The Effect of Heart Rate and Left Ventricular End-Diastolic Pressure on the Direction of ST Segment Displacement in Acute Ischemia


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Ino-Oka, E., Kitaoka, S., Shimizu, Y., Kyono, H., Maehara, K., Maruyama, Y., Ashikawa, K., Isoyama, S., Tamaki, K., Satoh, S., Suzuki, H., Ishide, N. and Takishima, T. The Effect of Heart Rate and Left Ventricular End-Diastolic Pressure on the Direction of ST Segment Displacement in Acute Ischemia. Tohoku J. exp. Med., 1984, 144 (1), 43-55 —— The correlation between the ST segment displacement and coronary blood flow in various hemodynamic conditions was studied. Five isolated, isovolumic contracting canine hearts were used. The left main and the right and left circumflex (LCx) coronary arteries were cannulated and perfused with support dog's arterial blood. Four pairs of Ag-AgCl ECG electrodes were attached to the epicardium and subendocardium in the LCx perfused area. Heart rate and left ventricular end-diastolic pressure (LVEDP) were controlled by means of right atrial electrical pacing and infusion or withdrawal of arterial blood into the left ventricle, respectively. LCx flow was reduced by 75, 50, 25% of the control level under the condition of 200 beats/min of heart rate and 20 mmHg or 5 mmHg of LVEDP, and ECGs were recorded. The ST segment elevation was observed in epicardial and subendocardial in the LCx perfused area. Heart rate and left ventricular end-diastolic pressure (LVEDP) were controlled by means of right atrial electrical pacing and infusion or withdrawal of arterial blood into the left ventricle, respectively. LCx flow was reduced by 75, 50, 25% of the control level under the condition of 200 beats/min of heart rate and 20 mmHg or 5 mmHg of LVEDP, and ECGs were recorded. The ST segment elevation was observed in epicardial and subendocardial lead ECGs when LCx flow was reduced from 110±27.5 ml/min/100 g to 72±3 ml/min/100 g under the condition of normal LVEDP (5 mmHg) and a high heart rate (200 beats/min), whereas the same degree of reduction in LCx flow under the condition of high LVEDP (20 mmHg) and high heart rate (200 beats/min) resulted in an epicardial ST segment depression associated with marked subendocardial ST segment elevation. The results suggest that the coronary flow reduction with a higher LVEDP will induce subendocardial ischemia, whereas the same degree flow reduction with a normal LVEDP induce transmural ischemia. —— ST segment deviation; heart rate; LVEDP; coronary blood flow; angina pectoris

It is widely known that there are two types of angina pectoris from the viewpoint of ST segment deviation at anginal attack, one shows ST segment depression and the other shows ST segment elevation.

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In clinical cases, the anginal attack associated with ST segment depression is more common than that with ST segment elevation. On the other hand, many experimental studies have revealed that the ST segment elevation results from coronary arterial stenosis and gradual coronary blood flow reduction (Wegria et al. 1949; Khuri et al. 1975; Lekven et al. 1975; Smith et al. 1975; Irvin and Cobb 1977). Only a few reports have shown ST segment depression by the reduction of coronary blood flow (Kato et al. 1968; Guyton et al. 1977). However, it is not clear why such a discrepancy has occurred. Thus, we attempt to produce the two different types of ST segment deviation by the reduction of coronary blood flow, and to analyze the effect of hemodynamics on the direction of ST segment deviation in coronary stenosis.

**METHODS**

Five adult mongrel dogs, weighing 18-28 kg were used as doner dogs and two mongrel dogs were used as support dogs in each experiment. The experimental arrangement is schematically presented in Fig. 1. The dogs were anesthetized by intravenous injection of 25-30 mg/kg sodium pentobarbital. The doner dog was thoracotomized under artificial respiration and the heart was exposed. The teflon bands were prepared around the great vessels, such as the aorta, pulmonary arteries and veins, superior and inferior vena cavae and the azygos vein.

