Tohoku J. Exp. Med., 1995, **177**, 233-248

Beta-Adrenergic Stimulation Induces ST-Segment Elevation in Dogs with Healing Myocardial Infarction

RYO KATORI, KEIZO YAMASHITA, TOSHIO MIYAZAKI, YOSHIHIDE SAKAGUCHI, TATSU INOKI, TADAHIKO YAMAMOTO and TOSHIYUKI SHIBUTANI

The First Department of Internal Medicine, Kinki University School of Medicine, Osaka-Sayama 589

KATORI, R., YAMASHITA, K., MIYAZAKI, T., SAKAGUCHI, Y., INOKI, T., YAMAMOTO, T. and SHIBUTANI, T. *Beta-Adrenergic Stimulation Induces ST-Segment Elevation in Dogs with Healing Myocardial Infarction.* Tohoku J. Exp. Med., 1995, **177** (3), 233-248 —— There is controversy with regard to the mechanism of the exercise-induced ST-segment elevation in myocardial infarction. The purpose of the present study was to investigate the mechanism of ST-segment elevation through pharmacologic interventions. Transmural anterior myocardial infarction was produced by gelatin sponge embolization of the left anterior descending artery in seven closed-chest dogs. One and four weeks after myocardial infarction, the dogs underwent the following three interventions: right atrial pacing, norepinephrine infusion (3.75, 7.5, and 15 μg/min) with the pacing, and methoxamine injection (2.5 and 5.0 mg) with the pacing. All dogs had transmural infarction with a mean infarct size of $12.0 \pm 4.2\%$ of the left ventricular weight. Right atrial pacing did not induce significant changes in ST-segment. Norepinephrine induced a marked elevation of ST-segment at leads V_1 to V_4, while methoxamine did not. Norepinephrine induced a significant increase in left ventricular ejection fraction, while methoxamine produced a marked decrease in the ejection fraction and an increase in ventricular volume. The mean percent radial shortening of the non-infarct ventricular wall showed a significant increase with norepinephrine, but a decrease with methoxamine. In conclusion, myocardial ischemia and wall motion abnormality may be excluded as possible mechanisms of ST-segment elevation and an enhanced beta-adrenergic mechanism in the non-infarct myocardium is suggested to be responsible for ST-segment elevation

—— myocardial infarction; exercise; norepinephrine; methoxamine; ST-segment elevation

Exercise-induced ST-segment elevation is relatively common on the leads where QS waves are present in patients with prior transmural myocardial infarction (Weiner et al. 1978; Haines et al. 1987). Most of these patients have anterior myocardial infarction with single-vessel disease and large infarction, ventricular

Received April 26, 1995; revision accepted for publication September 20, 1995.

Address for reprints: Ryo Katori, The First Department of Internal Medicine, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589, Japan.

aneurysm, or low ejection fraction (Atterhög et al. 1971; Chahine et al. 1976; Lahiri et al. 1980; Fox et al. 1983; Sullivan et al. 1984; Yamaki et al. 1985). Concerning the mechanism of the exercise-induced ST-segment elevation, both wall motion abnormalities in the infarction zone (Chahine et al. 1976; Weiner et al. 1978; Lahiri et al. 1980; Sullivan et al. 1984; Yamaki et al. 1985; Haines et al. 1987) and ischemia in the peri-infarction zone (Atterhög et al. 1971; Fox et al. 1983) have been proposed, but both have been highly controversial for two decades. The purpose of the present study was to investigate the mechanism of the ST-segment elevation through pharmacologic interventions using an experimental canine model of myocardial infarction. The interventions we used were right atrial pacing alone, and the pacing with norepinephrine infusion or methoxamine injection, which are modeled on similar hemodynamic responses to exercise, i.e., tachycardia, positive inotropic action and elevated blood pressure. We found that an enhanced beta-adrenergic mechanism plays an important role in producing the ST-segment elevation.

Materials and Methods

Preparation of myocardial infarction

All studies were performed with the approval of the Animal Care and Use Committee of Kinki University, in accordance with guidelines specified in the National Institutes of Health "Guide for Care and Use of Laboratory Animals." A total of 18 healthy, adult, heart-worm-negative mongrel dogs (weight, 14–30 kg) were anesthetized with intravenous sodium pentobarbital (25 mg/kg) and ventilated intratracheally with a Harvard respirator. Under sterile condition, the left exterior carotid artery was dissected and a No. 5 French introducer was inserted. After bolus injection of heparin (2,000 units), a No. 5 French pigtail catheter was inserted into the introducer and advanced under x-ray fluoroscopy until its tip lay within the left ventricle. The cine ventriculography was performed with injection of iopamidol (1.0 ml/kg of body weight) in 30-degree right anterior oblique position after 12-lead electrocardiography and measurement of left ventricular pressures. The pigtail catheter was then replaced with a No. 5 French Judkins catheter and left coronary cineangiography was performed with manual injection of 5 or 6 ml of iopamidol.

Transmural anterior myocardial infarction was produced by embolization of a mixture of sliced gelatin sponge and gelatin powder (Gelfoam®, Japan Upjohn Co., Tokyo) into the left anterior descending artery (LAD) under sterile condition. A commercially available PTCA guidewire of 0.016-inch diameter was introduced into the LAD through the Judkins catheter, and the catheter was replaced with a No. 3 French Kifa catheter, after which the guidewire was withdrawn. The Kifa catheter was advanced so that its tip lay at the site targeted for LAD occlusion. Thirty mg of the gelatin sponge cut into 0.5 mm cubes and the same weight of the sponge powder (116 ± 9 μm in diameter, mean $\pm$ S.E.) were mixed with 5 ml of

iopamidol and 5 ml of the saline. This mixture was slowly infused in order to occlude the LAD through the Kifa catheter under fluoroscopic guidance until it started to flow back upstream. Electrocardiograms and blood pressures were monitored, and treatments for arrhythmias and cardiac failure were applied continuously until the dog had completely recovered.

