ORIGINAL

Mechanism of ST segment depression during exercise tests in patients with liver cirrhosis

Toshifumi Mori[1], Masahiro Nomura[2], Ayuko Hori[3], Noriyasu Kondo[1], Shigenobu Bando[4], and Susumu Ito[1]

[1]*Department of Digestive and Cardiovascular Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School,* [2]*Faculty of Integrated Art and Sciences, The University of Tokushima,* [3]*Department of Radiology, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima ; and* [4]*Division of Cardiology, Kagawa Prefectural Shirotori Hospital, Kagawa, Japan*

Abstract : *Purpose :* To our experience, ST segment depression is sometimes detected in an exercise electrocardiogram (ECG) test in patients with liver cirrhosis who have no significant coronary stenosis. In this study, the mechanism of ST segment depression in liver cirrhosis was examined using ^{99m}Tc-methoxy-isobutyl-isonitrile (MIBI) myocardial scintigraphy.
***Methods :* Six patients with liver cirrhosis (LC group), and 15 normal subjects (N group) were examined. To evaluate the level of myocardial blood flow, a Bull's eye display of myocardial blood flow was performed after dividing the left ventricle into 9 segments. Exercise myocardial scintigraphy with MIBI was performed to obtain the increase in % uptake. Angiographies were performed with a CAG system by inserting a 5 French Judkins catheter via the right femoral artery.**
***Results :* No significant coronary stenosis was found in any of the LC patients. Neither a decrease in MIBI uptake nor defect was observed on Bull's eye images from the LC group. The mean % uptake increase was 61.0 ± 5.6% in the N group. In the LC group, although neither a decrease in MIBI uptake nor a defect was visually observed on Bull's eye images obtained during exercise, the % uptake increases (mean : 52.5 ± 5.8%) were lower than those of the N group (p<0.05).**
***Conclusion :* These findings suggest that a disorder in coronary flow reserve occurs in liver cirrhosis patients, because the decreased MIBI uptake during exercise is due to the depression of flow-mediated vasodilatation controlled by the endothelium of the coronary artery and the estrogenic digitalis action of blood flow independency. J. Med. Invest. 54 : 109-115, February, 2007**

***Keywords* :** *liver cirrhosis, exercise test, ST-T abnormality, coronary microcirculation, digitalis-like effects*

INTRODUCTION

We sometimes experienced that ST segment depression is detected in exercise electrocardiogram (ECG) tests in patients with liver cirrhosis who have no significant coronary stenosis. It is thought that a hormone imbalance and a disorder in the microcirculation of the coronary artery are responsible, but the subject had not been studied the detail until now.

Coronary arterial hemodynamics can be easily detected by myocardial scintigraphy, and not only coro-

Received for publication December 4, 2006 ; accepted December 27, 2006.

Address correspondence and reprint requests to Toshifumi Mori M.D., Department of Digestive and Cardiovascular Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-9235.

nary artery stenosis but the evaluation of the coronary microcirculation is possible (1). Moreover, coronary arterial flow reserve can be predicted by quantitatively evaluating the level of accumulation of myocardial radioisotope during exercise and at rest (2).

In the present study, the mechanism of ST segment depression in liver cirrhosis was examined using ^{99m}Tc-methoxy-isobutyl-isonitrile (MIBI) myocardial scintigraphy from the viewpoint of micovascular coronary circulation.

METHODS

1) Subjects (Table 1)

Six patients with liver cirrhosis, and age-matched 15 normal subjects were examined. The subjects were 15 healthy male adults (N group ; mean age : 60.3 ± 9.8 years) and 6 HCV antibody-positive male patients with liver cirrhosis (LC group : mean age : 61.4 ± 8.6 years). The N group subjects were evaluated as being clinically healthy, based on normal physical findings, a resting blood pressure of 140/90 mmHg or less, and the absence of abnormalities in a standard 12-lead ECG, chest X-ray, urinalysis, and blood biochemistry findings, with no history of cardiopulmonary disease.