Meanwhile, the femoral arteries and veins of the support dog that was anesthetized with sodium pentobarbital (25-30 mg/kg) were exposed and polyethylene tubes were inserted into each four vessels. One femoral arterial tube was used for monitoring blood pressure of the support dog and another was separated to three ways for coronary perfusion of the heart. At the tip of one tube, a Gregg's cannula was set for left main coronary perfusion and fine

![Fig. 1. Schematic diagram of experimental arrangement.](image)

RC, right coronary artery; Lad + Sep. left anterior descending coronary artery and septal artery; LC, branch of left circumflex coronary artery; LVP, left ventricular pressure.
cannulae were set at the tips of two other tubes for right coronary and for branch of left circumflex coronary perfusion, respectively.

Each circuit has a pneumatic resister and a peristaltic pump (Harvard Apparatus, model 1215) to control the coronary blood flow, a square wave electromagnetic flow probe (Nihonkoden type MF 27), a pressure transducer (Toyosokki, type LPU 0.5) and thermocouples. The warm bath system was used for adjusting the temperature of perfused blood constantly at 37°C. \( \text{P}O_2, \text{P}CO_2 \) and pH of perfused blood were also checked frequently by Astrup apparatuses (Radiometer, BMS-MK 2 and PHM 72-MK Digital Acid-base Analyzer) during experiment and \( \text{P}O_2, \text{P}CO_2 \) and pH were kept over 70 mmHg and within their physiological range by \( O_2 \) inhalation and infusion of sodium bicarbonate and fresh arterial blood to the support dog, respectively. First, the Gregg’s cannula was inserted into the aorta of the donor dog for preparing Langendorff type perfusion and the heart was excised under the ventricular fibrillation which was induced by AC electroshock.

Then the Gregg’s cannula was inserted into the ostium of main left coronary artery. Two other fine cannulae were inserted each into the branch of left circumflex coronary artery and the right coronary artery. The aortic ostium was ligated and the rubber plug was sutured at the mitral ostium to make the isovolumetric contraction. The plug has two connecting tubes, one is used for measuring the left ventricular pressure and the other is used for adjusting the left ventricular pressure by infusion or withdrawal of warmed fresh arterial blood.

Bipolar electrodes for electrical pacing were attached to the right atrium. Five pairs of Ag-AgCl electrodes were attached to the epicardium and subendocardium (in Fig. 1, 5 epicardial electrodes were seen, subendocardial electrodes were set under each epicardial electrode) in the area perfused by the left circumflex artery. Subendocardial electrograms were recorded by means of teflon-coated stainless steel “hooked” electrodes in which 1-2 mm of teflon coating was removed at their tips. The Ag-AgCl plate was attached at the root of the aorta for an indifferent electrode. After preparing all experimental arrangement, AC electroshock was performed for defibrillation and the preparation was set into an air chamber in which temperature and humidity were kept at 38°C and 100%, respectively.

We waited 30-60 min following defibrillation till the hemodynamics and ECG ST segment level were stabilized. The left ventricular end-diastolic pressure (LVEDP) was kept at 3-10 mmHg to get the systolic pressure over 100 mmHg and each coronary flow was kept at 75-150 ml/min/100 g and then the following procedures were performed. After control recording, LVEDP and heart rate were elevated to 20 mmHg and 200 beats/min, respectively and the flow of left circumflex branch (LCx) was reduced to 75, 50 and 25% of the control level for 5 min duration. After recovery from the flow reduction, the same degree of flow reduction was performed again during LVEDP and heart rate were kept at 5 mmHg and 200 beats/min, respectively.

Finally, the heart was arrested and coronary angiography was performed from Gregg’s cannula to confirm the position of the electrodes and perfused area. The ST segment level for 5 min of reduced coronary flow was measured at 80 msec later the peak of R wave and showed as \( \Sigma \Delta \) ST, which was the sum of the ST segment changes of 4 electrodes in the epicardium and subendocardium, respectively.