Ten of the 18 dogs survived more than four weeks. The other eight dogs died due to heart failure and arrhythmias within one week. Three of the 10 surviving dogs underwent the preliminary experiment only, and the remaining seven dogs underwent the complete set of experiments described in the present report. The occlusion site of the LAD was just distal to the bifurcation of the second diagonal branch in six dogs and of the first diagonal branch in one dog. Serial precordial electrocardiograms showed a typical time course of transmural anterior myocardial infarction. Plasma creatine phosphokinase was 102 ± 18 IU/liter before coronary embolization, increased to 669 ± 140 IU/liter at three hours after the embolization, and reached the peak value of $3{,}908 \pm 720$ IU/liter at 12 hr in the six dogs in which it was measured.

Experimental protocol

The experiment was performed in the same manner both one week and four weeks after myocardial infarction. The dogs were anesthetized with sodium pentobarbital (25 mg/kg) supplemented with an additional 5 mg/kg when needed during the experiment. They were ventilated via an intratracheal tube connected to a Harvard respirator and lain in the right decubitus position on the fluoroscopic table. Under sterile condition, a No. 7 French Zucker pacing catheter was introduced into the femoral vein and advanced until its tip lay within the right atrium for right atrial pacing. A No. 5 French Judkins catheter was inserted, and the cineangiography of the left coronary artery was performed. The catheter was then replaced with a No. 5 French pigtail catheter, the tip of which was placed in the left ventricle.

Control measurements for 12-lead electrocardiography, left ventricular pressure, and left ventricular angiography were made under sinus rhythm. The three interventions were then applied in the order of right atrial pacing, norepinephrine infusion under the same pacing, and methoxamine injection under the same pacing. The pacing rate was set at about 1.5 times the control heart rate using a cardiac stimulator (Model 3F51; Sanei Sokki, Co., Tokyo) until the end of the experiment. Norepinephrine was infused at the successive doses of 3.75, 7.5, and 15 μg/min with a Harvard pump for 5 min each, except in two dogs in the experiment at one week, in which the results for 15 μg/min infusion were discarded because of frequent occurrence of premature ventricular beats. After recovery time of 30 min, methoxamine was slowly injected twice, (2.5 and 5.0 mg, respectively) at a 5-min interval under the atrial pacing.

The interventions were continued for 5 min and electrocardiography and left

ventricular pressures were recorded during the last one minute. Left ventriculography was recorded four times, i.e., under control heart rate, during right atrial pacing alone, infusion of the largest dose of norepinephrine, and injection of the highest dose of methoxamine. However, the electrocardiographic and left ventricular pressure data in two dogs in the experiment at one week was discarded, because pacing failure occurred during norepinephrine infusion of the highest dose. Also, the evaluation of the left ventriculograms after methoxamine injection was difficult in three dogs in the experiment at one week, because of pacing failure or frequent occurrence of ventricular premature beats during contrast medium injection into the left ventricle and in one dog in the experiment at four weeks ventriculography could not be performed because of a technical problem.

Measurements

The precordial electrocardiogram was recorded with a clip electrode, at the paper speed of 50 mm/sec and amplitude of cm/mV using a six-channel electrocardiographer (RM-6000; Fukuda Denshi, Co., Tokyo). The electrodes were placed on the chest as follows: V_1 at the right sternal border in the fourth intercostal space (ICS); V_2 at the left sternal border in the fourth ICS; V_3 at the mid-point between V_2 and V_4; V_4 on the left anterior axillar line in the fourth ICS; V_5 on the middle axillar line in the fourth ICS; and V_6 on the posterior axillar line in the fourth ICS. The shift of ST segment was measured at 40 msec after the J point.

The cine-films of left ventriculogram were directly displayed on the monitor of an image-analysis computer (Mipron, Kontron Electronik, Munich, Germany). Left ventricular cavity borders in end-diastolic and end-systolic frames were outlined with a cursor connected to a digital tablet and stored in the core memory. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV) and ejection fraction (LVEF) were calculated by digital computation from the traced end-diastolic and end-systolic silhouettes according to the area-length method of Sandler and Dodge (1968).

To evaluate regional ventricular wall motion, we used a polar coordinate system based on the midpoints of the long axes of the ventricular silhouettes (Scampardonis et al. 1973; Schröder et al. 1983). Excluding the aortic valve plane, the computer divided the silhouettes into 48 segmental radii with equal angles. The end-diastolic and end-systolic contours were superimposed on their long axes and mid-points. The systolic shortening of a segmental radius, i.e., the % radial shortening, was calculated by the formula; % radial shortening= $[(D\text{-}S)/D] \times 100$, where D=length of end-diastolic segmental radius and S= length of end-systolic segmental radius. The first five segmental radii (mitral valve area) and the last three (46-48, aortic junction) were excluded from evaluation (Shröder et al. 1983). The results were printed out as numerical data, and a histogram of percent shortening of systolic segmental radii was generated.

