虚血に対する心筋の反応の生理薬理学的解析

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昭和56年度科学研究費補助金（一般研究Ｂ）

研 究 成 果 報 告 書

昭和57年 3 月

研究代表者　　安孫子　保

（旭川医科大学薬理学講座）

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研　　究　　成　　果

A Physio-pharmacological Study of Myocardial Response to Ischemia

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I. Introduction

The mortality of the heart diseases, especially ischemic heart disease, is rising here in Japan, and therefore prevention and cure of the ischemic heart disease are our important and serious problem in the field of medicine. The first step to find an effective drug on the ischemic heart disease is to analyze pathophysiology of the ischemic heart and to find a principle for effective treatment of the ischemic heart disease.

In the present research project, we tried to understand the pathophysiology of the ischemic heart, and then to find the action of various antianginal drugs on the ischemic myocardium.

There are many faces in the pathophysiology of the ischemic heart; morphological, hemodynamic, and biochemical alterations. We picked up two specific points of the ischemic heart; one was thickness of the left ventricular wall and the other pH of the myocardial tissue. The former has been regarded as a sensitive indicator of the myocardial contractile ability (1, 2, 3) and the latter a sensitive indicator of metabolic changes of the myocardium (4, 5).

For this reason, the present study was divided into two; the first series of experiments in which left ventri-

cular thickness was measured, and the second series of experiments in which myocardial pH was determined.

II. Experimetal studies

1) First series of experiments

(a) Ultrasonic crystals

In this series of experiments, thickness of the left ventricular wall was measured continuously by two ultrasonic crystals that were sutured on the endocardial and epicardial surfaces of the left ventricular wall. The former was used for sending ultrasonic signals and the latter for receiving them. Fig. 1 illustrates the ultrasonic crystal for measurement of the myocardial wall thickness, and a calibration curve of the ultrasonic crystal. It can be seen that the distance between the two crystals is directly proportional to the output voltage of an ultrasonic analyzing system. Fig. 2 shows a block diagram of the ultrasonic analyzing system. By the use of A scope, one can measure the time during which ultrasonic signals transit from the endocardial surface to the epicardial. The transit time of the ultrasonic signals from the endocardial to the epicardial surface could be converted to the output voltage, which was proportional to the distance between two ultrasonic crystals, by the use of a time motion detector. Thus we can record changes in the left ventricular wall thickness on a chart paper of a polygraph continuously.

(b) Experimental procedure

Dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg) given intravenously. Under artificial respiration using room air, the left thorax was opened and the heart was exposed. The respiration gas was changed

