ELECTROCARDIOGRAPHIC AND HEMODYNAMIC EVALUATIONS OF ISOPROTERENOL TEST IN ELDERLY ISCHEMIC HEART DISEASE

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The validity of isoproterenol test in the diagnosis of ischemic heart disease in the aged was evaluated in 67 autopsied cases. The additional ST segment depression of 0.5 mm or greater of the ischemic type after the intravenous infusion of isoproterenol (ISP) at a rate of 0.02 $\mu\text{g/kg/min}$ for five minutes was considered to be the positive test.

The sensitivity in 25 severe coronary stenoses of 75% or more was 72.0%, and specificity in 42 mild coronary stenoses was 71.4%. The false negative results were observed in 6 cases of ten myocardial infarctions, and the false positive results were observed in 5 cases of seven stenotic valvular diseases. The sensitivity and specificity after excluding the myocardial infarction and stenotic valvular disease were 100% and 81.8%, respectively.

ST depression at rest was a poor indication of the coronary stenosis, and the specificity of the ISP test in the abnormal resting ST depression was 64.7%.

The increases in heart rate and cardiac index after ISP infusion were greater in severe coronary stenosis without myocardial infarction than in mild coronary stenosis, indicating the hypersensitivity to the beta-adrenergic stimulation. The hemodynamic responses in myocardial infarction to the ISP infusion were similar to the responses in mild coronary stenosis.

The isoproterenol test was a safe and useful method not only in the assessment of the coronary heart disease, but also in clarifying the pathophysiological mechanism.

THE evaluation of the ischemic heart disease in the elderly patients has encountered several difficulties. The subjective complaints of anginal attack are obscured by the loss of memories or dementia, and the objective exercise tests are hard to perform properly by the weakness of leg muscles. Nevertheless, the diagnosis of ischemic heart disease is needed in

various cardiac complaints, in cardiac failure of unknown etiology, and before the rehabilitation of the stroke, or the operative procedure.

Isoproterenol (ISP) infusion is known to provoke the similar hemodynamic changes to the exercise and to increase the myocardial oxygen demand by enhancing the heart rate and myocardial contractility. The ISP test has been employed in the diagnosis of ischemic heart disease.¹⁻⁴

In order to clarify the sensitivity and specificity of the ISP test, we correlated the ischemic changes in electrocardiogram with the

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TABLE I AGE AND SEX DISTRIBUTION OF THE PATIENTS

		Mild coronary sclerosis < 75%	Severe coronary sclerosis 75% ≤	Myocardial infarction	Stenotic valvular disease	Total
Cases		37	13	10	7	67
Age	mean SD	77.6 8.1	80.5 8.9	75.9 5.6	71.6 6.9	77.3 8.6
Sex	M : F	12 : 25	9 : 4	4 : 6	2 : 5	27 : 40

TABLE II ISOPROTERENOL TEST IN MILD AND SEVERE CORONARY STENOSES

		Coronary stenosis		Total
		< 75%	75% ≤	
ISP test	—	30 (71.4%)	7 (28.0%)	37
	+	12 (28.6%)	18 (72.0%)	30
Total		42	25	67

 $P < 0.001$

pathological findings of the coronary stenosis in 67 autopsied cases. The hemodynamic characteristics to the ISP infusion in ischemic heart disease were also evaluated.

METHODS

Sixty seven autopsied cases in which ISP infusion tests were performed three months to two years before death were the subjects of the study. Thirty seven cases were of mild coronary stenosis of less than 75%, and 13 cases were of severe coronary stenosis of 75% or more. Ten cases were of old myocardial infarction and seven cases were of aortic or mitral stenosis. The age and sex distributions are shown in Table I.

ISP test was performed in a supine position. ISP was infused at a rate of 0.02 $\mu\text{g/kg/min}$ for five minutes. The electrocardiograms were recorded before, during and until 5 minutes after the ISP infusion. Bipolar lead of C_5-C_{5R} was used. QRS-ST junction deviation was measured from a line connecting the onset of QRS complexes. The additional horizontal or down-sloping ST depression of 0.5 mm or more in comparison with the pre-infusion tracing was defined as a positive response. Blood pressure and cardiac output by means of dye dilution method were measured before and after the ISP infusion. At autopsy, epicardial coronary arteries were cross-sectioned by 3 to 5 mm apart, and the narrowing of the cross sectional area of

75% or more was defined as a severe stenosis. Sensitivity was expressed as a percent of positive tests in severe coronary sclerosis, and specificity was expressed as a percent of negative tests in mild coronary sclerosis.