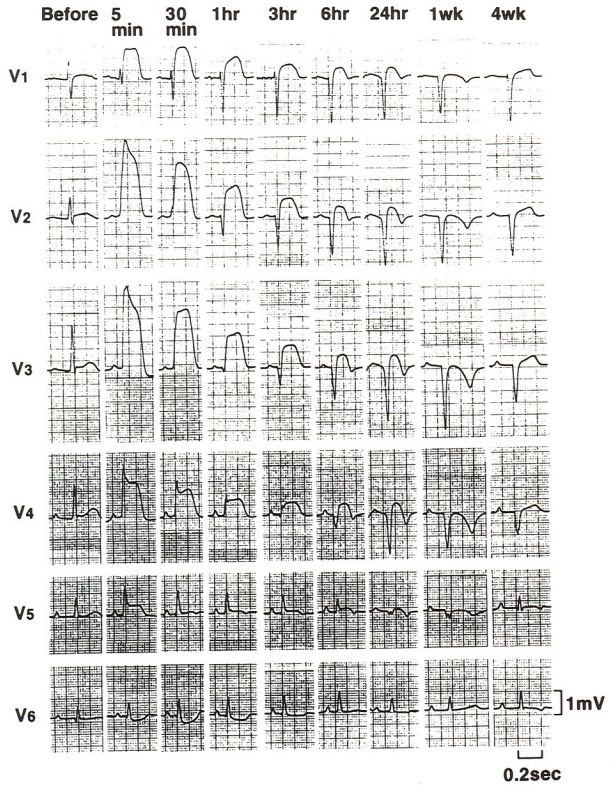

Fig. 1. Serial ECG at chest leads after coronary occlusion in one dog. ST-segment at V_1 to V_5 is markedly elevated 5 min after the occlusion and the elevated ST-segment gradually declined during the first 24 hr after occlusion. Abnormal Q waves persisted for four weeks.

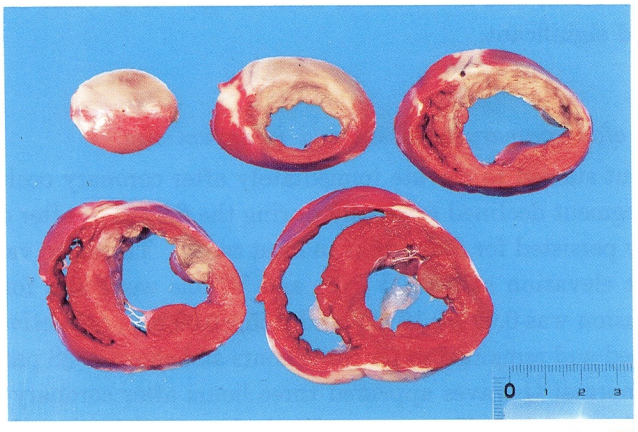

Fig. 2. Serial transverse sections of a ventricle stained by the TTC stain. Transmural anterior myocardial infarction is clearly observed. The volume of the infarction region was calculated as 20.8% of the left ventricle weight.

The left ventricular wall shown on the cine-ventriculogram for control measurement was divided into the infarct zone, border zone and non-infarct zone according to the following definitions. The infarct zone was defined as the territory consisting of successive chords equal to or less than a 10% value of radial shortening in the apex and anterior wall. The border zones were defined as the two territories adjacent to the infarct zone, with each border zone defined as the area consisting of five successive chords adjacent to the infarct zone. The non-infarct zones were defined as the territories outside each border zone. The mean radial shortening was defined as the average value of radial shortening of each zone.

Morphological measurement of infarction

The dogs were killed with intravenous injection of a large dose of sodium pentobarbital at the end of the experiment, and the heart was excised. For determination of gross infarction weight, the heart was transversely sectioned at 1-cm intervals, and the heart slices were then incubated in a solution of triphenyl tetrazolium chloride (TTC) (Lie et al. 1975). The TTC histochemical technique delineates infarct tissue by intensely staining normal myocardium. Each slice was photographed adjacent to a cm scale. The infarct and non-infarct areas on the photograph of each slice were measured, and the infarct size was then calculated as a percent ratio to left ventricular weight. Following the TTC staining the slices were fixed in formalin and stained with hematoxylin and eosin.

Statistical analysis

The results are expressed as mean$\pm$S.E. Analysis of variance with repeated measures followed by the Student-Newman-Keuls test (Glantz 1992) was used for multiple comparisons of electrocardiographic and hemodynamic data, LV volumes and ejection fraction, and mean radial shortenings. A p value of less than 0.05 was considered significant.

Results

ECG changes after coronary occlusion and infarction size

ST-segment started to elevate immediately after coronary occlusion, and the elevated ST-segment declined gradually during the first 24 hr after occlusion (Fig. 1), but usually persisted for four weeks in most cases. The mean value of the sum of ST-segment elevation at leads V_2, V_3 and V_4 one week and four weeks after coronary occlusion was 0.69 ± 0.17 mV and 0.55 ± 0.09 mV, respectively. R waves rapidly declined and remained so for three hours and showed QS pattern in almost all dogs. Abnormal Q waves appeared three hours after coronary occlusion and persisted for four weeks. T wave amplitude increased in accord with the ST-segment elevation, but rapid change to the negative coronary T wave was observed at about 6 hr. Fig. 2 shows the typical morphological appearance of trans-

mural myocardial infarction. All seven dogs had transmural anterior infarction as shown in Fig. 2. The infarct size ranged from 6.7% to 20.8% of the left ventricular weight, with a mean of 12.0±4.2%.

