THE CHANGES IN ECG ST SEGMENT AND MECHANICAL FUNCTION OF REGIONAL ISCHEMIC MYOCARDIUM DURING AFTERLOAD REDUCTION IN ISOLATED DOG HEARTS WITH CORONARY STENOSIS

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By measuring ECG ST segment deviation and regional mechanical dysfunction, we assessed the effects of an alteration in afterload pressure on regional myocardial ischemia due to a partial coronary occlusion of the left circumflex coronary artery (CFX). Eight isolated, perfused and paced dog hearts were loaded with an artificial arterial system which simulated the aortic input impedance of the dog arterial tree. Afterload pressure was altered by stepwise changes in peripheral resistance (R_p), while left ventricular end-diastolic pressure (LVEDP) and heart rate were kept constant. Coronary perfusion pressure (CPP) was kept equal to mean aortic pressure (AoP). ECG and myocardial systolic segment shortening (SS) were measured in both areas perfused by the CFX and the left anterior descending coronary artery (LAD).

In the presence of CFX stenosis, mean AoP decreased from 96 ± 7 to 46 ± 7 mmHg following a decrease in R_p and cardiac output increased progressively from 465 ± 30 to 1055 ± 100 ml/min. In this situation, CFX coronary blood flow decreased from 75 ± 2 to 28 ± 6 ml/100g/min. Epicardial ECG in the ischemic region showed two types of ST segment deviation after CFX stenosis: ST segment elevation and ST segment depression. Moreover, following afterload reduction, these individual ECG ST segment changes showed further deviations. The levels of mean AoP, below which further ST segment deviations significantly occurred, were as follows: 71 ± 6 mmHg in ST segment elevation cases and 52 ± 7 mmHg in ST segment depression cases. Myocardial systolic segment shortening in the ischemic region also significantly decreased following CFX stenosis ($91 \pm 8\%$ of pre-ischemic control, $p < 0.05$). Then, during afterload reduction, SS in the CFX area appeared to be bimodal and it definitely decreased when mean AoP was 46 ± 7 mmHg. To enhance the sensitivity of detection of further mechanical dysfunction throughout afterload reduction following regional myocardial ischemia, we calculated percentage values of the SS in the CFX area to the SS in the LAD area at each R_p . By this normalization, mechanical dysfunction was found when mean AoP was below 67 ± 5 mmHg. These results suggest that reduction in afterload pressure below a certain level aggravated the regional

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ischemia, despite an increase in cardiac output, and to detect this change in the ischemic region during afterload reduction, ECG ST segment deviation seems to be a useful indicator. On the other hand, unless the normalization for systolic segment shortening is performed, regional myocardial mechanical dysfunction in the ischemic area would not necessarily be a sensitive indicator for detecting the worsening of myocardial ischemia.

A reduction in afterload pressure has favorable effects on cardiac output and myocardial oxygen demand by unloading of the left ventricle. However, it will have unfavorable effects on coronary perfusion, especially when coronary autoregulation is exhausted by severe stenosis. Some investigators have reported that myocardial performance in the ischemic region due to coronary stenosis, worsened when afterload pressure decreased.¹⁻⁵ Therefore, it is quite important to monitor the degree of myocardial ischemia during afterload reduction in ischemic heart disease.

ECG ST segment deviation and regional mechanical dysfunction have been noted to be valuable indicators of myocardial ischemia. Some investigators have proposed that regional mechanical dysfunction is more sensitive for the detection of myocardial ischemia than is ECG ST segment deviation.⁶⁻⁸ They reported that regional mechanical dysfunction occurred more quickly than the ECG ST segment responded after a sudden decrease in coronary blood flow. However, the effects of afterload pressure on the ischemic myocardium were not investigated in these studies. Weber⁹ and Elzinga et al.¹⁰ reported that the relation between afterload and myocardial systolic shortening was linear with a negative slope. Accordingly, even if regional mechanical function deteriorates through a decrease in coronary blood flow by afterload reduction, i.e., a decrease in coronary perfusion pressure, further changes in myocardial mechanical dysfunction may be masked by this relationship. Rather, in this condition, as suggested by previous reports,¹¹⁻¹⁴ ECG ST segment deviation seems to be a useful indicator of myocardial ischemia, because ST segment deviation might not be mechanically influenced by afterload reduction. However, there is no report demonstrating simultaneous changes in ECG ST segment deviation and mechanical dysfunction of the regionally ischemic myocardium during afterload changes. The purpose of the present study was to examine the relationship between the changes in ECG ST segment deviation and regional mechanical function during afterload reduction

in a heart with coronary stenosis, and to know which of the two indicators is more useful for the detection of further changes in the regional myocardial ischemia during afterload reduction.