RESULTS

1. Isoproterenol test in the electrocardiographic diagnosis of the coronary stenosis

The sensitivity and specificity of the ISP test in 67 cases are shown in Table II. The positive ISP test was found in 18 out of 25 cases of the severe coronary stenosis of 75% or more, and the sensitivity was 72.0%. The negative ISP test was found in 30 out of 42 cases of mild coronary stenosis of less than 75%, and the specificity was 71.4% showing the significant difference.

Six out of 10 cases of old myocardial infarction showed false negative test. In stenotic valvular disease of aortic or mitral valve, 5 out of 5 cases with mild coronary stenosis showed false positive test. In 10 cases of regurgitant valvular diseases only one false positive test was observed (Table III).

Thus, in 50 cases excluding myocardial infarction and stenotic valvular diseases the sensitivity was 100%, and the specificity was 81.1% (Table IV).

The severity of coronary stenosis was correlated with the ISP test (Table V). The false positive test in mild coronary stenosis of less

TABLE III ISOPROTERENOL TEST IN MYOCARDIAL INFARCTION, AND IN STENOTIC AND REGURGITANT VALVULAR DISEASES

Myocardial infarction

		Coronary stenosis		Total
		< 75%	75% ≤	
ISP test	—	0	6	6
	+	0	4	4
Total		0	10	10

Stenotic valvular diseases (MS, AS)

		Coronary stenosis		Total
		< 75%	75% ≤	
ISP test	—	0	1	1
	+	5	1	6
Total		5	2	7

Regurgitant valvular diseases (MR, AR)

		Coronary stenosis		Total
		< 75%	75% ≤	
ISP test	—	8	0	8
	+	1	1	2
Total		9	1	10

 $P < 0.05$

TABLE IV ISOPROTERENOL TEST IN MILD AND SEVERE CORONARY STENOSIS EXCLUDING MYOCARDIAL INFARCTION AND STENOTIC VALVULAR DISEASES

		Coronary stenosis		Total
		< 75%	75% ≤	
ISP test	—	30 (81.1%)	0 (0)	30
	+	7 (18.9%)	13 (100 %)	20
Total		37	13	50

 $P < 0.001$

than 50% was observed in 21.4%, and in moderate coronary stenosis of 50% to 75% the false positive test was found in 17.4%. In severe coronary stenosis one vessel disease revealed slight ST depression, while in two vessel disease showed marked ST depression. ST depression in the resting electrocardiogram was observed in 21 cases in which severe coronary stenosis was

found only in 4 cases. In 17 cases of mild coronary stenosis with ST depression at rest ISP test was negative in 11 cases (67.4%) indicating the poor reliability of ST depression in the resting electrocardiogram as well as the validity of the ISP test in these cases.

2. Hemodynamic responses to isoproterenol in coronary heart disease.

TABLE V ISOPROTERENOL TEST IN VARIOUS GRADES OF CORONARY STENOSES

		Coronary stenosis				Total
		50%	50 ≤ < 75	75% ≤		
				One vessel	Two vessels	
ISP test		11 (4)	19 (7)	0	0	30 (11)
	Ischemic type 0.5—0.9	3 (3)	1 (1)	5 (1)	1 (1)	10 (6)
	Ischemic type 1.0mm—	0	2 (1)	2 (1)	5 (1)	9 (3)
	ST. Elevation	0	1 (1)	0	0	1 (1)
	Total	14	23	7	6	50

() ST depression present at rest.

TABLE VI HEMODYNAMIC CHANGES AFTER ISOPROTERENOL TEST (mean ± SD)

	Mild coronary stenosis n = 27		Severe coronary stenosis n = 10		Myocardial infarction n = 9	
	before	after	before	after	before	after
Heart rate /min	74.1 (12.1)	97.3 (12.1)	66.1 (13.1)	106.6* (18.7)	70.4 (9.4)	94.8 (13.3)
Cardiac index L/min/m ²	2.64 (0.83)	3.65 (1.11)	2.37 (0.36)	3.99* (0.73)	2.41 (0.71)	3.48 (1.47)
Stroke index ml/m ²	36.3 (12.3)	37.9 (12.7)	37.2 (9.6)	39.0 (12.4)	34.2 (12.0)	36.2 (12.5)
Systolic blood pressure mmHg	140.2 (30.3)	140.4 (27.6)	152.6 (34.9)	149.8 (30.4)	167.8 (30.2)	168.4 (24.5)
Diastolic blood pressure mmHg	73.5 (14.8)	70.6 (14.3)	77.8 (12.6)	76.7 (22.2)	84.9 (27.2)	77.8 (15.0)
Mean blood pressure mmHg	95.7 (18.0)	93.7 (17.2)	102.6 (17.6)	99.0 (16.1)	112.4 (25.6)	108.0 (15.4)
TPRI	3152 (1048)	2224 (800)	3520 (704)	2112* (608)	4120 (1424)	2840 (1056)

TPRI: Total peripheral resistance index, dyne. sec. cm⁻⁵. m²* $p < 0.01$ (Δ mild: Δ severe c. s.)