Changes in heart rate and left ventricular pressures

The heart rate and left ventricular pressures are shown in Table 1. The mean heart rate was 149.8±21.2 beats/min in the control in the experiment at one week, and increased to 212.0±4.9 beats/min by right atrial pacing. This pacing heart rate was maintained by the end of norepinephrine infusion and methoxamine injection. In the experiment at four weeks, the mean control heart rate was 142.0±9.5 beats/min and the atrial pacing rate was 197.1±6.8 beats/min.

In the control and right atrial pacing, left ventricular systolic pressure was 143.6±7.2 mmHg and 134.6±12.9 mmHg, respectively, in the experiment at one week. The pressure significantly increased during norepinephrine infusion at a rate of 15 μg/min and methoxamine injection at a dose of 5.0 mg (254.0±11.7 mmHg, $p<0.01$ and 226.0±18.7 mmHg, $p<0.01$, respectively). The left ventricular end-diastolic pressure was within the normal range in controls, right atrial pacing and norepinephrine infusion, but was significantly increased (31.0± 2.0 mmHg, $p<0.01$) with methoxamine injection.

The pressure-rate product increased significantly by both norepinephrine infusion and methoxamine injection compared with the control and right atrial

TABLE 1. *Changes in heart rate, LV systolic and end-diastolic pressures in controls, right atrial pacing, and norepinephrine infusion at 15 μg/min and methoxamine injection at 5.0 mg under right atrial pacing at one week and four weeks after myocardial infarction*

	HR (beats/min)	LVSP (mmHg)	LVEDP (mmHg)	PRP (mmHg · beats/min)
Intervention at 1 week ($n=5$)				
Control	149.8±21.2	143.6± 7.2	7.6±1.3	21806±3628
RAP	212.0± 4.9**	134.6±12.9	7.8±1.5	28532±2908
NE+RAP	212.0± 4.9**	254.0±11.7**,††	9.6±1.8	53960±3253**,††
MX+RAP	212.0± 4.9**	226.0±18.7**,††	31.0±2.0**,††,‡‡	47880±4160**,††
Intervention at 4 weeks ($n=7$)				
Control	142.0± 9.5	141.6±15.8	4.3±0.6	20539±3426
RAP	197.1± 6.8**	142.9±14.9	3.7±0.8	28557±3733**
NE+RAP	197.1± 6.8**	260.7±11.0**,††	7.9±2.1	51757±3706**,††
MX+RAP	197.1± 6.8**	251.7± 7.2**,††	19.4±3.0**,††,‡‡	49634±2242**,††

**$p<0.01$ vs. control; †† $p<0.01$ vs. RAP; ‡‡ $p<0.01$ vs. NE+RAP. HR, heart rate; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; PRP, pressure-rate product; RAP, right atrial pacing; NE, norepinephrine; MX, methoxamine. Data presented are mean±S.E.

pacing, but there was no significant difference between the norepinephrine infusion and methoxamine injection.

The hemodynamic data in the experiment at four weeks were similar to those at one week, except for slightly lower values for heart rate and left ventricular end-diastolic pressure, as shown in Table 1.

Changes in ST-segment

Fig. 3 shows the electrocardiographic changes on chest leads in one dog during the interventions at one week. Right atrial pacing did not induce significant changes in ST-segment. Norepinephrine infusion during right atrial pacing induced a marked elevation in ST-segment and positive change of negative T wave on leads V_1 to V_4. However, methoxamine injection did not result in any significant changes in ST-segment.

We represented the magnitude of ST-segment changes as the sum of those for

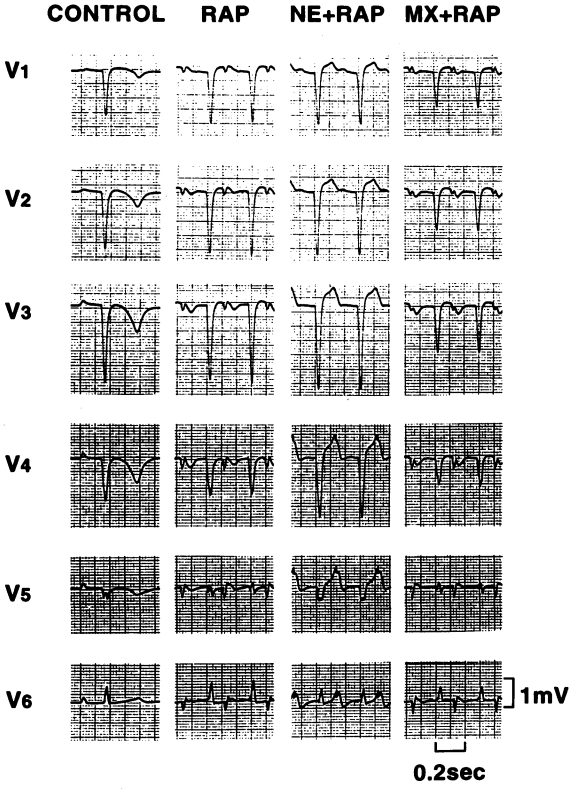

Fig. 3. Chest lead electrocardiographic changes produced by the three interventions in a dog with anterior myocardial infarction one week after coronary occlusion. RAP is right atrial pacing, NE+RAP norepinephrine infusion of 15 μg/min with RAP, and MX+RAP methoxamine injection of 5.0 mg with RAP.