**Results**

Fig. 2 represents the typical ECG changes induced by LCx flow reduction. In control tracings, LCx flow, LVEDP and heart rate were set at 70 ml/min/100 g (14 ml/min in total), 3 mmHg and 140/min, respectively. When the LCx flow was reduced to 30 ml/min/100 g (6 ml/min in total) under the condition of high LVEDP (20 mmHg) and high heart rate (200 beats/min) marked ST segment
Elevations in all but No. 2 subendocardial lead accompanied by ST segment depressions in all epicardial leads were seen. In the control recording, the heart rate was set at 200 beats/min just prior to recording for eliminating the false ST segment shift by the difference of heart rate.

Fig. 3 represents the coronary angiogram of the case whose ECG change was presented in Fig. 2. The position of ECG electrodes and coronary vasculature are shown. The avascular area was perfused by the LCx branch blood flow of which was reduced in each procedure. Another typical example showing the effect of LVEDP on the ECG ST segment shift is presented in the Fig. 4. The left panel shows ECGs under the control condition in which LVEDP, heart rate and coronary flow were set at 5 mmHg, 140/min and 130 ml/min/100 g, respectively. A slight degree of ST segment elevation was seen in subendocardial lead. The middle panel shows the ECG at 5 min after coronary flow reduction by 65 ml/min/100 g with high LVEDP (20 mmHg) and a high heart rate (200/min). A remarkable ST segment depression in epicardial lead and an ST segment elevation in subendocardial lead were seen. On the other hand, 5 min after LCx flow reduction with normal LVEDP and a high heart rate, both epicardial and suben-
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Fig. 3. The position of electrodes and coronary angiogram. Open circles indicate positions of the epicardial electrodes and hook type electrodes are seen at the subendocardium in coronary angiogram. The avascular area indicates the LCx perfused area. Four epicardial electrodes covered almost all LCx perfused area. LCx, branch of left circumflex coronary artery; LAD, left anterior descending coronary artery. The angiogram is obtained from Dog No. 3 whose ECGs are shown in Fig. 2.

<table>
<thead>
<tr>
<th>Control</th>
<th>Subend ischemia</th>
<th>Transmural ischemia</th>
</tr>
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<tbody>
<tr>
<td>Dog No. 7</td>
<td></td>
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<tr>
<td>EDP 5</td>
<td>EDP 20</td>
<td>EDP 5 mmHg</td>
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<tr>
<td>HR 140</td>
<td>HR 200</td>
<td>HR 200 beats/min</td>
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<tr>
<td>CBF 130</td>
<td>CBF 65</td>
<td>CBF 65 ml/min/100 g</td>
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Fig. 4. A typical example of ECG change in LCx flow reduction at different levels of LVEDP. When LCx flow was reduced from 130 ml/min/100 g under a high LVEDP, epicardial ST segment depression associated with subendocardial ST segment elevation is seen (middle panel), whereas the same degree of flow reduction under the normal LVEDP induced epicardial and subendocardial ST segment elevations. EDP, left ventricular end-diastolic pressure; CBF, LCx coronary blood flow.
The summary of hemodynamic and ST segment changes after flow reduction is presented in Table 1. In four of five dogs, subendocardial ST segment elevations accompanied by epicardial ST segment depressions were recorded by LCx flow reduction under a high LVEDP and high heart rate. In one experiment, an epicardial ST segment elevation was seen at the first step of flow reduction. On the other hand, the same degree of LCx flow reduction under the condition of normal LVEDP and high heart rate induced ST segment elevations in subendocardial ECGs with a slight ST segment elevation in epicardial ECGs.

**DISCUSSION**

The correlation of ST segment deviation and hemodynamics in coronary flow reduction

Many studies have suggested that the reduction of coronary blood flow below the metabolic requirement of the myocardium results in transmural redistribution of myocardial blood flow with preferential underperfusion of the subendocardial myocardium (Moir and Debra 1967; Griggs and Nakamura 1968; Ball and Bache 1976; Bache and Cobb 1977; Ellis and Klocke 1979). By the most widely accepted explanation of electrophysiological conception, such a subendocardial ischemia should result in a depression of the epicardial ST segment associated with an ST segment elevation in the subendocardial leads (Wolferth et al. 1945; Myers et al. 1948; Lepeshkin 1960; Ross 1976).