Hemodynamic data before and after the ISP infusion are shown in Table VI. Heart rate in severe coronary stenosis was lower than in mild stenosis before ISP, but increased significantly after ISP. The increase in heart rate after ISP was significantly larger in the severe coronary stenosis than in the mild stenosis. In myocardial infarction increase in heart rate was similar to the mild stenosis.

The cardiac index before ISP showed no difference in each group. However, the increase

in cardiac index after ISP was significantly larger in the severe coronary stenosis than in the mild stenosis, indicating the hyperresponsiveness to the beta-adrenergic stimulation in the severe coronary stenosis. In myocardial infarction increase in cardiac index was similar to the mild stenosis. The stroke index increased slightly in each group.

The systolic blood pressure showed no change after ISP in each group, and diastolic blood pressure declined slightly, thereby lowering mean

blood pressure in each group by similar amount. The total peripheral resistance index decreased after ISP in each group, but the decrease in severe coronary stenosis was significantly greater than in the mild stenosis.

DISCUSSION

The present study indicated that the sensitivity and the specificity of the ISP infusion test in the diagnosis of the coronary stenosis were 100% and 81.1% respectively, when myocardial infarction and stenotic valvular diseases were excluded. In other words, severe coronary stenosis was found in 65% of the positive ISP test, while no severe coronary stenosis was observed in the negative ISP test.

Isoproterenol increases myocardial oxygen consumption by elevating the heart rate and myocardial contractility, and produce a similar effect to the exercise.^{4,5} There exists the need in the geriatric patients for a screening test which can be applied safely in the outpatient setting. Isoproterenol infusion test has been used by several authors for differentiating normal subjects from coronary disease patients. Kimura et al.³ administered ISP of 2 $\mu\text{g}/\text{min}$ for 4 to 20 minutes and found ST depression in 21 of 25 patients of angina, and anginal pain was observed in 15 cases. Wexler et al.² utilized ISP of to 2 $\mu\text{g}/\text{min}$ until a heart rate of 130/min was obtained, and found to be able to differentiate normal from the old myocardial infarction. They observed that none of the patients had any chest pain during or after the ISP infusion. In predicting the presence of coronary artery disease Combs and Martin¹ found the ISP test (71%) to be comparable to the treadmill exercise test (68%). We compared the severity of ST segment depression in ISP and exercise test at the similar heart rate response, and found greater ST depression in ISP test than exercise test.⁴ We also defined the dose of the ISP infusion as 0.02 $\mu\text{g}/\text{kg}/\text{min}$ for five minutes. Since the heart rate response to the same ISP dose was greater in the severe coronary stenosis, a fixed dose of ISP would be a sensitive measure to differentiate from the control subjects. As a result of the small dose used, we had no untoward reaction. The anginal pain or premature beats of ventricular origin were quite rare even though the patients had abnormal ST responses.

The severity of ST depression after ISP test has been correlated with the extent of narrowing and the number of the stenotic branches in the

present study. Bartel et al.⁶ found the positive exercise test in one, two and three vessel diseases to be 40%, 60% and 76% respectively. Kaplan et al.⁷ reported that positive treadmill test was found when coronary stenosis exceeded 75%, and stress test was of no value in predicting the specific coronary artery involved. However, marked ST segment depression in exercise testing aided in identifying the triple vessel disease or proximal lesions of the left anterior descending artery.⁸

The present results indicated that ST-T abnormalities in the resting electrocardiogram were poor indicators of severe coronary stenosis, and ISP test could differentiate the non-coronary ST-T changes from the coronary stenosis. Cohn et al.⁹ examined the postexercise electrocardiogram in patients with abnormal resting electrocardiogram, and revealed that 86% of coronary artery disease and 27% of the normal coronary artery group had positive postexercise electrocardiograms. Similar results were reported by Kansal et al.¹⁰ by means of near maximal graded exercise test and coronary angiogram. Using the criteria of additional ST segment depression of 0.1 mV or more the sensitivity of the stress test was 0.92, and the specificity was 0.75. Linhart and Turnoff¹¹ also found that the validity of exercise test in differentiating the coronary artery disease was only slightly reduced with control ST-T abnormalities.