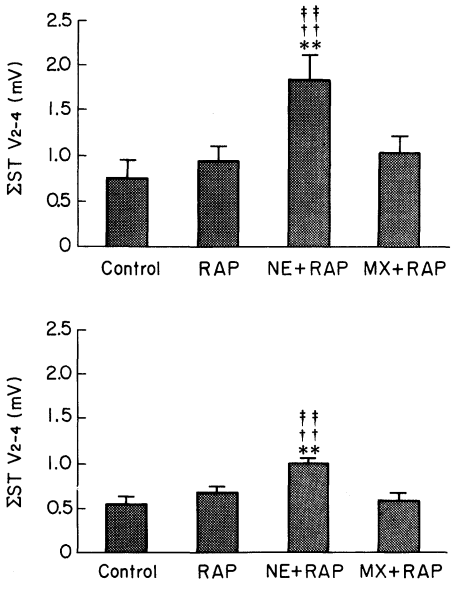

Fig. 4. Mean summed ST-segment elevation in controls, right atrial pacing (RAP), norepinephrine infusion with RAP (NE+RAP), and methoxamine injection with RAP (MX+RAP) at one week (top, $n=5$) and four weeks (bottom, $n=7$) after myocardial infarction. $\Sigma ST\ V_{2-4}$ is the sum of ST-segment elevation at leads V_2, V_3 and V_4. $^{**}p<0.01$ vs. control; $^{\dagger\dagger}p<0.01$ vs. RAP; $^{\ddagger\ddagger}p<0.01$ vs. MX+RAP.

leads V_2, V_3 and V_4 ($\Sigma ST\ V_{2-4}$). As shown in Fig. 4, right atrial pacing did not cause a significant change in ST-segment at either one week or four weeks. However, norepinephrine infusion induced a significant elevation in $\Sigma ST\ V_{2-4}$ both at one week and at four weeks, although the elevation in the latter was lower than that in the former. The ST-segment elevation during norepinephrine infusion was dose-dependent at both times (Fig. 5). The $\Delta\Sigma ST\ V_{2-4}$ (difference from the control of $\Sigma ST\ V_{2-4}$) with 3.75, 7.50 and 15.0 μg/min of norepinephrine was 0.46 ± 0.09 mV, 0.70 ± 0.18 mV, and 1.05 ± 0.19 mV, respectively, at one week ($n=5$), and 0.05 ± 0.03 mV, 0.26 ± 0.05 mV, and 0.32 ± 0.06 mV, respectively, at four weeks ($n=7$). On the other hand, methoxamine injection did not result in any changes in ST-segment.

Changes in left ventricular global and regional wall motion

At one week, right atrial pacing resulted in slight decreases in LVEDV and LVEF, but norepinephrine induced a significant increase in LVEF and a slight decrease in LVESV compared with atrial pacing alone, as listed in Table 2. Methoxamine produced a significant decrease in LVEF ($24.5\pm3.7\%$) compared with norepinephrine infusion ($55.0\pm6.8\%$), and significant increases in LVEDV (73.5 ± 7.5 ml) and LVESV (53.5 ± 5.8 ml). At four weeks, the pattern of changes

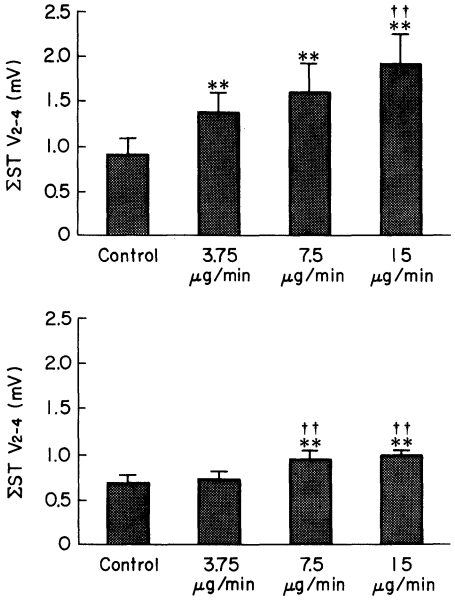

Fig. 5. Dose-dependent changes in ST-segment elevation induced by norepinephrine infusion with right atrial pacing at one week (top, $n=5$) and four weeks (bottom, $n=7$) after myocardial infarction. $\Sigma ST\ V_{2-4}$ is the sum of ST-segment elevation at leads V_2, V_3 and V_4. $^{**}p<0.01$ vs. control; $^{\dagger\dagger}p<0.01$ vs. 3.75 μg/min infusion.

TABLE 2. *Changes in LV volumes and ejection fraction in controls, right atrial pacing, and norepinephrine infusion at 15 μg/min and methoxamine injection at 5.0 mg under right atrial pacing at one week and four weeks after myocardial infarction*

	LVEDV (ml)	LVESV (ml)	LVEF (%)
Intervention at 1 week ($n=4$)			
Control	61.5±8.3	37.0±5.0	39.3±1.3
RAP	46.0±6.2	34.0±7.4	25.8±1.8
NE+RAP	58.3±7.5	26.8±5.6	55.0±6.8*††
MX+RAP	73.5±7.5††	53.5±5.8**,††,‡‡	24.5±3.7‡‡
Intervention at 4 weeks ($n=6$)			
Control	52.7±4.9	27.7±3.7	48.5±2.7
RAP	40.5±3.6*	23.7±2.9	42.8±2.5
NE+RAP	48.2±4.1	21.0±3.5	57.8±4.1*††
MX+RAP	58.0±6.3††,‡	41.5±4.7**,††,‡‡	19.8±2.4**,††,‡‡

$^{*}p<0.05$, $^{**}p<0.01$ vs. control; †† $p<0.01$ vs. RAP; ‡$p<0.05$, ‡‡ $p<0.01$ vs. NE+RAP. LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; LVEF, LV ejection fraction; RAP, right atrial pacing; NE, norepinephrine; MX, methoxamine. Data presented are mean±S.E.