In the LC group, the etiology of cirrhosis was a chronic HCV infection in all patients. Patients with alcoholic or hepatitis B-related liver cirrhosis were excluded from the study. The diagnosis of liver cirrhosis was made based on patient history, a physical examination, biochemical blood tests, coagulation function tests, upper gastrointestinal endoscopy, abdominal ultrasonography, and a liver biopsy. Patients in whom esophageal varices were demonstrated by upper gastrointestinal endoscopy, and in whom a reduction in liver size, irregularity of the liver surface, and the presence of splenomegaly were confirmed by abdominal ultrasonography, were selected as subjects. Moreover, all patients of the LC group showed a ST-T abnormality in treadmill stress ECG. However, patients with abnormal coronary angiographic findings, patients with liver cirrhosis of uncompensated stage and patients who exercise test is impossible were excluded from the present study.

Table 1 Patients characteristics

	N group	LC group
Age (years)	60.3±9.8	61.4±8.6
T-Bil (mg/dl)	0.7±0.2	1.4±0.3
Alb (mg/dl)	3.9±0.3	3.3±0.4
Child stage		
Child A		4
Child B		2
Child C		0

T-Bil, total birilbin ; Alb, albumin ; * p<0.05 vs N group

No history of cardiopulmonary disease was evident in the LC group. Chest X-rays, and echocardiograms revealed no abnormalities. The criteria for exclusion were : smokers, systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, hyperlipidemia, recent gastrointestinal bleeding, diabetes mellitus, obese (body mass index > 25.0) and neurological disease. In addition, the subjects in the LC group consisted of 4 of Child A patients and 2 with Child B patients (Table 1). These studies were approved by the local Ethics Committee, and the patients provided written, informed consent prior to their participation.

2) Treadmill exercise

The treadmill exercise ECG tests were performed using MAT-2100 (Fukuda Denshi, Tokyo, Japan). A positive ECG response for ischemia was defined as a 1 mm or greater horizontal or downsloping ST depression at 80msec after the J point during an exercise test. The targeted heart rate [(220-age) × 90%], chest pain, fatigued lower extremities, ST changes on ECG, or pressure-rate product levels were above 25,000. In this study, however, chest symptoms did not appear during exercise test in all subjects in the LC group.

3) Acquisition of myocardial single photon emission computed tomography (SPECT) images (Fig. 1)

The exercise tolerance test was performed using the one-day protocol of the stress-rest method, and the % uptake increase in blood flow during exercise

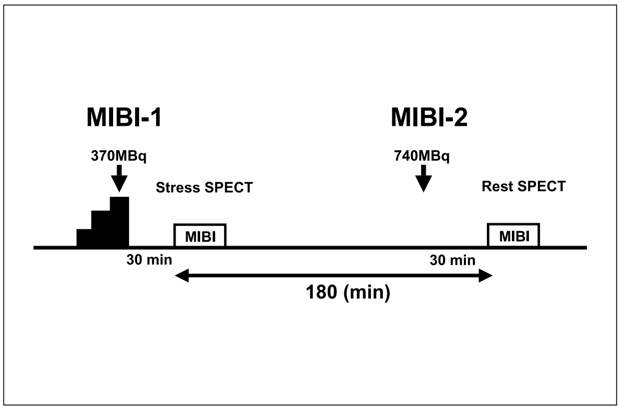

Fig. 1 Acquisition of myocardial SPECT images.
MIBI, ^{99m}Tc-methoxy-isobutyl-isonitrile ; SPECT, single photon emission computed tomography.

was evaluated by measuring the increase in uptake using MIBI. Using a cycle ergometer, the exercise tolerance test was started at 50 W, and the load intensity was gradually increased in 25 W increments at 3-minute intervals until one of the following conditions was observed as the same protocol of previous treadmill exercise : targeted heart rate [(220-age) × 90%], chest pain, fatigued lower extremities, ST changes on ECG, or pressure-rate product levels above 25,000. During the maximal load of exercise, 370 MBq of MIBI was administered intravenously, and the exercise was continued for another 90 seconds.