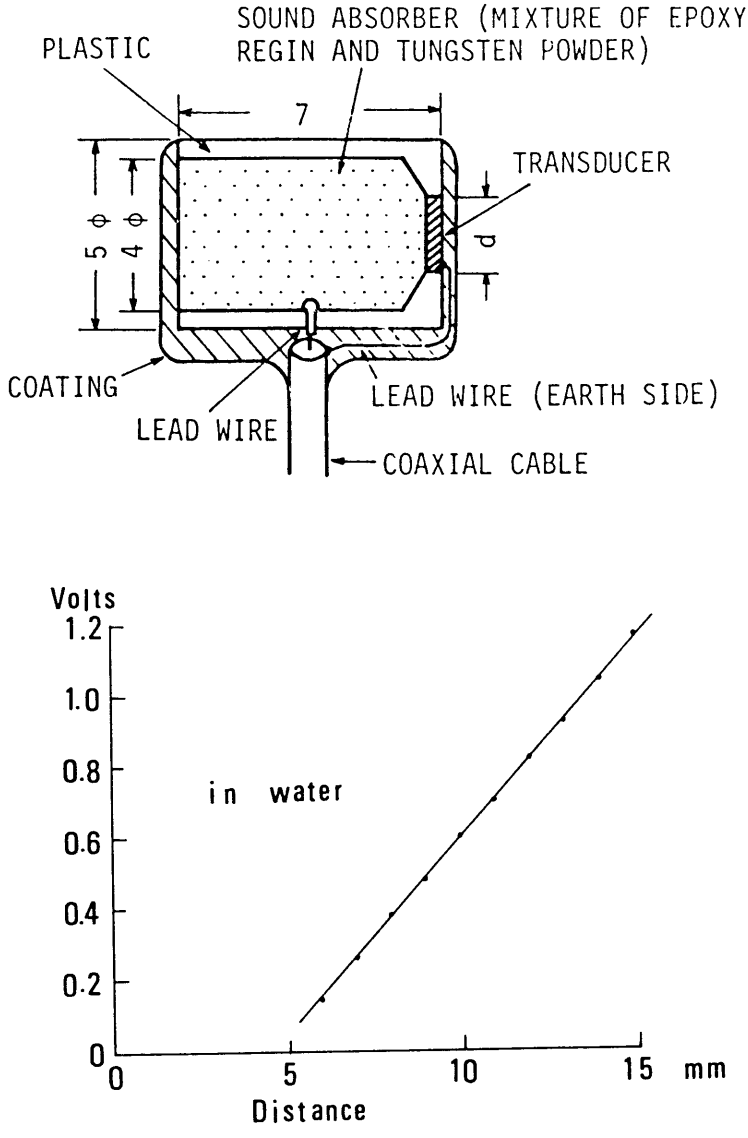


Fig. 1 Upper panel: an ultrasonic crystal (transducer) Lower panel: a calibration curve of the ultrasonic crystal. "Distance" indicates distance between two ultrasonic crystals, and "volts" indicates output voltage of an ultrasonic analyzer.

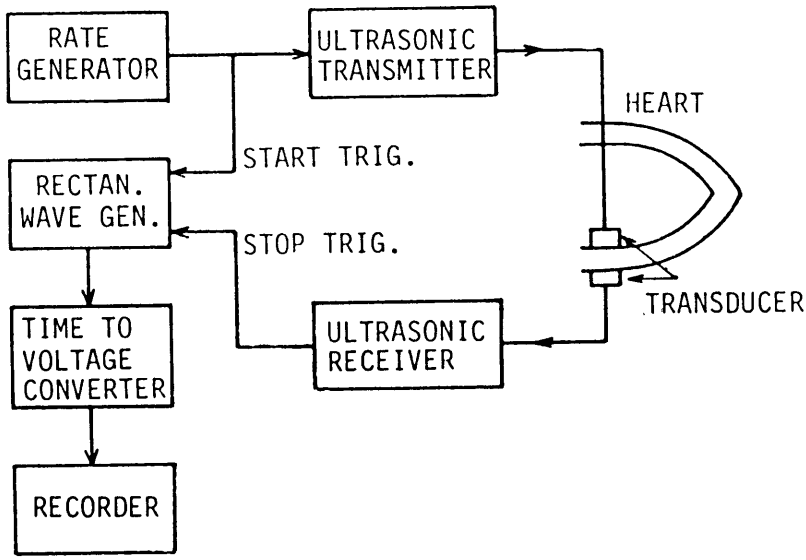


Fig. 2 Block diagram of the system for measurement of myocardial wall thickness.

from room air to pure oxygen before sutures of ultrasonic crystals, which were performed as follows. After 30 min of oxygen respiration, both superior and inferior venae cavae were occluded and an electrical stimulus (about 5 V, 50 Hz) was applied to the ventricle for few seconds to induce ventricular fibrillation. Immediately after the ventricular fibrillation, a hole was made in the apical area, through which an ultrasonic crystal was inserted to the ventricular cavity. The crystal was sutured to the endocardial surface of the area that was considered to be nourished by the left anterior descending coronary artery. Then the apical hole was sutured so that blood would not come out of the ventricular cavity, and the heart was defibrillated by a defibrillator, allowing the heart to beat again. Next, both venae cavae were released. The procedure from fibrillation to defibrillation of the heart was less than 3 min. The epicardial ultrasonic crystal was sutured so that the distance between the endocardial and epicardial crystals could be shortest. This was done by monitoring the myocardial wall thickness using A scope. Thus changes in the left ventricular wall thickness were continuously recorded on a polygraph. The left ventricular pressure and electrocardiogram were also recorded. In some experiments, the left ventricular contractile force was measured by a Walton-Brodie strain gauge arch that was sutured to the area (surface) of the left ventricle nourished by the left anterior descending coronary artery (LAD). Aortic flow and LAD flow were also measured by means of magnetic flow probes in some cases.