TABLE 3. *Changes in mean radial shortening of infarct, border and non-infarct zones in controls, right atrial pacing, and norepinephrine infusion at 15 μg/min and methoxamine injection at 5.0 mg under right atrial pacing at one week and four weeks after myocardial infarction*

	Mean radial shortening (%)		
	Infarct zone	Border zone	Non-infarct zone
Intervention at 1 week ($n=4$)			
Control	1.1±1.9	23.0±1.0	33.7±2.5
RAP	1.4±4.1	15.4±3.6	19.9±6.7
NE+RAP	12.5±7.7	37.2±9.9†	58.4±11.3*,††
MX+RAP	1.1±3.1	9.5±2.2‡‡	18.0±3.5‡‡
Intervention at 4 weeks ($n=6$)			
Control	4.2±1.3	22.6±1.4	35.9±3.4
RAP	4.5±2.8	20.9±2.1	32.3±3.7
NE+RAP	6.1±4.1	28.6±6.6	47.0±4.5*,†
MX+RAP	0.3±2.8	5.6±1.5**,††,‡‡	11.9±1.7**,††,‡‡

*$p<0.05$, **$p<0.01$ vs. control; †$p<0.05$, ††$p<0.01$ vs. RAP; ‡‡ $p<0.01$ vs. NE+RAP. RAP, right atrial pacing; NE, norepinephrine; MX, methoxamine. Definition of the infarct, border and non-infarct zones is described in the methods. Data presented are mean±S.E.

in left ventricular volumes and ejection fraction produced by the interventions was almost the same as that at one week.

The infarct zone showed very low values for regional wall motion evaluated as mean radial shortening (%) of each zone (1.1±1.9% and 4.2±1.3% at one week and four weeks, respectively) in the control state, and no significant changes were produced by the interventions, as shown in Table 3. The non-infarct zone showed a significant increase compared with the control in mean percent radial shortening during norepinephrine infusion and a decrease during methoxamine injection both at one week and four weeks. The border zone showed intermediate changes at both one week and four weeks.

DISCUSSION

Experimental model of myocardial infarction in dogs

It has been reported (Agress et al. 1952; Jacobey et al. 1962; Eaton and Bukley 1981) that the production of transmural myocardial infarction by ligation of the epicardial large coronary artery in dogs is not usually feasible, but is facilitated by embolization of the coronary arteries. Eaton and Bukley (1981) reported that transmural myocardial infarction was successfully obtained by coronary artery ligation in only two of 20 mongrel dogs, while it was obtained by coronary artery embolization in 19 of 24 dogs, nine of which survived more than one week. Jacobey et al. (1962) produced transmural myocardial infarction by

injection of microspheres 297 to 350 μm in diameter into the coronary artery in closed-chest dogs and obtained survival rate of 42%. They noted that minimal dose of emboli and small territory of occluded arteries were important as conditions of success. We used a mixture of gelatin sponge cubes 0.5 mm in length and gelatin sponge powder as emboli and occlusion site just distal to the bifurcation of the second diagonal branch in the LAD in all dogs except one. The four-week survival rate was 55.5% and the infarct size was 6.7 to 20.8% of left ventricular weight with a mean of $12.0 \pm 4.2\%$.

Since 1950, many substances have been used as emboli, such as microspheres (Agress et al. 1952), mercury (Lluch et al. 1969), ivalon sponge (Zollikofer et al. 1981), gelatin sponge (Birkui et al. 1981) and metallic beads (Flowers et al. 1978). Coronary embolization with these substances leads to complete luminal occlusion of the entire length of the coronary artery up to the periphery, so that the development of collateral vessels is prevented and it is feasible to produce transmural myocardial infarction. Coagulation necrosis is usually observed in embolization, while contraction band necrosis is predominant in coronary artery ligation dogs (Eaton and Bukley 1981). In the present study, transmural anterior wall infarction with coagulation necrosis was produced (Data were not shown). This model in which gelatin sponge is used as the emboli is considered suitable for the experimental production of transmural myocardial infarction.

Relation between hemodynamic changes and ST-segment elevation

In order to elucidate the mechanism of exercise-induced ST-segment elevation after myocardial infarction, the dogs were subjected to three interventions which were designed to simulate representative exercise hemodynamics such as tachycardia, hypertension and positive inotropism. Right atrial pacing has been used as a method of inducing myocardial ischemia by increasing myocardial oxygen demand. Both norepinephrine and methoxamine induced the elevation in blood pressure by adrenergic mechanisms, but the former has both alpha and beta adrenergic actions and the latter only alpha adrenergic action. Therefore, norepinephrine infusion more mimicks exercise hemodynamics to a greater extent than do the other two interventions. It is very interesting that norepinephrine induced significant ST-segment elevation while the other two interventions did not. It is likely that beta adrenergic stimulation plays an important role in the ST-segment elevation observed in the present study.