Using a three-headed gamma camera (PRISM 3000, PICKER/Shimadzu Corp., Kyoto, Japan) equipped with a low-energy, high-resolution collimator and an analytical computer (ODYSSEY, Shimadzu), SPECT images were acquired from 72 directions (64 × 64 matrices/direction for 30 seconds) at 5-degree intervals, which were used as the SPECT images during exercise (stress-SPECT). At 180 minutes after the scan of the stress SPECT, 740 MBq of MIBI was again administered intravenously, and resting SPECT images (rest-SPECT) were acquired 30 minutes later. During exercise and at rest, the radioactivity in the syringe was measured before and after the administration of MIBI using a dose calibrator (CURIEMETER ICG-3, Aloca, Tokyo, Japan), together with the radioactivity in the three-way valve after MIBI administration. The actual dose of MIBI was subsequently calculated based on the radioactivity before and after MIBI administration. The absence of any leakage from the injection site was confirmed by examining the injection site using a gamma camera during SPECT image acquisition.

4) Measurement of % uptake increase in coronary blood flow during exercise

To evaluate the level of myocardial blood flow, a Bull's eye display of myocardial blood flow was performed after dividing the left ventricle into 9 segments ; basal anterior wall, basal septum, basal lateral wall, basal inferior wall, middle anterior wall, middle septum, middle lateral wall, middle inferior wall, and apical region. The radioactivities in these 9 myocardial segments were subsequently measured on a rest-SPECT image and a stress-SPECT image in order to calculate the % uptake increase based on the corrected resting coefficient and the % increase in blood flow using the following equation :

$$\%\ \text{uptake increase} = [\{C1 \times R - (C2 - C1')\} / (C2 - C1')] \times 100 (\%)$$

C1 : radioactivity in the myocardium immediately after the initiation of exercise (stress-SPECT image)
C1' : decay correction of C1
C2 : radioactivity in the myocardium immediately after the initiation of exercise (rest-SPECT image)
R : ^{99m}Tc-MIBI dosage at rest)/^{99m}Tc-MIBI dosage at stress

5) Coronary angiography (CAG) and left ventriculography (LVG)

Angiographies were performed with a CAG system (Philips medical system, Tokyo, Japan) by inserting a 5 French Judkins catheter via the right femoral artery. The results were visually evaluated by 3 cardiologists. Based on the severity of stenosis in the proximal region of the main coronary artery, the presence of 75% or more stenosis was defined as a significant stenosis, while the presence of less than 25% stenosis was defined as normal. LVG was performed in the 30-degree right anterior and 60-degree left anterior oblique projections.

6) Statistical Analysis

All values are expressed as the mean ± standard deviation (SD), and statistical analyses were performed using StatView 5.0 (SAS Institute Inc. USA). Values were compared between the two groups using the unpaired t test. $P<0.05$ was regarded as significant.

RESULTS

1) Treadmill exercise test

Fig. 2 shows representative examples of ECGs during a treadmill exercise test of a 53 year old male liver cirrhotic patient. In the standard 12-lead ECG at rest (panel a), horizontal or down sloped ST depression was recognized in the I, II, III, aV_F, $V_{5,6}$ leads.

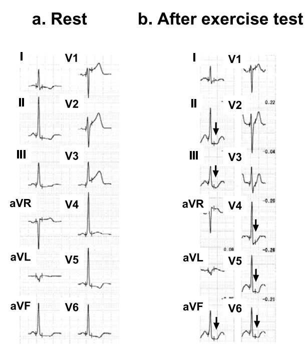

Fig. 2 Representative examples of ECGs during a treadmill exercise test. (53 year old male liver cirrhotic patient)

In the ECG immediately after the exercise test (panel b), a 1 mm greater horizontal and/or downsloping ST depression was recognized in the II, III, aV_F, $V_{4\text{-}6}$ leads, suggesting the presence of myocardial ischemia. In the present study, significant ST-T change in the treadmill exercise test was recognized in all patients of the LC group.

2) CAG and LVG

Fig. 3 shows the CAG and LVG for the same patient of Fig. 2. Neither the left nor right coronary artery showed any significant stenosis, and left ventricular wall motion was normal. No significant coronary stenosis was found in any of the other 5 patients in this study.