Many previous studies, however, failed to show the epicardial ST segment elevations and disappearance of the R wave (right panel of Fig. 4).

**TABLE 1. Summary of hemodynamics and ST segment deviation in acute ischemia**

<table>
<thead>
<tr>
<th>LVEDP (mmHg)</th>
<th>Heart rate (beat/min)</th>
<th>LCx flow (ml/min/100 g)</th>
<th>Mean Σ ST (mV)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epi</td>
</tr>
<tr>
<td>20</td>
<td>200</td>
<td>74±10</td>
<td>−11.5±0.6</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>72±3</td>
<td>1.8±2.4</td>
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<tr>
<td>20</td>
<td>200</td>
<td>44±9</td>
<td>−9.5±5.4</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>35±10</td>
<td>2.7±2.9</td>
</tr>
<tr>
<td>5</td>
<td>140</td>
<td>0</td>
<td>11.3±4.6</td>
</tr>
<tr>
<td>5</td>
<td>140</td>
<td>110±27.5</td>
<td>0</td>
</tr>
</tbody>
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LVEDP, left ventricular end-diastolic pressure; LCx flow, left circumflex coronary arterial flow (values are mean±s.d.); ΣST, Sum of ST segment changes in 4 electrodes at LCx perfused area (values are mean±s.d.); Epi, epicardium; Endo, endocardium. Statistical analysis was performed by variance analysis.
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Kato et al. (1968) showed ST segment depressions in epicardial lead ECGs by coronary stenosis. Guyton et al. (1977) reported that subendocardial ischemia, as well as tachycardia, could result from coronary stenosis which also induced ST segment elevations in subendocardial lead ECGs associated with ST segment depressions in epicardial lead ECGs. However, they did not analyze the correlation of ST segment changes and hemodynamics in coronary flow reduction.

Because we did not measure the regional blood flow distribution in LCx flow reduction, we have no direct evidence of subendocardial ischemia in the case in which epicardial ST segment depressions were shown. But we have performed additional experiments to support that the subendocardial ischemia was induced when ST segment depressions were shown in epicardial leads.

First, we simulated the time course of ST segment deviation following LCx flow reduction. Fig. 5 represents the typical example of time course of ST segment change in LCx flow reduction. LCx flow is reduced from 130 to 43 ml/min/100 g under the condition of high EDP and high heart rate at the left side arrow. ST segment in subendocardial lead shows a temporary depression followed by a marked elevation (upper curve), whereas ST segment depression is seen continuously in epicardial lead (lower curve). When the LCx flow recovers to the control level, the ST segment returns to the control level quickly.

The ECG is obtained from No. 1 electrode of Dog No. 3 which is seen in Fig. 2.

Fig. 5. A typical example of the time course of ST segment change in LCx flow reduction. LCx flow is reduced from 130 to 43 ml/min/100 g under the condition of high EDP and high heart rate at the left side arrow. ST segment in subendocardial lead shows a temporary depression followed by a marked elevation (upper curve), whereas ST segment depression is seen continuously in epicardial lead (lower curve). When the LCx flow recovers to the control level, the ST segment returns to the control level quickly.

Edo, subendocardial lead ECG; Epi, epicardial lead ECG; EDP, left ventricular end-diastolic pressure (mmHg); HR, heart rate (beats/min); CBF, LCx coronary blood flow.

The ECG is obtained from No. 1 electrode of Dog No. 3 which is seen in Fig. 2.
later from the peak of R wave was measured continuously. In the control condition, LCx flow, heart rate and LVEDP were set at 130 ml/min/100 g, 140/min and 5 mmHg, respectively. Then, LCx flow was reduced to 43 ml/min/100 g with a higher LVEDP (20 mmHg) and a higher heart rate (200/min) as shown in left arrow. In subendocardial leads (upper panel), the ST segment showed a transient depression followed by a marked elevation, on the other hand, in epicardial leads, a steady ST segment depression was seen (lower panel). Both ST segment shifts recovered after the hemodynamic condition was changed to the control (right arrow) level.