The two leading opinions regarding the mechanism of exercise-induced ST-segment elevation in patients with prior myocardial infarction are the effect of myocardial ischemia (Dunn et al. 1980; Fox et al. 1983) and that of wall motion abnormality in the infarct or peri-infarct zone (Chahine et al. 1976; Lahiri et al. 1980), but there are still many controversial points. The myocardial ischemia induced by exercise results from increased myocardial oxygen consumption except for coronary artery spasm. In the present study, ST-segment elevation did not

occur during pacing tachycardia or methoxamine injection during tachycardia. In contrast, norepinephrine infusion during tachycardia induced a significant ST-segment elevation even though the pressure-rate product was not significantly different between norepinephrine infusion and methoxamine injection. These results indicate that norepinephrine-induced ST-segment elevation does not result from only tachycardia or myocardial ischemia. Furthermore, the ST-segment elevation during norepinephrine infusion was accompanied by the improvement in mean radial shortening in border and non-infarct zones and an increase in LVEF. These data also support the assertion that norepinephrine-induced ST-segment elevation does not result from the impairment of wall motion abnormality.

It is noteworthy that the mean radial shortening of the left ventricular wall in the infarct zone did not change when ST-segment was elevated during norepinephrine infusion, while an improved mean radial shortening was observed in the border and normal zones. As mentioned above, one hypothesis for the mechanism of exercise-induced ST-segment elevation is exacerbation of wall motion abnormalities in the infarct or border zone. In that case, the ventricular wall motion in these zones would become more dyskinetic or akinetic during the interventions. Brody (1956) postulated the increase of intracavitary blood volume in the left ventricle, and Amoore (1985) assumed the increased proximity of the heart to the chest wall due to the distention of the ventricular wall as a cause of ST-segment elevation. In the present study, such hemodynamic abnormalities were observed during methoxamine injection, but ST-segment showed no significant change. In contrast, even though LVEDV and LVESV tended to decrease and LVEF increased, norepinephrine infusion induced distinctive ST-segment elevation. These findings are in disagreement with the hypothesis that wall motion abnormality participates in exercise-induced ST-segment elevation.

Relationship between norepinephrine and ST-segment elevation

We observed that norepinephrine induced an ST-segment elevation while methoxamine did not, even though both produced marked elevation of left ventricular systolic pressure under right atrial pacing tachycardia. These data indicate that beta rather than alpha adrenergic stimulation brought about the ST-segment elevation. Since the pressure rate product with norepinephrine did not differ from that with methoxamine administration and the former was associated with improved wall motion in the non-infarct zone, the production of myocardial ischemia or wall motion abnormality may have been negligible. Mirvis et al. (1985) produced an experimental model of transmural infarction in dogs and demonstrated increase of ST-segment elevation with tachycardia. In their experiment, the epicardial action potential duration was found to decrease and its amplitude to diminish, and the injured myocardium maintained a less negative transmembrane potential during diastole. They stated that the combi-

nation of these phenomena in regions adjacent to healthy myocardium may lead to ST-segment elevation. In the present study, however, pacing tachycardia alone did not produced, but beta-adrenergic stimulation induced significant ST-segment elevation.

Enchanced beta-adrenergic mechanism may produce a difference between the transmembrane potentials in the infarct region and those in the adjacent normal myocardium, because the hyperpolarization may be more strongly induced in the normal myocardium than in the infarct region by beta-adrenergic stimulation of electrogenic Na^+-K^+ pump activity (Wasserstrom et al. 1982; Désilets and Baumgarten 1986). In diastole, the adjacent normal myocardium has more positive extra-cellular potential than the infarct region does, so that the vector of the current is outward on the infarct region, and ST-segment elevation may be produced according to the diastolic injury current theory. In systole, the enhancement of the Ca^{2+} channel activity in the adjacent normal myocardium would be important for the mechanism of ST-segment elevation. Beta-adrenergic stimulation increases the slow inward current of the action potentionls. As a result, the adjacent normal myocardium is more depolarized than the infarct region does, so that the vector of the extra-cellular current is inward on the infarct region, and ST-segment elevation may be produced according to the systolic injury current theory. We reported (Katori et al. 1994) that the plasma norepinephrine levels at maximal workload were significantly increased in patients with exercise-induced ST-segment elevation after myocardial infarction, compared with those in patient groups without ST-segment elevation. These data suggest a close relation between enhanced beta-adrenaergic mechanism and ST-segment elevation.

In conclusion, norepinephrine infusion during right atrial pacing induced a significant ST-segment elevation in experimental transmural myocardial infarction in dogs. We propose that an enhanced beta-adrenergic mechanism in the peri-infarct or non-infarct area may be responsible for the exercise-induced ST-segment elevation observed in patients with prior transmural myocardial infarction.

References

1) Agress, C.M., Rosenberg, M.J., Jacobs, H.I., Binder, M.J., Schneiderman, A. & Clark, W.G. (1952) Protracted shock in the closed-chest dog following coronary embolization with graded microspheres. *Am. J. Physiol.*, **170**, 536-549.
2) Amoore, J.N. (1985) The Brody effect and change of volume of the heart. *J. Electrocardiol.*, **18**, 71-75.
3) Atterhög, J.H., Ekelund, L.G. & Kaijser, L. (1971) Electrocardiographic abnormalities during exercise 3 weeks to 18 months after anterior myocardial infarction. *Br. Heart J.*, **33**, 871-877.
4) Birkui, P.J., Georgiopoulos, G., Riche, M.C., Perrauet, M., Puisieux, F., Merland, J. & Saumor, R. (1981) Closed-chest myocardial ischemia in dog. *Med. Progr. Technol.*, **8**, 121-127.
5) Brody, D.A. (1956) A theoretical analysis of intracavitary blood mass influence on