3) % uptake increase in blood flow during exercise

Fig. 4 shows a Bull's eye map of stress-SPECT and rest-SPECT images, and % uptake increase for a liver cirrhosis patient. Although neither a decreased MIBI uptake nor a filling defect was visually observed, the % uptake increase in each myocardial segment (48-55%) was lower than that in healthy subjects.

Table 2 shows a comparison of % uptake increases in 9 myocardial segments between the LC and N groups. The % uptake increase was significantly lower in the LC group than in the N group in all myocardial segments ($p<0.05$), indicating a decreased coronary flow reserve. However, there were no significant differences in the % uptake increases among the myocardial segments in liver patients. In the N group, although the % uptake increase in the middle lateral wall significant differed from that in the basal anterior wall, there were no significant differences in % uptake increases among other myocardial segments.

Table 2 Comparison of % uptake increases in 9 myocardial segments between the LC and N groups

	LC group	N group	p value
Total	52.8±5.8(%)	61.0±5.6(%)	<0.05
Apical.	48.6±4.4	56.9±5.4	<0.05
Mid. Lat.	58.4±3.9	67.9±7.1	<0.05
Mid. Ant.	51.6±3.9	60.9±3.0	<0.05
Mid. Sept.	45.0±3.6	57.5±3.0	<0.05
Mid. Inf.	56.4±4.3	64.8±7.0	<0.05
Bas. Lat.	53.3±5.4	60.5±6.4	<0.05
Bas. Ant.	46.3±6.0	53.6±7.1	<0.05
Bas. Sept.	54.0±3.9	59.8±4.8	<0.05
Bas. Inf.	60.1±4.1	66.8±4.5	<0.05

Mid. Lat, middle lateral wall ; Mid. Ant, middle anterior wall ; Mid. Sep, middle septal wall ;
Mid. Inf, middle inferior wall ; Bas. Lat, basal lateral wall ; Bas. Ant, basal anterior wall ;
Bas. Sep, basal septal wall ; Bas. Inf, basal inferior wall ;

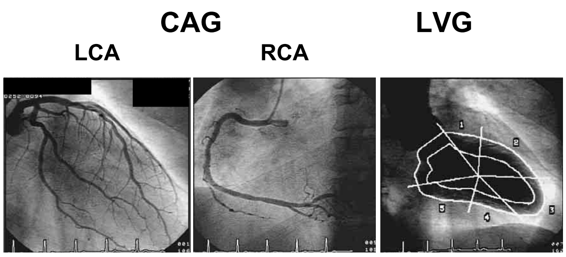

Fig. 3 CAG and LVG for the same patient described in Fig. 2.

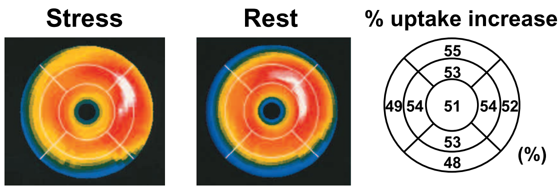

Fig. 4 Bull's eye map of stress-SPECT and rest-SPECT images, and % uptake increase for a liver cirrhosis patient.

DISCUSSION

Though depressed ST is found in exercise ECG tests in liver cirrhosis, some patients show no significant evidence for coronary artery stenosis. In the present study, the mechanisms of ST depression in exercise ECG tests were investigated using ^{99m}Tc-MIBI stress myocardial scintigraphy in liver cirrhosis. It is possible that the decreased ^{99m}Tc-MIBI uptake during exercise is due to the depression of flow-mediated vasodilatation controlled by the endothelium of the coronary artery, and a coronary endothelium dysfunction typically exists in patients with cirrhosis. The findings indicate that a disorder in coronary flow reserve occurs in liver cirrhosis patients without any significant coronary stenosis.

1) Coronary circulation and myocardial scintigraphy

Since a decreased isotope uptake is visually observed in the myocardium perfused by flow mediated vasodilatation during exercise, the % uptake increase may be lower in patients with coronary microcirculation disorders. In the present study, the % increase in blood flow decreased significantly during exercise in cirrhotic patients, even in myocardial segments that did not show a visual decrease in perfusion during myocardial SPECT using MIBI.