(c) Results and Discussion

Fig. 3 shows tracings of electrocardiogram (ECG), left ventricular pressure (LVP), aortic flow (AF), myocardial contractile force determined by the Walton-Brodie strain gauge arch (CF), and left ventricular wall thickness (LVWT) in two dogs. It is clear from this figure that the wall thickness increases during contraction of the heart and decreases after contraction. Changes in CF was similar to that in LVWT except that the peak increase in LVWT occured after a peak increase in CF. Fig. 4 illustrates chronological changes of the left ventricular pressure (LVP), myocardial contractile force determined by the strain gauge arch (CF), and left ventricular wall thickness (WT). At the point "a", LVP, CF, and WT started to increase simultaneously; this was considered to be the beginning of myocardial contraction. There was a rapid increase in LVP and CF after the point "a", and at the point "b" both LVP and CF started to decrease. On the other hand, WT continued to increase even after the point "b", and reached maximum at the point "c" when LVP and CF decreased and returned to the pre-contraction level. It is of intrest that WT reached maximum after contraction of the heart. The reason for this is unclear, but it is considered that ability of the heart to increase its wall thickness even after contraction is important because of complete ejection of blood from the left ventricular cavity (6).

The difference in wall thichness (WT) between at the points of "b" and "c" compared to the point "a" was defined as h_1 and h_2, respectively in Fig. 4. Fig. 5 shows the values of h_1 and h_2, and the effect of LAD occlusion on the

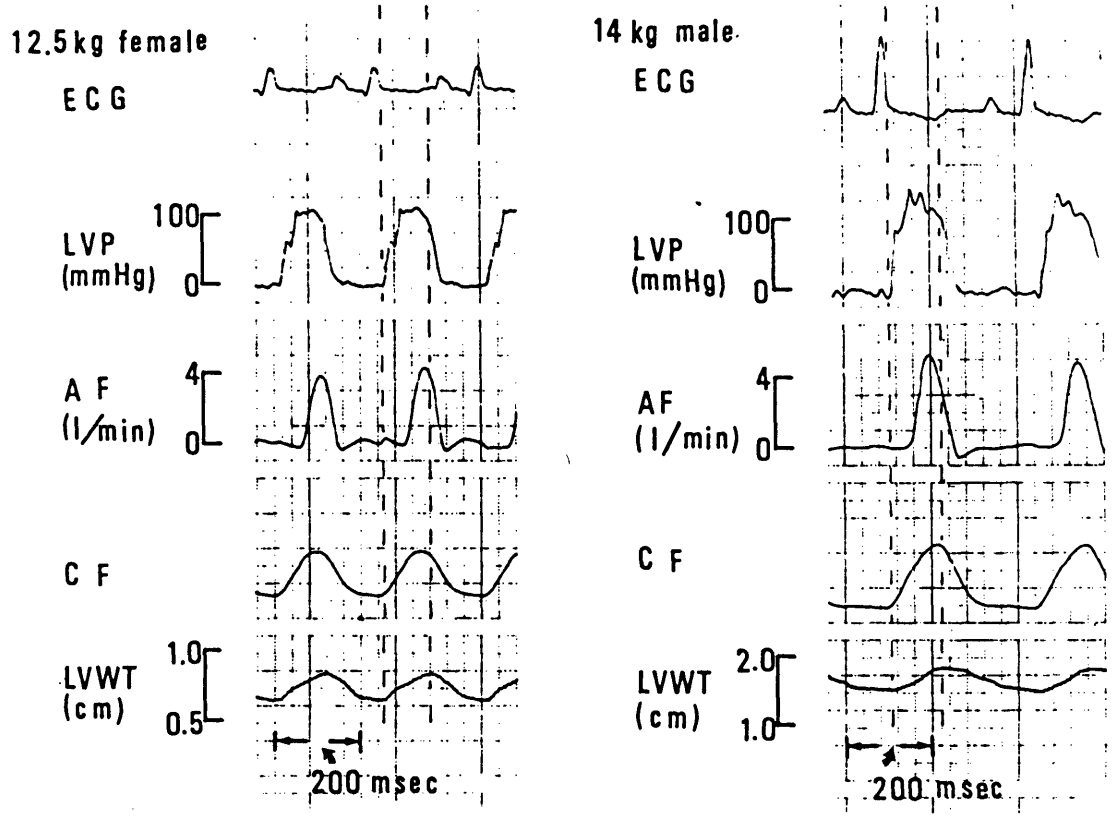


Fig. 3 Example of recordings. From top, electrocardiogram (ECG), left ventricular pressure (LVP), aortic flow (AF), myocardial contractile force determined by a Walton-Brodie strain gauge arch (CF), and left ventricular wall thickness (LVWT).