METHODS

Preparation

We used 8 mongrel dogs weighing 14.5 to 20 kg (average 16.7 kg). The isolated dog heart preparation and experimental layout (Fig. 1) have been described in detail by Isoyama et al.^{1,15} Briefly, the isolated heart was perfused by a support dog's arterial blood via a Gregg-type cannula which was inserted into an ostium of the left common coronary artery. The right coronary artery was ligated at its origin and the right ventricular free wall was resected. The coronary venous blood was collected and returned to the support dog's femoral vein. The coronary perfusion blood was frequently sampled to measure pH, P_{O_2} , P_{CO_2} and hemoglobin (PHM72-MK2, BMS-MK2 and hemoxymeter OSM3 Radiometer), and the arterial blood gas and hemoglobin were maintained within their physiological ranges (pH: 7.40 ± 0.5 , P_{O_2} : 70–120 mmHg and the hemoglobin: 11–14 g/dl) by blood transfusion, infusion of sodium bicarbonate and/or O_2 inhalation to the support dog. The temperature in the coronary perfusion line was regulated with a thermostatic system at $37.0 \pm 0.5^\circ\text{C}$ and as a result, the temperature of the left ventricle monitored by a thermister thermometer (Model MGA3-239 Shibaura Denshi) was also maintained at the same level.

The aorta was cut at a point about 1.5 cm distal from the aortic valve and connected to an artificial arterial system with the equilibrium input impedance of a dog's systemic arterial tree. The system consisted of four components, i.e., inertance (L), total arterial compliance (C), characteristic resistance (R_c), and peripheral resistance (R_p). In this study, we kept the values of L, C, and R_c constant within their respective physiological ranges, i.e., $L = 10 \text{ dynes} \cdot \text{sec}^2 \cdot \text{cm}^{-5}$, $C = 2 \times 10^{-4} \text{ dynes}^{-1} \cdot \text{cm}^5$ and $R_c = 200 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$ and changed only the R_p value in a

Fig.1. Schematic diagram of experimental setup. The isolated heart is loaded with an artificial arterial system which consists of four components. L represents the inertance of the blood. Rc represents characteristic resistance. C represents total arterial capacitance. Rp represents peripheral resistance. OF, a small reservoir with an overflow system, is connected to the left atrium. The height of the OF is variable so that LVEDP can be adjusted under different loading conditions. R is a large reservoir with a thermostatic system. The heart is perfused with the support dog's arterial blood, using a servo-controlled peristaltic pump (SP). F is a blood filter and B is an air buffer. Electromagnetic flow probes (EMF) are mounted on the inlet of the artificial arterial system for aortic flow, coronary perfusion line for total left coronary blood flow and proximal portion of left circumflex artery for circumflex coronary blood flow. SC is a screw clamp which is mounted on a portion just distal to circumflex EMF.

TABLE I SYSTEMIC AND CORONARY HEMODYNAMICS DURING AFTERLOAD REDUCTION

	Control $R_p (\times 10^3 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5})$		After CFX stenosis			
	10.5	16.1	10.5	6.2	4.7	3.3
LVP (mmHg)	125 ± 3	118 ± 4	$108 \pm 4 \dagger \dagger$	$91 \pm 5^*$	$78 \pm 6^{**}$	$73 \pm 5^{**}$
Mean AoP (mmHg)	99 ± 2	96 ± 7	$86 \pm 5 \dagger$	$67 \pm 5^*$	$55 \pm 5^{**}$	$46 \pm 7^{**}$
CO (ml/min)	715 ± 30	465 ± 30	$625 \pm 26 \dagger$	$821 \pm 71^*$	$900 \pm 92^{**}$	$1055 \pm 100^{**}$
CFX CorF (ml/100g/min)	132 ± 12	75 ± 2	$65 \pm 5 \dagger \dagger$	$50 \pm 8^*$	$34 \pm 7^{**}$	$28 \pm 6^{**}$
LAD CorF (ml/100g/min)	132 ± 16	148 ± 22	133 ± 23	104 ± 14	$91 \pm 12^{**}$	$90 \pm 11^{**}$

Systemic and coronary hemodynamic measurements for eight dogs.