Coronary arterial hemodynamics can be readily evaluated by myocardial scintigraphy, which facilitate the diagnosis of significant coronary arterial stenosis and the evaluation of coronary arterial microvascular disorders to be evaluated (2-8). In recent years, several studies have reported that coronary arterial flow reserve can be predicted by quantitatively evaluating the level of myocardial radioisotope that accumulates during exercise and at rest using ^{99m}Tc-tetrofosmin-myocardial SPECT, which also facilitated measurement of the coronary arterial flow reserve (1, 2).

Nagamine, *et al.* (9) reported that conjugated estrogen induces sludging and stasis in the microcirculation, of which is the magnitude approximately proportional to the concentration and dose. However, many studies (10, 11) have indicated that estrogen acts protectively for vascular endothelium functions. Therefore, it is difficult to attribute the decrease in % uptake increase from the viewpoint of estrogen.

2) Effects of microcirculation and action potential by estrogen

A number of reports have appeared that indicate sex steroid hormones are involved the false positive of an exercise ECG test (12-18). Kanda, *et al.* (19) reported on the mechanism of coronary artery spasms, and that the gene of the smooth muscle of the human coronary artery can be activated by estrogen and that this activation was preventable by the administration of progesterone. It is possible that the decreased ^{99m}Tc-MIBI uptake during exercise is due to the depression of flow-mediated vasodilatation, which is controlled by the endothelium of the coronary artery, and a coronary endothelium dysfunction exists in patients with cirrhosis.

On the other hand, there is clinical condition called cardiac syndrome X in pre-menopausal women in which significant coronary arterial stenosis is absent (20). It has been hypothesized that an estrogen deficiency may play a major role in the pathogenesis associated with this condition. Minshall, *et al.* (21) hypothesize that vascular hyperreactivity, which may be a critical factor in the increased incidence of coronary artery vasospasm and ischemic heart disease in postmenopausal women, can be normalized by estradiol and/or progesteron through a direct action on coronary artery vascular muscle cells.

Holdright, *et al.* (22) however, reported that conventionally used hormone replacement therapy had no acute effect on a treadmill performance in the postmenopausal women with coronary artery disease. Bakhari, *et al.* (23) emphasized the importance of progesterone, and suggested that estrogen increases the false positive rate of stress ECG, and this decreased specificity can be countered by the coadministration of progesterone. Therefore, it is possible that an estrogen and progesterone imbalance causes the coronary artery circulation disorder.

Tanabe, *et al.* (24) reported on the effects of estrogen on action potential and membrane currents. They suggested that 17beta-estradiol prolonged the action potential duration mainly by inhibiting the outward K^+ current and the slowly activating component and prolonged the QT interval. This electrophysiological effect of estrogen might be related to the ST change in an ECG.

3) Liver cirrhosis and arteriosclerosis

In the present study, cirrhotic patients with significant coronary stenosis were not investigated, but ^{99m}Tc-MIBI myocardial scintigraphy could be clinically useful, because it facilitate both the diagnosis of significant coronary arterial stenoses and the evaluation of coronary arterial microvascular disorders.

It has been reported that liver cirrhosis developed with difficulty in cases of arteriosclerosis such as coronary artery disease (25-28), but arteriosclerosis was recently found to be complicated with a high frequency in this disease, in a study of pulse wave velocity (PWV) which facilitated the objective evaluation of the severity of arteriosclerosis (29, 30).

It has been also suggested recently that arteriosclerosis is closely associated with inflammation (31). Even in patients with viral hepatitis, vascular wall inflammation caused by chronic infections may play an important role in the development of arteriosclerosis. In patients with hepatitis C, positivity for the HCV core protein is an independent risk factor for plaque formation in the carotid artery (32). Furthermore, increased levels of high-sensitivity CRP in LC patients suggests the presence of arterial wall sclerosis induced by micro-inflammatory reactions (31).