the heart-lead relationship. *Circ. Res.*, **4**, 731-738.
6) Chahine, R.A., Raizner, A.E. & Ishimori, T. (1976) The clinical significance of exercise-induced ST-segment elevation. *Circulation*, **54**, 209-213.
7) Désilets, M. & Baumgarten, C.M. (1986) Isoproterenol directly stimulates the Na^+-K^+ pump in isolated cardiac myocytes. *Am. J. Physiol.*, **251** (*Heart Circ. Physiol.* **20**), H218-H225.
8) Dunn, R.F., Bailey, I.K., Uren, R. & Kelly, D.T. (1980) Exercise-induced ST-segment elevation. Correlation of thallium-201 myocardial perfusion scanning and coronary arteriography. *Circulation*, **61**, 989-995.
9) Eaton, L.W. & Bukley, B.H. (1981) Expansion of acute myocardial infarction: Its relationship to infarct morphology in a canine model. *Circ. Res.*, **49**, 80-88.
10) Flowers, N.C., Hand, R.C., Sridharan, M.R., Horan, L.G. & Sohi, G.S. (1978) Surface reflections of cardiac excitation and the assessment of infarct volume in dogs. A comparison of methods. *Circ. Res.*, **43**, 406-413.
11) Fox, K.M., Jonathan, A. & Selwyn, A. (1983) Significance of exercise induced ST segment elevation in patients with previous myocardial infarction. *Br. Heart J.*, **49**, 15-19.
12) Glantz, S.A. (1992) *Primer of Biostatistics*, 3rd ed. McGraw-Hill, Inc., New York, p. 95.
13) Haines, D.E., Beller, G.A., Watson, D.D., Kaiser, D.L., Sayre, S.L. & Gibson, R.S. (1987) Exercise-induced ST segment elevation 2 weeks after uncomplicated myocardial infarction. Contributing factors and prognostic significance. *J. Am. Coll. Cardiol.*, **9**, 996-1003.
14) Jacobey, J.A., Taylor, W.J., Smith, G.T., Gorlin, R. & Harken, D.E. (1962) A new therapeutic approach to acute coronary occlusion. I. Production of standardized coronary occlusion with microspheres. *Am. J. Cardiol.*, **9**, 60-73.
15) Katori, R., Miyazaki, T., Ohno, M., Yamashita, K., Sakaguchi, Y., Takada, K., Inoki, T., Yamamoto, T. & Shibutani, T. (1994) Exercise-induced ST-segment elevation and hemodynamic responses one month after myocardial infarction. *Jpn. Circ. J.*, **58**, 757-766.
16) Lahiri, A., Balasubramanian, V., Craig, M.W.M., Crawley, J. & Raftery, E.B. (1980) Exercise-induced ST segment elevation. Electrocardiographic, angiographic, and scintigraphic evaluation. *Br. Heart J.*, **43**, 582-588.
17) Lie, J.T., Pairolero, P.C., Holley, K.E. & Titus, J.L. (1975) Macroscopic enzyme-mapping verification of large, homogeneous, experimental myocardial infarcts of predictable size and location in dogs. *J. Thorac. Cardiovasc. Surg.*, **69**, 599-605.
18) Lluch, S., Moguilevsky, H.C., Pietra, G., Shaffer, A.B., Hirsch, L.J. & Fishman, A.P. (1969) A reproducible model of cardiogenic shock in the dog. *Circulation*, **39**, 205-218.
19) Mirvis, D.M., Wilson, J.L. & Ramanathan, K.B. (1985) Effects of experimental myocardial infarction on the ST segment response to tachycardia. *J. Am. Coll. Cardiol.*, **6**, 665-673.
20) Sandler, H. & Dodge, H.T. (1968) The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *Am. Heart J.*, **75**, 325-334.
21) Scampardonis, G., Yang, S.S., Maranhão, V., Goldberg, H. & Gooch, A.S. (1973) Left ventricular abnormalities in prolapsed mitral leaflet syndrome: Review of eighty-seven cases. *Circulation*, **48**, 287-297.
22) Schröder, R., Biamino, G. & Leitmer, E.R. (1983) Intravenous short-term infusion of streptokinase in acute myocardial infarction. *Circulation*, **67**, 536-548.
23) Sullivan, I.D., Davies, D.W. & Sowton, E. (1984) Submaximal exercise testing early after myocardial infarction: Prognostic importance of exercise induced ST segment elevation. *Br. Heart J.*, **52**, 147-153.
24) Wasserstrom, J.A., Schwartz, D.J. & Fozzard, H.A. (1982) Catecholamine effects on

intracellular sodium activity and tension in dog heart. *Am. J. Physiol.*, **243** (*Heart Circ. Physiol.*, **12**), H670-H675.

25) Weiner, D.A., McCabe, C., Klein, M.D. & Ryan, T.J. (1978) ST segment changes postinfarction: Predictive value for multivessel coronary disease and left ventricular aneurysm. *Circulation*, **58**, 887-891.

26) Yamaki, M., Kubota, I., Ikeda, K., Tonooka, I., Tuiki, K. & Yasui, S. (1985) The clinical significance of exercise-induced ST-segment elevation in previous anterior myocardial infarction. *Jpn. Circ. J.*, **49**, 849-859.

27) Zollikofer, C., Castaneda-Zuniga, W., Vlodaver, Z., Rysavy, J., Gomes, A.S. & Amplatz, K. (1981) Experimental myocardial infarction in the closed-chest dog: A new technique. *Invest. Radiol.*, **16**, 7-12.