Abbreviations: LVP = left ventricular pressure; AoP = aortic pressure; CO = cardiac output; CFX CorF = mean left circumflex coronary blood flow; LAD CorF = mean left anterior descending coronary blood flow, R_p = peripheral resistance

* $p < 0.05$ and ** $p < 0.01$, compared to the value at $R_p = 10.5 \times 10^3 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ during afterload reduction by an analysis of variance. $\dagger p < 0.05$ and $\dagger \dagger p < 0.01$ compare the values of pre- and post- and post-CFX stenosis at $R_p = 10.5 \times 10^3 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ using Student's paired t test.

stepwise fashion, to alter afterload pressure. These R_p values were 16.1, 10.5, 6.2, 4.7 and $3.3 \times 10^3 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$. A wide cannula was introduced into the left atrium via the pulmonary vein and connected to a small overflow reservoir which was filled with saline. The height of the overflow reservoir was variable so that we

were able to control left ventricular end-diastolic pressure (LVEDP). Ejected and overflow saline was collected in a large reservoir and pumped back to the overflow reservoir. The temperature of the ejected saline was maintained at $37.0 \pm 0.5^\circ\text{C}$ by the thermostatic system in the large reservoir. Heart rate was kept constant at

Fig. 2. Simultaneous tracings of pressures, flows, ECGs and segment lengths. This is a typical which shows ST segment depression of ECG in the left circumflex coronary artery (CFX) perfused area after CFX stenosis and during afterload reduction. See text for details. Abbreviations: LVP = left ventricular pressure, AoF = aortic flow, LAD = left anterior descending coronary artery, Rp = peripheral resistance.

100–130 beats/min by an electrical pacemaker (Model SEN-7103M Nihon Kohden) throughout each experiment.

Measurements

Left ventricular pressure (LVP), aortic pressure (AoP) and left coronary perfusion pressure (CPP) were measured with strain gauge pressure transducers (MPU0.5 Toyo Sokki). A stiff polyethylene cannula which was introduced via the apex into the left ventricle allowed for pressure measurement in this cavity. AoP was measured at the inlet of the artificial arterial system and CPP at the side-arm of the coronary perfusion line. Instantaneous aortic flow (AoF), mean total left coronary blood flow (T CorF) and left circumflex coronary blood flow (CFX CorF) were measured using electromagnetic flow

Fig. 3. A typical tracing which shows CFX ST segment elevation after CFX stenosis and during afterload reduction. See text for details. Abbreviations: same as Fig. 2.

probes (MF-46, FF-030T or FF-020T Nihon Kohden). The value of the mean left anterior descending coronary blood flow (LAD CorF) was calculated by subtracting the value of CFX CorF from that of T CorF. Cardiac output (CO) was measured by collecting the saline ejected from the periphery of the afterload hydraulic model over 20 seconds (Fig. 1).

To assess regional mechanical function, we measured myocardial segment lengths with an ultrasonic technique.¹⁶ Two pairs of ultrasonic crystals (diameter 1.0 to 2.0 mm) were implanted in the subendocardium of the left ventricle at the centers of the areas perfused by the LAD and CFX branches (LAD and CFX areas). The crystals were oriented on the transverse axis of the ventricle and separated by about 1.0 cm. End-diastolic length (EDL) was defined at the beginning of the upstroke of the LVP trace and end-systolic length (ESL) at the end-ejection of the AoF trace. The values of EDLs were normalized so that initial EDLs (in the control

TABLE II ST SEGMENT DEVIATION AND REGIONAL MECHANICAL FUNCTION DURING AFTERLOAD REDUCTION

		Control Rp ($\times 10^3$ dyne $\cdot$ sec $\cdot$ cm $^{-5}$)		After CFX stenosis			
		10.5	16.1	10.5	6.2	4.7	3.3
<i>ST segment deviation</i>							
CFX elevation	CFX	0	1.4 ± 0.99	$1.7 \pm 1.24^\dagger$	$3.4 \pm 1.83^*$	$4.3 \pm 1.78^{**}$	$5.1 \pm 1.81^*$
(mV) n = 4	LAD	0	-0.1 ± 0.07	-0.1 ± 0.3	-0.4 ± 1.20	-0.9 ± 1.20	-0.7 ± 0.98
CFX depression	CFX	0	-1.6 ± 0.86	$-1.5 \pm 0.99^\dagger$	-2.1 ± 1.19	$-2.9 \pm 1.31^{**}$	$-4.1 \pm 1.25^{**}$
(mV) n = 4	LAD	0	0.8 ± 1.01	0.5 ± 1.30	0.7 ± 1.30	-1.0 ± 0.64	-1.4 ± 1.00
<i>Regional function</i>							
CFX (mm)	EDL	10.0	10.0 ± 0.07	10.0 ± 0.08	10.0 ± 0.10	9.9 ± 0.10	9.9 ± 0.10
n = 8	SS	1.02 ± 0.06	0.85 ± 0.08	$0.93 \pm 0.08^\dagger$	0.90 ± 0.10	0.82 ± 0.14	$0.80 \pm 0.15^*$
LAD (mm)	EDL	10.0	10.2 ± 0.13	10.1 ± 0.10	10.1 ± 0.10	10.0 ± 0.06	10.0 ± 0.12
n = 8	SS	0.85 ± 0.06	0.86 ± 0.08	$0.94 \pm 0.08^\dagger$	$1.08 \pm 0.05^*$	$1.19 \pm 0.07^{**}$	$1.27 \pm 0.12^{**}$

ECG ST segment deviation and regional mechanical function for eight dogs.