4) Aanalogy of chemical constitution between steroid sex hormones and digitalis

Sundqvist, *et al.* and Jaeschke *et al.* reported that digoxin has influence on the exercise ECG (33-35). In male liver cirrhosis patients, and the possibility that increased estrogen levels caused an ST-T change in resting and exercise ECG, similar to digitalis. The findings of this study suggest that the causes of ST depression during exercise on ECG test in cirrhotic patients are a decrease in coronary blood flow increase response and the estrogenic digitalis action of blood flow independency.

In conclusion, these findings suggest that a disorder in coronary flow reserve occurs in liver cirrhosis patients, and that estrogen might decrease the coronary microcirculation and also have digitalis-like effects.

REFERENCES

1. Buell U, Kaiser HJ, Dupont F, Uebis R, Kleinhans E, Hanrath P : Methoxyisobutylisonitrile (MIBI) Tc 99m SPECT to establish a correlate to coronary flow reserve, the perfusion reserve, from global and regional myocardial uptake after exercise and rest. Eur J Nucl Med 16 : 3-9, 1990
2. Sugihara H, Yonekura Y, Kataoka K, Fukai D, Kitamura N, Taniguchi Y : Estimation of coronary flow reserve with the use of dynamic planar and SPECT images of Tc-99m tetrofosmin. J Nucl Cardiol 8 : 575-579, 2001
3. Clarke GD, Eckels R, Chaney C, Smith D, Dittrich J, Hundley WG, NessAiver M, Li HF, Parkey RW, Peshock RM : Measurement of absolute epicardial coronary artery flow and flow reserve with breath-hold cine phase-contrast magnetic resonance imaging. Circulation 91 : 2627-2634, 1995
4. Sakuma H, Blake LM, Amidon TM, O'Sullivan M, Szolar DH, Furber AP, Bernstein MA, Foo TK, Higgins CB : Coronary flow reserve : noninvasive measurement in humans with breath-hold velocity-encoded cine MR imaging. Radiology 198 : 745-750, 1996
5. Buell U, Dupont F, Uebis R, Kaiser HJ, Kleinhans E, Reske SN, Hanrath P : ^{99}Tcm-methoxy-isobutyl-isonitrile SPECT to evaluate a perfusion index from regional myocardial uptake after exercise and at rest. Results of a four hour protocol in patients with coronary heart disease and in controls. Nucl Med Commun 11 : 77-94, 1990
6. Buell U, Schicha H : Nuclear medicine to image applied pathophysiology : evaluation of reserves by emission computerized tomography. Eur J Nucl Med 16 : 129-135, 1990
7. Miller DD, Younis LT, Chaitman BR, Stratmann H : Diagnostic accuracy of dipyridamole technetium 99m-labeled sestamibi myocardial tomography for detection of coronary artery disease. J Nucl Cardiol 4 : 18-24, 1997
8. Houghton JL, Frank MJ, Carr AA, von Dohlen TW, Prisant LM : Relations among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in hypertensive patients without obstructive coronary artery disease. J Am Coll Cardiol 15 : 43-51, 1990
9. Nagamine Y, Komatsu S, Suzuki J : New embolization method using estrogen : effect of estrogen on microcirculation. Surg Neurol 20 : 269-275, 1983
10. Kaski JC : Cardiac syndrome X in women : the role of oestrogen deficiency. Heart 92 (Suppl 3) : iii5-9, 2006
11. Yoshioka J, Hasegawa S, Node K, Nakatani D, Kitakaze M, Hori M, Nishimura T : Oestrogen increases myocardial blood flow in men : assessment by 13N-ammonia positron emission tomography. Nucl Med Commun 25 : 557-62, 2004
12. Naftolin F, Taylor HS, Karas R, Brinton E, Newman I, Clarkson TB, Mendelsohn M, Lobo RA, Judelson DR, Nachtigall LE, Heward CB, Hecht H, Jaff MR, Harman SM : Women's Health Initiative. The Women's Health Initiative could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition. Fertil Steril 81 : 1498-1501, 2004
13. Rosano GM, Leonardo F, Pagnotta P, Pelliccia F, Panina G, Cerquetani E, della Monica PL, Bonfigli B, Volpe M, Chierchia SL : Acute anti-ischemic effect of testosterone in men with coronary artery disease. Circulation 99 : 1666-1670, 1999
14. Morise AP, Dalal JN, Duval RD : Frequency of oral estrogen replacement therapy in women with normal and abnormal exercise electrocardiograms and normal coronary arteries by angiogram. Am J Cardiol 72 : 1197-1199, 1993

