myocardial perfusion scan at peak exercise was considered to be a negative response for inducible ischemia. Given the sensitivity (mid 90s) and specificity (mid to high 80s) of ^{99}Tc myocardial perfusion imaging, some patients with a normal scan could certainly have CAD. However, it has been shown that a normal perfusion scan at peak exercise carries a <1% risk for cardiac death and nonfatal myocardial infarction.[17]

Conclusion

On the basis of the present study, we infer that slow upsloping ST-segment depression does not signify more severe ischemia, more extensive CAD, or more stress-induced backward LV failure. Thus, it would be reasonable to consider patients with slow upsloping ST-segment changes during exercise as having a very low likelihood of CAD, similar to patients with rapid upsloping ST-segment depression.

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References

1. Chaitman BR. Exercise stress testing. In: Braunwald E, Zipes DP, Libby P, editors. Heart disease: a textbook of cardiovascular medicine. 6th ed. Philadelphia: WB Saunders; 2001. p. 129-55.
2. Ellestad MH. ECG patterns and their significance. In: Ellestad MH, editor. Stress testing: principles and practice. 4th ed. Philadelphia: FA Davis; 1996. p. 237-91.
3. Ellestad MH, Wan M. Predictive implications of stress testing. Circulation 1975;51:363-7.
4. Robb GP, Marks HH. Postexercise electrocardiograms in arteriosclerotic heart disease: its value in diagnosis and prognosis. JAMA 1967;200:918-26.
5. Goldschlager N, Selzer A, Cohn K. Treadmill stress tests as indicators of presence and severity of coronary artery disease. Ann Intern Med 1976;85:277-86.
6. Stuart RJ, Ellestad MH. Upsloping ST segments in exercise stress testing: six-year follow-up study of 438 patients and correlation with 248 angiograms. Am J Cardiol 1976;37:19-22.
7. Kurita A, Chaitman BR, Bourassa MG. Significance of exercise induced junctional ST depression in evaluation of coronary artery disease. Am J Cardiol 1977;40:492-7.
8. Sansay V, Watson DD, Beller GA. Significance of slow upsloping ST segment depression on exercise stress testing. Am J Cardiol 1997;79:709-12.
9. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on

Practice Guidelines (Committee on Exercise Testing). Circulation 1997;96:345-54.
10. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium 201/stress technetium-99m sestamibi dual isotope myocardial single photon emission computed tomography: a clinical validation study. J Am Coll Cardiol 1993;22:1455-64.
11. Garcia EV, Cooke CD, Van Train KF, et al. Technical aspects of myocardial perfusion SPECT imaging with technetium-99m sestamibi. Am J Cardiol 1990;66:23-31E.
12. DePuey EG, Nichols KN, Dobrinsky C. Left ventricular ejection fraction from gated technetium-99m-sestamibi SPECT. J Nucl Med 1993;34:1871-6.
13. Bachier-stier C, Sarir T, Kavanagh PB, et al. Post exercise lung uptake of 99m Tc-sestamibi determined by a new automatic technique: validation and application in determination of severe and extensive coronary artery disease and reduced left ventricular function. J Nucl Med 2000;41:1190-7.
14. Hurwitz GA, Fox SP, Driedger AA, et al. Pulmonary uptake of sestamibi on early post-stress images: angiographic relationships, incidence and kinetics. Nucl Med Commun 1993;14:15-22.
15. Kumita S, Nishimura T, Uehara T, et al. Increased lung uptake and transient left ventricular dilatation and stress myocardial scintigraphy with Tc-99-m sestamibi. Kaku Igaku 1993;30:621-6.
16. Mazzanti M, Germano G, Kiat H, et al. Identification of severe and extensive coronary artery disease by automatic measurement of transient ischemic dilatation of the left venricle in dual isotope myocardial perfusion SPECT. J Am Coll Cardiol 1996;27:1612-20.
17. Pamelia FX, Gibson RS, Watson DD, et al. Prognosis with chest pain and normal thallium-201 exercise scintigrams. Am J Cardiol 1985;55:920-6.