Abbreviations: same as Table I

condition: before CFX stenosis at $R_p = 10.5 \times 10^3$ dynes $\cdot$ sec $\cdot$ cm $^{-5}$) were 10 mm. Regional mechanical function was evaluated by systolic segment shortening (SS) calculated from segment lengths as follows: $SS = 10 \times (EDL - ESL) / EDL$ (mm). This normalization was performed to compare the changes in EDL and SS between different areas and dogs in which the distances of each pair of crystals were arbitrary. Moreover, following CFX stenosis, CFX SS at individual R_p values was expressed as a percentage of the corresponding LAD SS in the non-ischemic area in order to evaluate change in regional mechanical function in the ischemic area during afterload reduction, compared with that of the non-ischemic area.

Epicardial ECGs were obtained by means of two Ag-AgCl electrodes which were located close to the ultrasonic crystals in the LAD and CFX areas. The indifferent electrode was placed on the aortic root. ST segment level was determined at 100 msec after the onset of the QRS complex.¹⁷ The change in ST segment is calculated as the deviation from the ST segment level in the control condition (before CFX stenosis at $R_p = 10.5 \times 10^3$ dynes $\cdot$ sec $\cdot$ cm $^{-5}$). The cases of ST segment depression and elevation in the CFX area after CFX stenosis were separately analyzed. This particular point will be discussed later.

Experimental protocol

After surgical preparation (approximately 60 min after isolation of the heart), we adjusted LVEDP for mean AoP of 100 mmHg at the value of $R_p = 10.5 \times 10^3$ dynes $\cdot$ cm $\cdot$ sec $^{-5}$ (R_p 10.5) and adjusted LVEDP (mean value, 6 ± 1.5 mmHg) over the range 3 to 12 mmHg. It was kept constant within ± 1 mmHg throughout the experiment. CPP was kept equal to mean AoP by means of the servo-controlled coronary perfusion system throughout the experiment. A period of 30 to 45 min was allowed in order to stabilize the hemodynamics and ECG recordings. Particular care was taken with transient ST changes due to acute injury currents which accompanied the surgical procedures, and as a result, ST segments were stabilized at acceptable levels (LAD region; 0.1 ± 0.6 mV, CFX region; -0.5 ± 0.4 mV).

CFX was then partially occluded by a metal screw clamp placed just distal to the flow probe so that CFX CorF was reduced by about 50% of the pre-ischemic value at R_p 10.5; we then changed the R_p value from 16.1 to 3.3 in a stepwise manner to alter afterload pressure. At each R_p value, a period of about 3 minutes was allowed for stabilization of hemodynamics, myocardial segment lengths and ECGs. All of the data were obtained in such a steady state. In the control condition, before and after this

Fig.4. Panel A: the relationship between ST segment changes and mean AoP. ST segment elevations became significant (3.4 ± 1.8 mV; $p < 0.05$) when mean AoP was 71 ± 6 mmHg (Rp 6.2) and ST segment depression (-3.0 ± 1.3 mV; $p < 0.01$) 52 ± 7 mmHg (Rp 4.7), compared to the values at mean AoP = 91 ± 5 and 81 ± 5 mmHg (Rp 10.5), respectively. Panel B: the relationship between SS and mean AoP. CFX SS and LAD SS were expressed as a percentage of the control value (the Rp 10.5 without stenosis), with the reduction of mean AoP. LAD SS progressively increased and CFX SS appeared to be bimodal. See text for details. Abbreviations: CFX ST = ECG ST segment in the area where circumflex coronary artery distributed (CFX area); CFX SS = systolic shortening in CFX area; LAD SS = systolic shortening in LAD area; * $p < 0.05$; ** $p < 0.01$ compared to the values at Rp 10.5 without CFX stenosis.

protocol (i.e., pre- and post-protocol controls), we recorded all parameters to examine their reversibility. After these protocols, we occluded the CFX branch and injected indocyanine green from the Gregg-type cannula to delineate the areas of myocardium perfused by the LAD and CFX branches. Then the positions of the ultrasonic crystals and ECG leads were confirmed and each area of myocardium was weighed.