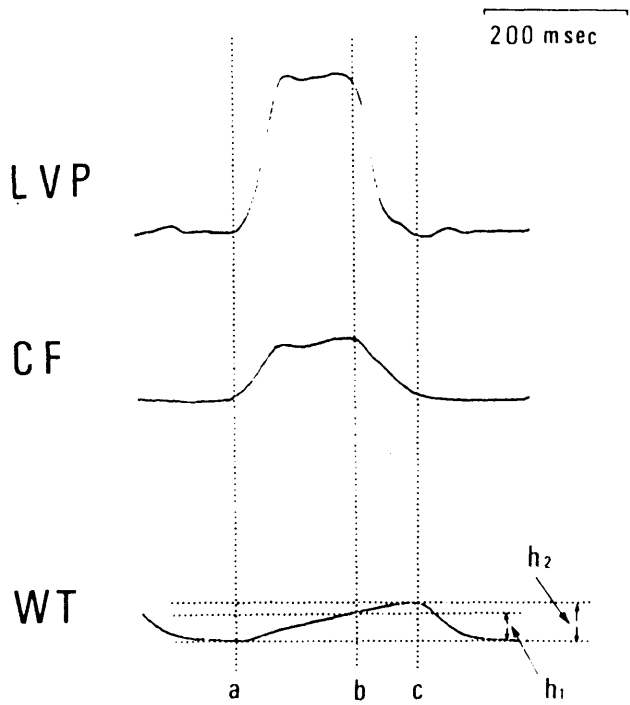


Fig. 4 Left ventricular pressure (LVP), contractile force determined by Walton-Brodie strain gauge arch (CF), and left ventricular wall thickness (WT).

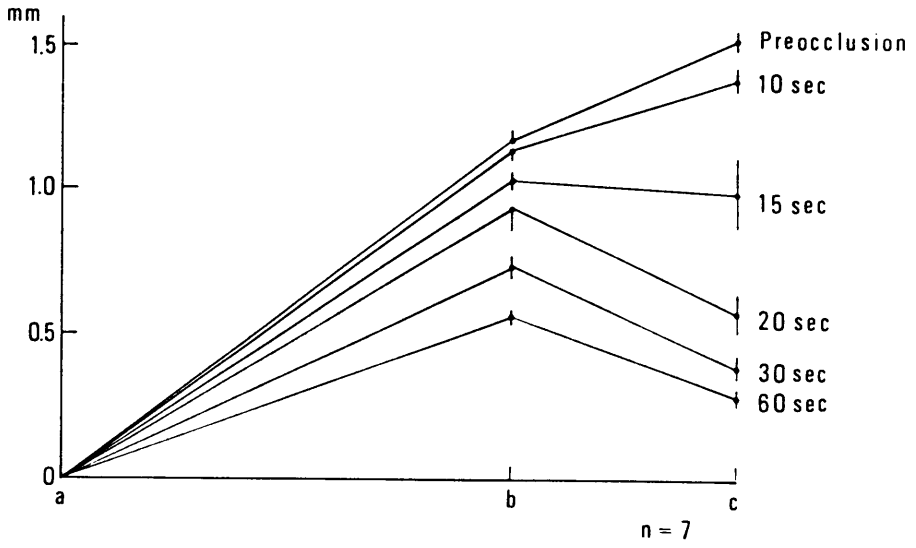


Fig. 5 Values of h_1 and h_2, which are thickness of the left ventricular wall measured at the point of "b" and "c", respectively. The values of thickness were expressed by relative values compared to the value measured at the point "a".

h_1 and h_2 values. Before LAD occlusion, h_1 was smaller than h_2; a peak increase in wall thickness was observed at the point "c". After LAD occlusion, both h_1 and h_2 values decreased, being the decrease in h_2 value was greater, and the peak increase in wall thickness moved from the point "c" to the point "b" immediately after LAD occlusion (within 15 sec). Thus h_2 was more sensitive in reflecting ischemia than h_1. This evidence can be supported by the fact illustrated in Fig. 6. Since h_2 is the wall thickness after contraction, ischemia must affect increases in wall thickness after contraction more effectively. Fig. 7 shows an example of the effect of LAD occlusion on the left ventricular wall thickness (LVWT) as well as left ventricular pressure (LVP), myocardial contractile force (MCF), LAD flow (CF), and aortic flow (AF). It can be seen from the figure that LAD occlusion reduces LVWT changes during and after contraction as well as the time for peak LVWT. Changes in MCF during LAD occlusion was not prominent compared to those in LVWT. Other hemodynamic parameters such as LVP and AF were not so prominent either. Accordingly, changes in the left ventricular wall thickness is a sensitive parameter of regional ischemia of the myocardium. These changes in the wall thickness during LAD occlusion, however, were not significantly affected by propranolol (1 mg/kg) or nitroglycerin (20 μg/kg) given intravenously before LAD occlusion (7).