15. Vaitkevicius P, Wright JG, Fleg JL : Effect of estrogen replacement therapy on the ST-segment response to postural and hyperventilation stimuli. Am J Cardiol 64 : 1076-1077, 1989
16. Marmor A, Zeira M, Zohar S : Effects of bilateral hystero-salpingo-oophorectomy on exercise-induced ST-segment abnormalities in young women. Am J Cardiol 71 : 1118-1119, 1993
17. Morise AP, Beto R : The specificity of exercise electrocardiography in women grouped by estrogen status. Int J Cardiol 60 : 55-65, 1997
18. Morise AP, Dalal JN, Duval RD : Value of a simple measure of estrogen status for improving the diagnosis of coronary artery disease in women. Am J Med 94 : 491-496, 1993
19. Kanda I, Endo M : Coronary artery spasm : a hypothesis on prevention by progesterone. Med Hypotheses 49 : 183-185, 1997
20. Kaski JC : Cardiac syndrome X in women : the role of oestrogen deficiency. Heart 92 (Suppl 3) : iii5-9, 2006
21. Minshall RD, Miyagawa K, Chadwick CC, Novy MJ, Hermsmeyer K : *In vitro* modulation of primate coronary vascular muscle cell reactivity by ovarian steroid hormones. FASEB J 12 : 1419-1429, 1998
22. Holdright DR, Sullivan AK, Wright CA, Sparrow JL, Cunningham D, Fox KM : Acute effect of oestrogen replacement therapy on treadmill performance in postmenopausal women with coronary artery disease. Eur Heart J 16 : 1566-1570, 1995
23. Bokhari S, Bergmann SR : The effect of estrogen compared to estrogen plus progesterone on the exercise electrocardiogram. J Am Coll Cardiol 40 : 1092-1096, 2002
24. Tanabe S, Hata T, Hiraoka M : Effects of estrogen on action potential and membrane currents in guinea pig ventricular myocytes. Am J Physiol 277(2 Pt 2) : H826-833, 1999
25. Creed DL, Baird WF, Fisher ER : The severity of aortic arteriosclerosis in certain diseases ; a necropsy study. Am J Med Sci 230 : 385-391, 1955
26. Loyke HF : The relationship of cirrhosis of the liver to hypertension : a study of 504 cases of cirrhosis of the liver. Am J Med Sci 230 : 627-632, 1955
27. Ruebner BH, Miyai K, Abbey H : The low incidence of myocardial infarction in hepatic cirrhosis. A statistical artefact? Lancet 2 : 1435-1436, 1961
28. Ruebner BH : Is there a decreased incidence of myocardial infarction in patients with cirrhosis of the liver? Am Heart J 64 : 135, 1962
29. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI : Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 26 : 485-490, 1995
30. Ishizaka N, Ishizaka Y, Takahashi E, Tooda E, Hashimoto H, Nagai R, Yamakado M : Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. Lancet 359 : 133-135, 2002
31. Ross R : Atherosclerosis - - an inflammatory disease. N Engl J Med 340 : 115-126, 1999
32. Ishizaka Y, Ishizaka N, Takahashi E, Unuma T, Tooda E, Hashimoto H, Nagai R, Yamakado M : Association between hepatitis C virus core protein and carotid atherosclerosis. Circ J 67 : 26-30, 2003
33. Sundqvist K, Atterhog JH, Jogestrand T : Effect of digoxin on the electrocardiogram at rest and during exercise in healthy subjects. Am J Cardiol 57 : 661-665, 1986
34. Jaeschke M, Erbel R, Fallen H, Belz GG : Influence of digoxin upon the exercise ECG of healthy men. Med Klin 71 : 2059-2065, 1976
35. LeWinter MM, Crawford MH, O'Rourke RA, Karliner JS : The effects of oral propranolol, digoxin and combination therapy on the resting and exercise electrocardiogram. Am Heart J 93 : 202-209, 1977