Data analysis

All data are expressed as mean $\pm$ standard error. Significant changes were tested by an analysis of variance during afterload changes with CFX stenosis. The comparison between before and after CFX stenosis at Rp 10.5 was performed with the Student's paired *t* test.

RESULTS

Systemic and coronary hemodynamics

Table I shows the systemic and coronary hemodynamics data in the control condition (Rp 10.5) and during afterload changes (Rp 16.1, Rp10.5, Rp6.2, Rp4.7 and Rp 3.3) after CFX stenosis in eight dogs. With CFX stenosis

at Rp 10.5, CO decreased from 715 ± 30 to 625 ± 26 ml/min ($p < 0.01$), and mean AoP decreased from 99 ± 2 to 86 ± 5 mmHg ($p < 0.05$). With afterload reduction of Rp from 16.1 to 3.3, mean AoP decreased from 96 ± 7 to 46 ± 7 mmHg. CFX and LAD CorFs decreased from 75 ± 2 to 28 ± 6 and from 148 ± 22 to 90 ± 11 ml/100g/min, respectively, while CO increased from 465 ± 30 to 1055 ± 100 ml/min.

ST segment deviation and regional function during afterload reduction

Figures 2 and 3 show ECGs and segment lengths with simultaneous LVP and AoF tracings. In four out of eight cases, CFX ST segment decreased after CFX stenosis (-1.5 ± 0.99 mV, $p < 0.05$) and continued to decrease along with the Rp reduction as shown in Fig. 2. In the other four cases, CFX ST segment elevation occurred after CFX stenosis (1.7 ± 1.2 mV, $p < 0.05$) and progressed with the Rp reduction as shown in Fig. 3. ST segment deviation data for eight dogs is shown in the upper part of Table II. There was no statistically significant difference between the ST segment depression cases and the ST segment elevation cases in the

Fig. 5. The relationship between CFX SS/LAD SS (%) and mean AoP. CFX SS/LAD SS (%) progressively decreases and becomes significant when mean AoP was 67 ± 5 mmHg (Rp 6.2), compared to the value at mean AoP = 86 ± 5 mmHg (Rp 10.5), as are 85 ± 10 vs. $105 \pm 17\%$ ($p < 0.05$). See text for details.

Abbreviations: CFX SS = systolic shortening in CFX area; LAD SS = systolic shortening in LAD area; * $p < 0.05$; ** $p < 0.01$ compared to the values at Rp 10.5 with stenosis.

values of mean AoP, CFX CorF and CFX SS after CFX stenosis at Rp 10.5. That is, in the four depression cases, mean AoP, CFX CorF and CFX SS at Rp 10.5 were 91 ± 4 mmHg, 62 ± 9 ml/min/100g and 0.94 ± 0.06 mm, respectively. In the other four elevation cases, these values were 81 ± 5 mmHg, 68 ± 6 ml/min/100g and 0.98 ± 0.07 mm, respectively.

Figure 4A shows the relationship between mean AoP and CFX ST segment deviation during afterload reduction in the presence of CFX stenosis. CFX ST segment deviations progressively changed with the reduction of mean AoP in both the ST segment elevation and depression cases. In the four ST segment elevation cases, CFX ST segment elevation became significant when Rp was reduced from 10.5 to 6.2 or less. Mean AoP in these cases at Rp 6.2, was 71 ± 6 mmHg. In the other four ST segment depression cases, further significant ST segment depression was found at Rp 4.7 or less and mean AoP at Rp 4.7 was 52 ± 7 mmHg. However, LAD ST segment deviations after CFX stenosis and during afterload reduction with CFX stenosis were not statistically significant (Table II).

The lower part of Table II shows the CFX and LAD SS data in the control condition and during afterload reduction after CFX stenosis in eight

hearts. Figure 4B shows the relationship between mean AoP and SS in the LAD and CFX areas following CFX stenosis, in which SS is expressed as a percentage of the value at Rp 10.5 after CFX stenosis. CFX SS was reduced by CFX stenosis from 1.02 ± 0.06 to 0.93 ± 0.08 mm ($p < 0.05$), and with Rp changes from 16.1 to 10.5, it slightly increased from 0.85 ± 0.08 to 0.93 ± 0.08 mm, but with a further reduction in Rp from 10.5 to 3.3 it continued to decrease from 0.93 ± 0.08 to 0.80 ± 0.15 mm. A significant decrease in CFX SS occurred at Rp 3.3 ($p < 0.05$), compared with the value of Rp 10.5 after CFX stenosis. That is, SS in the ischemic area appeared to be bimodal. In contrast, LAD SS increased from 0.85 ± 0.06 to 0.94 ± 0.08 mm ($p < 0.05$) after CFX stenosis at Rp 10.5, and progressively increased from 0.86 ± 0.08 to 1.27 ± 0.12 mm with Rp reduction from 16.1 to 3.3 (Table II, Fig. 4B). Figure 5 shows the values of CFX SS/LAD SS (%) at each Rp value following CFX stenosis. The value decreased from 112 ± 22 to $63 \pm 10\%$ with a reduction in mean AoP from 96 ± 7 to 46 ± 7 mmHg. Compared with the value at Rp 10.5, a significant decrease in the ratio of CFX SS to LAD SS was found at Rp 6.2. Mean AoP at this Rp 6.2 was 67 ± 5 mmHg, and it was higher ($p < 0.01$) than the value at which a significant decrease in CFX SS occurred.