2) Second series of experiments

(a) Micro glass pH electrode

In this series of experiments, pH of the beating myocardium was measured and recorded continuously. A micro

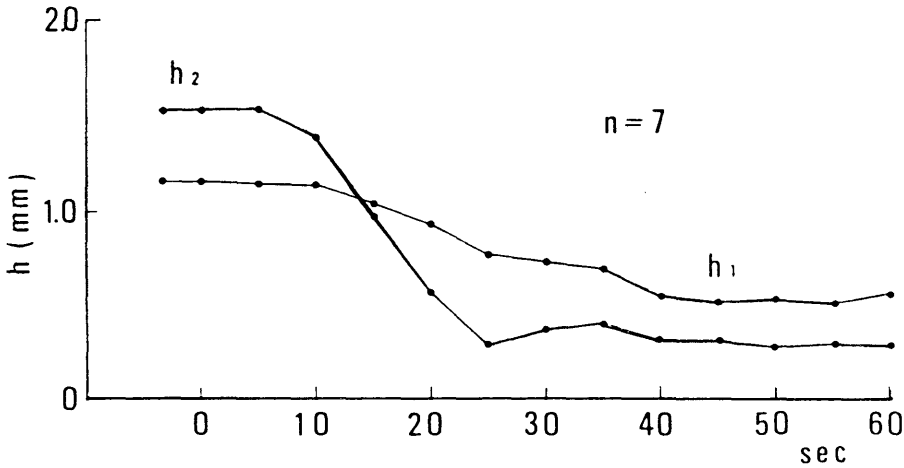
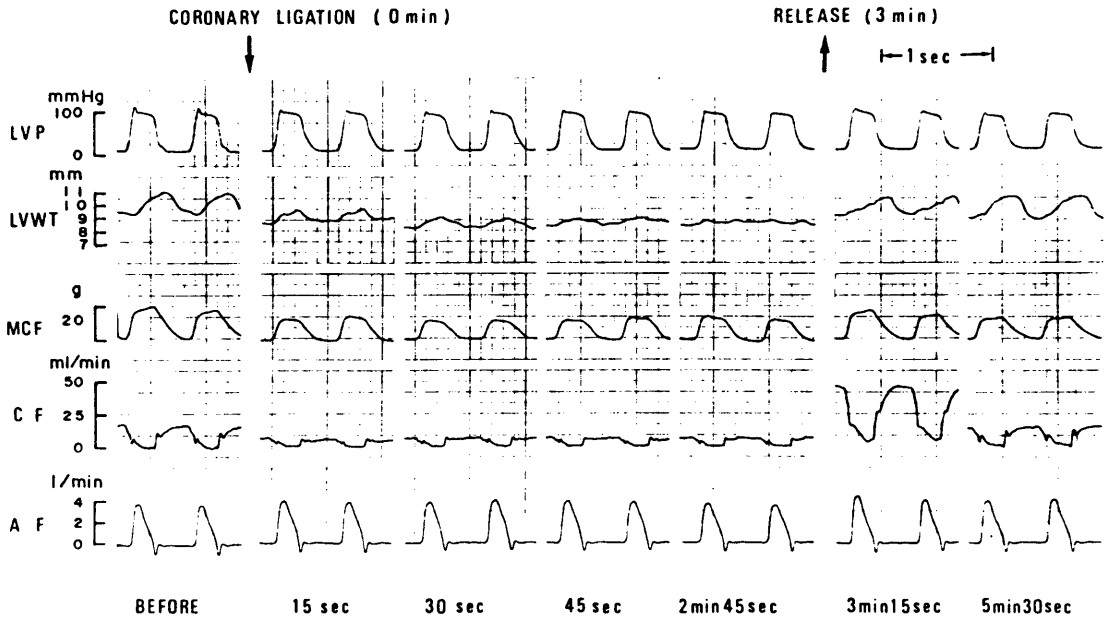


Fig. 6 Changes in the values of h_1 and h_2. Time after coronary occlusion is expressed as sec on the abscissa.