The false positive results in ISP test was observed frequently in patients with stenotic valvular disease or old myocardial infarction. Aronow and Harris¹² found the false positive exercise test to be in 37% with aortic stenosis and in 20% with mitral stenosis and attributed this false results to an unfavorable balance between myocardial oxygen supply and demand. The results were controversial in myocardial infarction. Wexler et al.² found ST depression by ISP test in old myocardial infarction, while we found false negative results in 60%. Borer et al.¹³ also reported false negative exercise test in 67% of patients with old myocardial infarction, typical angina or both. The coronary sclerosis supplying non infarction area might be responsible to these discrepancies.

The hemodynamic responses after ISP infusion were enhanced in severe coronary stenosis in the present results. Horwitz et al.¹⁴ found the increase in cardiac output after isoproterenol to be greater in the coronary disease than in the normal group. In the coronary disease the

percent increase in coronary blood flow was less than the percent increase in cardiac output. On the other hand, Cohen et al.¹⁵ showed that the response of cardiac output to isoproterenol in the anginal group was smaller than the nonanginal and normal subjects. From these results, augment hemodynamic responses to the beta adrenergic stimulation in severe coronary stenosis increased the myocardial oxygen consumption and induced coronary insufficiency. These responses might be counterbalanced by the myocardial loss or failure in the myocardial infarction.

REFERENCES

1. COMBS, D. T. & MARTIN, C. M.: Evaluation of isoproterenol as a method of stress testing. *Am. Heart J.* 87: 711, 1974.
2. WEXLER, H., KUAITY, J. & SIMONSON, E.: Electrocardiographic effects of isoprenaline in normal subjects and patients with coronary atherosclerosis. *Brit. Heart J.* 33: 759, 1971.
3. KIMURA, E., USHIYAMA, K., KIKUCHI, H. & MABUCHI, G.: Diagnosis of angina pectoris by intravenous infusion of isoproterenol. *J. Jap. Soc. Intern. Med.* 57: 944, 1968. (in Japanese)
4. KURAMOTO, K., MATSUSHITA, S., MIFUNE, J., SAKAI, M., KUWAJIMA, I., IWASAKI, T. & MURAKAMI, M.: Diagnosis of ischemic heart disease of the aged by isoproterenol infusion test, the hemodynamic and electrocardiographic evaluations. *Saishin-Igaku* 32: 1006, 1977. (in Japanese)
5. KRASNOW, N., ROLETT, E. L., YURCHAK, P. M., HOOD, W. B. & GORLIN, R.: Isoproterenol and cardiovascular performance. *Am. J. Med.* 37: 514, 1964.
6. BARTEL, A. G., BEHAR, V. S., PETER, R. H., ORGAIN, E. S. & KONG, Y.: Graded exercise stress tests in angiographically documented coronary artery disease. *Circulation* 49: 348, 1974.
7. KAPLAN, M. A., HARRIS, C. N., ARONOW, W. S., PARKER, D. P. & ELLESTAD, M. H.: Inability of the submaximal treadmill stress test to predict the location of coronary disease. *Circulation* 47: 250, 1973.
8. GOLDMAN, S., TSELOS, S. & COHN, K.: Marked depth of ST-segment depression during treadmill exercise testing. Indicator of severe coronary artery disease. *Chest* 69: 729, 1976.
9. COHN, P. F., VOKONAS, P. S., HERMAN, M. V. & GORLIN, R.: Postexercise electrocardiogram in patients with abnormal resting electrocardiograms. *Circulation* 43: 648, 1971.
10. KANSAL, S., ROITMAN, D. & SHEFFIELD, L. T.: Stress testing with ST-segment depression at rest: An angiographic correlation. *Circulation* 54: 636, 1976.
11. LINHART, J. W. & TURNOFF, H. B.: Maximum treadmill exercise test in patients with abnormal control electrocardiograms. *Circulation* 49: 667, 1974.
12. ARONOW, W. S. & HARRIS, C. N.: Treadmill exercise test in aortic stenosis and mitral stenosis. *Chest* 68: 507, 1975.
13. BORER, J. S., BRENSIKE, J. F., REDWOOD, D. R., ITSCOITZ, S. B., PASSAMANI, E. R., STONE, N. J., RICHARDSON, J. M., LEVY, R. I. & EPSTEIN, S. E.: Limitations of the electrocardiographic response to exercise in predicting coronary-artery disease. *New Engl. J. Med.* 293: 367, 1975.
14. HORWITZ, L. D., CURRY, G. C., PARKEY, R. W. & BONTE, F. J.: Differentiation of physiologically significant coronary artery lesions by coronary blood flow measurements during isoproterenol infusion. *Circulation* 49: 55, 1974.
15. COHEN, L. S., ELLIOTT, W. C., ROLETT, E. L. & GORLIN, R.: Hemodynamic studies during angina pectoris. *Circulation* 31: 409, 1965.