LVEDP was kept constant throughout each experiment, as described in the 'Methods' section. CFX stenosis and the Rp reduction did not significantly change EDL in either the LAD or CFX areas, as shown in Figs. 2, 3 and Table II.

Reversibility of the experimental model

In the post-protocol control condition about 10 minutes after the release of CFX stenosis, CO decreased by 4 to 15% ($11 \pm 3\%$, NS) and the change in peak LVP was within 10% ($-6 \pm 2\%$, NS) compared to the value of the pre-protocol control, ECG ST segment and SS returned to nearly the level of the pre-protocol control condition i.e., ECG ST segment (LAD region: 0.3 ± 0.7 mV, CFX region: -0.3 ± 0.6 mV), SS (LAD region; 0.9 ± 0.08 mm, CFX region; 1.0 ± 0.09 mm).

DISCUSSION

This study was performed to demonstrate the simultaneous changes in ECG ST segment deviation and regional mechanical dysfunction during afterload reduction in a heart with

coronary stenosis and also to clarify which is more sensitive for the detection of further changes in myocardial ischemia during the intervention. Both ECG ST segment deviation and myocardial systolic shortening indicated the aggravation of regional ischemia when afterload was reduced beyond a certain level, and the former seemed to be a more sensitive indicator for detecting it. Further significant changes in ECG ST segment depression and elevation occurred at higher Rp values (i.e., higher mean AoP values) than the value in which myocardial systolic shortening significantly decreased. This relative insensitivity of myocardial systolic shortening was improved by the normalization, CFX SS/LAD SS (%).

Methodological considerations

Since we could change the Rp value at will under constant LVEDP and heart rate in our experimental model, it was possible to investigate the effects of loading changes alone on the ischemic myocardium. However, the present data should be considered in light of the following limitations. The first is the time-course effect of the heart which might modify these results because of the excised perfused heart preparation. However it is not likely that such factors would play an important role, since there was no significant change between before and after the intervention. Second, it is quite possible that in an isolated heart in air, the electrode on the aortic root is even less indifferent and unipolar leads are considered to be actually bipolar leads. However, since this reference electrode remains the same for each lead, we consider that the present conclusions are still valid. Third, we evaluated regional mechanical function by regional systolic shortening as in other studies.^{1-5,18} However, many other indicators of regional mechanical function have been proposed, i.e., maximum dl/dt ,¹⁹ mean velocity of shortening over the first 1/3 of shortening,⁷ segment work²⁰ and pressure-length loop.²¹⁻²³ It remains to be clarified which indicator of mechanical function is the most sensitive in detecting the regional ischemic change without being modified by afterload pressure. Fourth, in this study, the regional myocardial ischemia was induced by a given partial coronary occlusion. The grade of coronary stenosis may have influenced the present results. For example, in the case of total occlusion, the severity of regional ischemia might

be mainly dependent on the collateral coronary blood flow from the intact coronary branches and less dependent on the myocardial loading condition, because active shortening extremely depresses or disappears in the ischemic area.

ST segment deviation during afterload reduction after CFX stenosis

We found either ST segment depression ($n = 4$) or elevation ($n = 4$) in CFX epicardial ECG with afterload reduction after CFX stenosis. The ST segment elevation never followed the ST segment depression and vice versa in the ranges of afterload pressure examined. Furthermore, these two directional changes in CFX ST segment deviation progressively increased, as shown in Figs. 2, 3 and 4A, indicating that the regional myocardial ischemia was further aggravated by reducing afterload below a certain level of mean AoP.

Maroko et al.¹¹ Smith et al.¹² Redwood et al.¹³ and Watanabe et al.¹⁴ have reported that ST elevation due to coronary ligation was reduced by an increase in aortic blood pressure, while it was increased by afterload reduction.¹¹ Accordingly, our results concerning ST segment elevation tended to be similar to those of Maroko et al.¹¹ However, it should be noted that they used a complete rather than partial coronary occlusion. Moreover, they did not simultaneously examine the mechanical function in the ischemic area during afterload reduction.