We assumed that those ST segment deviations could be induced by subendocardial ischemia as follows: A spherical heart model, with 2 cm inner and 3 cm outer diameter, was set and electrodes were attached at Po (epicardium) and Pi (middle of myocardium or subendocardium) (Fig. 6). In this model, we assumed that ischemic boundary gradually extended from C to I, and II, that is, following LCx flow reduction ischemia extended from the subendocardium to the epicardium (Fig. 6, left panel). The change in ST segment of each electrode is shown in the right panel. The theoretical ST segment change was similar to typical change in ST segment as shown in Fig. 5.

Further, we calculated a solid angle from each electrode as follows: The heart was reconstructed based on transsectional coronary angiograms and an avascular area was shown on its endocardial surface (Fig. 7, upper panel). Then, the boundary and each electrode were projected on the x-y co-ordinate (Fig. 7, lower panel). The boundary was separated equally to 36 segments and solid angle from each electrode was calculated assuming that each segment was a part of disk with each radius of curvature (Fig. 8). Following solid angle theory (Holland and

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**Fig. 6.** Simulation study of ST segment deviation by subendocardial ischemia (for detail see text).
Arnsdorf 1977), the amplitude of ST segment shift correlated with the solid angle. The measured ST segment change and calculated solid angle showed a good correlation in both epicardial and subendocardial leads (Fig. 9). The subendocardial lead which showed the ST segment depression was located at the ischemic boundary. From those data we suggest the subendocardial ischemia should occur in our experiments.

Bache and Cobb (1977) pointed out that the tachycardia with maximal coronary vasodilation resulted in the decrease in subendocardial blood flow. O’riordan et al. (1977), and Ball and Bache (1976) also reported that the tachycardia or exercise will impair the inner layer of the myocardium. Hoffman (1978) suggested the increased preload will result in underperfusion of the inner layer of the myocardium. Moir and Debran (1967) reported left ventricular hypertension with flow reduction induced subendocardial underperfusion. Although Guyton et al. (1977) did not comment on the effect of preload, the filling pressure was elevated to a high level when the epicardial ST segment depression was induced.
where $d\sigma$ and $\Delta V$ are area and potential of shaded part and $r$ is a distance from shaded area to electrode $P_0$. Solid angle $\Omega$ is calculated as a summation of $\Delta \Omega$ as follows:

$$\Delta \Omega = \frac{b \cdot l \cdot dl \cdot d\Phi}{(\sqrt{a^2 + l^2 + b^2 - 2a \cdot l \cdot \cos \Phi})^3}$$

$$P = \frac{k \cdot \Delta V}{4\pi} \int_0^{2\pi} \int_0^\pi \frac{b \cdot l}{(\sqrt{a^2 + l^2 + b^2 - 2a \cdot l \cdot \cos \Phi})^3} \cdot dl \cdot d\Phi$$

$$= \frac{k \cdot \Delta V}{4\pi} \cdot \Omega$$

**Fig. 8.** The calculation of solid angles.

Each divided segment was assumed a part of disk with each curvature ($R$) and was put into a homogeneous medium with conductance $k$. The potential $P$ originated from shaded area at electrode $P_0$ was represented as follows (Holland and Arnsdorf 1977):

$$\Delta P = \frac{k \cdot \Delta V}{4\pi} \cdot \frac{d\sigma \cdot r}{r^3} = \frac{k \cdot \Delta V}{4\pi}$$

where $d\sigma$ and $\Delta V$ are area and potential of shaded part and $r$ is a distance from shaded area to electrode $P_0$. Solid angle $\Omega$ is calculated as a summation of $\Delta \Omega$ as follows:

$$\Delta \Omega = \frac{b \cdot l \cdot dl \cdot d\Phi}{(\sqrt{a^2 + l^2 + b^2 - 2a \cdot l \cdot \cos \Phi})^3}$$

$$P = \frac{k \cdot \Delta V}{4\pi} \int_0^{2\pi} \int_0^\pi \frac{b \cdot l}{(\sqrt{a^2 + l^2 + b^2 - 2a \cdot l \cdot \cos \Phi})^3} \cdot dl \cdot d\Phi$$

$$= \frac{k \cdot \Delta V}{4\pi} \cdot \Omega$$

**Fig. 9** Comparison between measured ST deviation ($\Delta ST$) and calculated solid angle.

Endo, endocardial lead ECG; Epi, epicardial lead ECG.

The measured ST deviation ($\Delta ST$) is from dog No. 3 shown in Fig. 2. □, measured $\Delta ST$; □, calculated solid angle.
Our results suggest that the reciprocal epicardial ST segment depression is induced by subendocardial ischemia and that the direction and magnitude of ST segment deviation in ischemia are affected not only by the coronary blood flow but also by the hemodynamic condition of the heart.

**The characteristic and validity of our experimental model**

We used isovolumetrically contracting canine heart preparations, in which coronary blood flow was perfused by blood of the support dog and controlled by a Harvard pump at a constant rate. In this model, LVEDP, heart rate, temperature, pH, Po2 and Pco2 of perfused blood were also controlled. Those parameters may affect the ST segment deviation (Braunwald and Maroko 1976). In most previous experimental studies of coronary flow reduction, the authors did not control such parameters. Changes in those parameters by coronary stenosis should modify the pure effect of coronary stenosis. In our model, those parameters can be controlled and we could show the effect of only one variable of such factors. However, we have some problems in this model, when we apply our data to clinical cases or compare with other experimental results.

First, we set the heart preparation in the air chamber. This may alter the amplitude of QRS and ST segment levels.

Second, we sutured indifferent electrode at the root of the aorta in which the electrical potential would not be affected by the injury current of myocardial ischemia. We performed two preliminary experiments to evaluate our model. The ECG was recorded during the heart preparation was dipped into the warm saline to compare the QRS amplitude with that recorded in the air chamber. The amplitude of QRS complex was diminished approximately by 30-50% when it was recorded in the saline.

Thus, the amplitude of epicardial ST segment depression in our study may be larger than in other experimental studies. But the quantitative analysis is difficult, because in other “in situ” experiments, the epicardial lead ECG will be recorded under the condition of the cardiac surface which is exposed to the air. Thus our results could be compared with other experimental studies. Furthermore, we performed the ligation of coronary artery in open chest anesthetized dogs and recorded ECG at the aortic root using a Wilson indifferent electrode. There was no detectable change in ST segment level of ECG at the aortic root during the coronary ligation (Kitaoka et al. 1978). Thus we set the indifferent electrode at the aortic root in our experiments.

**Clinical implications**

It is well known that there are two types of angina pectoris, one shows ST segment depression and the other shows ST segment elevation at anginal attack. The former, the classic type of angina pectoris is induced by exercise or atrial pacing and some studies reported that the increase in LVEDP and a high heart
rate were observed at anginal attack (Russel and Balcon 1978; Mann et al. 1979). Furthermore, many experimental reports showed that the high heart rate and increasing preload would disturb the flow distribution to the subendocardial layer. On the contrary, anginal attack with an ST segment elevation occurs mainly at rest in which neither tachycardia nor higher level of LVEDP is observed in its initial stage. Such a hemodynamic state in anginal attack was thought similar to our study. We expect that our experiments could simulate each type of angina. This study will contribute to analyze the pathophysiological mechanism of ST segment deviation in angina pectoris. However, there are some problems in applying our results to clinical situations, because we observed only direct lead ECG and did not record the surface lead ECG. To inverse the direct lead ECG to the surface ECG is difficult. It may depend on the shape of ischemic border and relative position of electrodes (Holland and Brooks 1975). Further study will be needed to clear this relationship.

References