In general, ST segment depression is related to partial thickness ischemia¹⁷ and ST segment elevation to transmural ischemia. However, according to solid angle theory,²⁴ ST depression is thought to be found even under transmural ischemia. Since we used only one electrode at each perfused area, it is quite difficult to determine whether ST depression indicates true partial thickness ischemia in our present study. In addition, since we did not examine regional coronary blood flow and there were no significant differences in CFX CorF, mean AoP and CFX SS between the ST segment depression and elevation cases at Rp 10.5 after CFX stenosis, it is unclear whether the greater ischemia was induced in the ST segment elevation cases or in the depression cases. Whatever the reason for the different ST segment deviations after CFX stenosis is, further changes in ST segment deviation during afterload reduction may suggest an aggravation of myocardial ischemic injury.

The relationship between ST segment deviation and mechanical dysfunction

We show the effects of afterload reduction on CFX SS (the ischemic area) and LAD SS (normal area) in Table II and Fig. 4B. CFX SS appeared to be bimodal. When mean AoP decreased to a certain level, a significant decrease in CFX SS occurred. The levels of mean AoP, below which ECG ST segment deviation and CFX SS showed further significant changes, differed from each other, i.e., changes in ECG ST segment deviation, especially in ST segment elevation cases, occurred at relatively higher levels of mean AoP. Thus, myocardial systolic shortening in the ischemic area seems to be a less sensitive indicator, when afterload reduction is performed in the presence of myocardial ischemia. As previously described in this manuscript, afterload reduction might mechanically increase CFX SSs, despite inadequate coronary perfusion. Namely, a presumed decrease in CFX SS due to the reduced CFX CorF is partially cancelled by the above-mentioned effect. To exclude the cancellation and to enhance the sensitivity, normalization of CFX SSs to individual non-ischemic LAD SSs, at the common afterload pressures, might be valuable. As shown in Figs. 5 and 4A, the significant changes in CFX SS/LAD SS during afterload reduction were observed at almost the same level of mean AoP at which further significant ECG ST segment deviation occurred in the cases of ST elevation. Accordingly, this normalization seemed to be valuable in increasing the sensitivity of CFX SS for detection of further changes in regional ischemia during afterload reduction.

Finally, our results seem to imply that marked afterload reduction aggravated the regional ischemia assessed by ECG ST segment changes and regional mechanical dysfunction despite an increase in cardiac output. Both ECG ST segment deviation and myocardial systolic shortening are valuable indicators for detecting the aggravation of myocardial ischemia, but the former seems to be more sensitive. To enhance the sensitivity of the latter indicator, it is necessary to take the information from the normal area into account. In the clinical situation, the afterload reduction would induce the changes in LVEDP, heart rate and cardiac contractility through the hemodynamic changes or a neuro-humoral mechanism. In addition, since the grade of coronary stenosis is quite different, it might be unrealistic to expect the

exact critical level of aortic pressure in each patient. Although there are some limitations in applying our results to clinical cases, the present study will lay the foundation for the practice of afterload reduction therapy in patients with coronary stenosis. Namely, ECG monitoring during afterload reduction therapy will give us important information as well as that of the regional mechanical dysfunction.

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REFERENCES

1. ISOYAMA S, MARUYAMA Y, ASHIKAWA K, SATO S, SUZUKI H, WATANABE J, SHIMIZU Y, INO-OKA E, TAKISHIMA T: Effects of the afterload reduction on global left ventricular and regional myocardial functions in the isolated canine heart with a stenosis of a coronary arterial branch. *Circulation* **67**: 139, 1983
2. SASAYAMA S, OSAKADA G, TAKAHASHI M, SHIMADA T, KAWAI C: Modification of regional function of ischemia myocardium by the alteration of arterial pressure in dogs. *Cardiovasc Res* **14**: 93, 1980
3. LEKVEN J, KILL F: Myocardial function in general and regional left ventricular ischemia in dogs at control and high aortic pressure. *Cardiovasc Res* **9**: 373, 1975
4. WYATT HL, PROSTASIO LL, WATERS DD, SWAN HJC, FORRESTER JS: Contrasting influences of alterations in ventricular preload and afterload upon systemic hemodynamics, function, and metabolism of ischemic myocardium. *Circulation* **55**: 318, 1977
5. PROTASIO LL, FORRESTER JS, WYATT HL, TYVERG JV, CHAGRASULIS R, PARMLEY WW, SWAN HJC: Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium. *Circulation* **52**: 400, 1975
6. BATTLER A, FROELICHER VF, GALLAGHER KP, KEMPER WS, ROSS J Jr: Dissociation between regional and ECG changes during ischemia in the conscious dog. *Circulation* **62**: 735, 1980
7. ROSS J Jr, FRANKLIN D: Analysis of regional myocardial function, dimensions and wall thickness in the characterization of myocardial ischemia and infarction. *Circulation* **53** (Suppl. I): I-188, 1976
8. SMITH HJ, KENT KM, FPSTEIN SE: Relationship between regional contractile function and S-T segment elevation after experimental coronary artery occlusion in the dog. *Cardiovasc Res* **12**: 444, 1978
9. WEBER KT, JANICKI JS, REEVES RC, HEFNER LL, REEVES TJ: Determinants of stroke volume in the isolated canine heart. *J Appl. physiol* **37**: 742, 1974
10. ELZINGA G, WESTERHOF N, The pump ability

- of the heart and the effect of coronary occlusion. *Circ Res* **38**: 297, 1976
11. MAROKO PR, KJEKSHUS JK, SOBEL BE, WATANABE T, COVELL JW, ROSS J Jr, BRAUN BRAUNWALD E: Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* **43**: 67, 1971
 12. SMITH ER, REDWOOD DR, MCCARRON WE, EPSTEIN SE: Coronary artery occlusion in the conscious dog. Effects of alterations in arterial pressure produced by nitroglycerin, hemorrhage, and alpha-adrenergic agonists on the degree of myocardial ischemia. *Circulation* **47**: 51, 1973
 13. REDWOOD DR, SMITH ER, EPSTEIN SE: Coronary artery occlusion in the conscious dog. Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia. *Circulation* **46**: 323, 1972
 14. WATANABE T, COVELL JW, MAROKO PR, BRAUNWALD E, ROSS J Jr: Effect of increased arterial pressure and positive inotropic agents on the severity of myocardial ischemia in the acutely decreased heart. *Am J Cardiol* **30**: 371, 1972
 15. ISOYAMA S, MARUYAMA Y, KOIWA Y, ISHIDE N, KITAOKA S, TAMAKI K, SATO S, SHIMIZU Y, INO-OKA E, TAKISHIMA T: Experimental study of afterload reducing therapy. The effect of the reduction of systemic vascular resistance on cardiac output, aortic pressure and coronary circulation in isolated, ejecting canine hearts. *Circulation* **64**: 490, 1981
 16. THEROUX P, FRANKLIN D, ROSS J Jr: Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. *Circ Res* **35**: 896, 1974
 17. GUYTON RA, McCLENATHAN JH, NEWMAN GE, MICHAELIS LL: Significance of subendocardial S-T segment elevation caused by coronary stenosis in the dog. *Am J Cardiol* **40**: 373, 1977
 18. WATERS DD, LUZ PD, WYATT HL, SWAN HJC, FORRESTER JS: Early changes in regional and global left ventricular function induced by graded reduction in regional coronary perfusion. *Am J Cardiol* **39**: 537, 1977
 19. SMITH HJ, GOLDSTEN RA, GRIFFITH JM, KENT KM, EPSTEIN SE: Regional contractility. Selective depression of ischemic myocardium by verapamil. *Circulation* **54**: 629, 1976
 20. TYBERG JV, FORRESTER JS, WYATT HL, GOLDNER SJ, PARMLEY WW, SWAN HJC: An analysis of segmental ischemic dysfunction utilizing the pressure-length loop. *Circulation* **49**: 478, 1974
 21. WYATT HL, FORRESTER JS, TYBERG JV, GOLDNER SJ, LOGAN SE, PARMLEY WW, SWAN HJC: Effect of graded reduction in regional coronary perfusion on regional and total cardiac function. *Am J Cardiol* **36**: 185, 1975
 22. PAGANI M, VATNER SF, BAIG H, BRAUNWALD E: Initial myocardial adjustments to brief periods of ischemia and reperfusion in the conscious dog. *Circ Res* **43**: 83, 1978
 23. MARUYAMA Y, ASHIKAWA K, ISOYAMA S, SATOH S, SUZUKI H, WATANABE J, SHIMIZU Y, INO-OKA E, TAKISHIMA T: Pressure-length loop in the ischemic segment during left circumflex coronary artery stenosis and its modification by afterload reducing in excised perfused canine hearts. *Basic Res Cardiol* **79**: 155, 1985
 24. HOLLAND RP, BROOKS H: Precordial and epicardial surface potentials during myocardial ischemia in the pig. *Circ Res* **37**: 471, 1975