Fi. 7 Effect of coronary artery occlusion (complete ligation) on hemodynamic parameters. From top, left ventricular pressure (LVP), left ventricular wall thickness (LVWT), myocardial contractile force determined by a Walton-Brodie strain gauge arch (CF), and aortic flow (AF).

glass pH electrode (MI-410, Microelectrodes, Inc., Londonderry, New Hampshire, U.S.A.) was used for this purpose. The pH electrode had a tip of 1.2 mm in diameter, and was calibrated by standard pH solutions (pH 6.84 and 7.38) before each experiment. The myocardial pH was analyzed by a pH meter (F-7, Horiba Co., Ltd.), and was recorded on a chart paper by means of a pen recorder (R-10, Rikadenki Electronics, Tokyo).

(b) Experimental procedure

Dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg) given intravenously. The left side of the thorax was opened under artificial respiration using room air, and the left ventricular wall was exposed. Fig. 8 illustrates the experimental setup (5). LAD was separated free from adjacent tissues, and a flow probe was placed around the LAD. A snare was placed just proximal to the flow probe in order to occlude the LAD partially. In the ischemic heart experiments, the LAD flow was reduced by the snare so that the flow was reduced to about 1/3 of the original flow. The reduced LAD flow was kept constant by controlling the degree of occlusion by the snare for 90-95 min. Drugs were injected 30-35 min after partial occlusion, and the effect of drugs was observed during partial occlusion that continued for 60 min after the drug injection. In some experiments, myocardial pO_2 was also measured.

(c) Results and Discussion

Fig. 9 illustrates the control experiments in which saline solution, instead of drug solution, was injected 30-35 min after partial occlusion of the LAD. Partial oc-

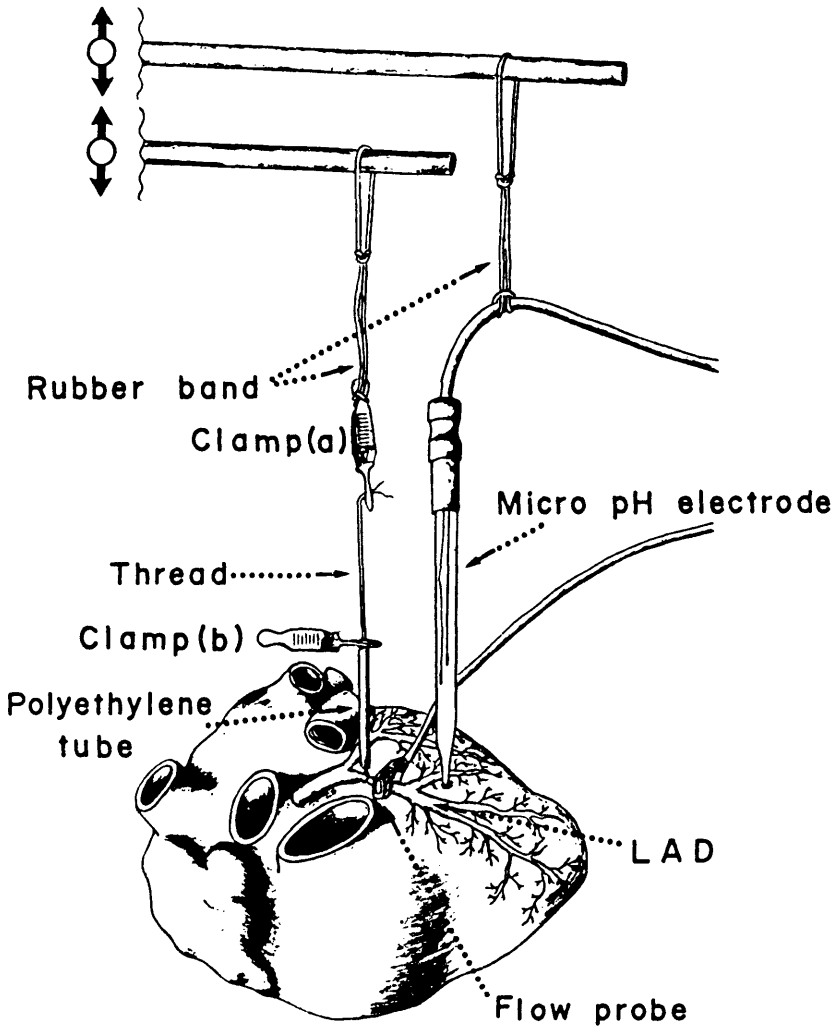


Fig. 8 Experimental setup for measuremnts of myocardial pH. The myocardial pH was measured by micro pH electrode, and blood flow in the left anterior descending coronary artery was monitored by a flow probe connected to a magnetic flow analyzer. The blood flow was reduced by a snare consisting of a polyethylene tube and a rubber band.

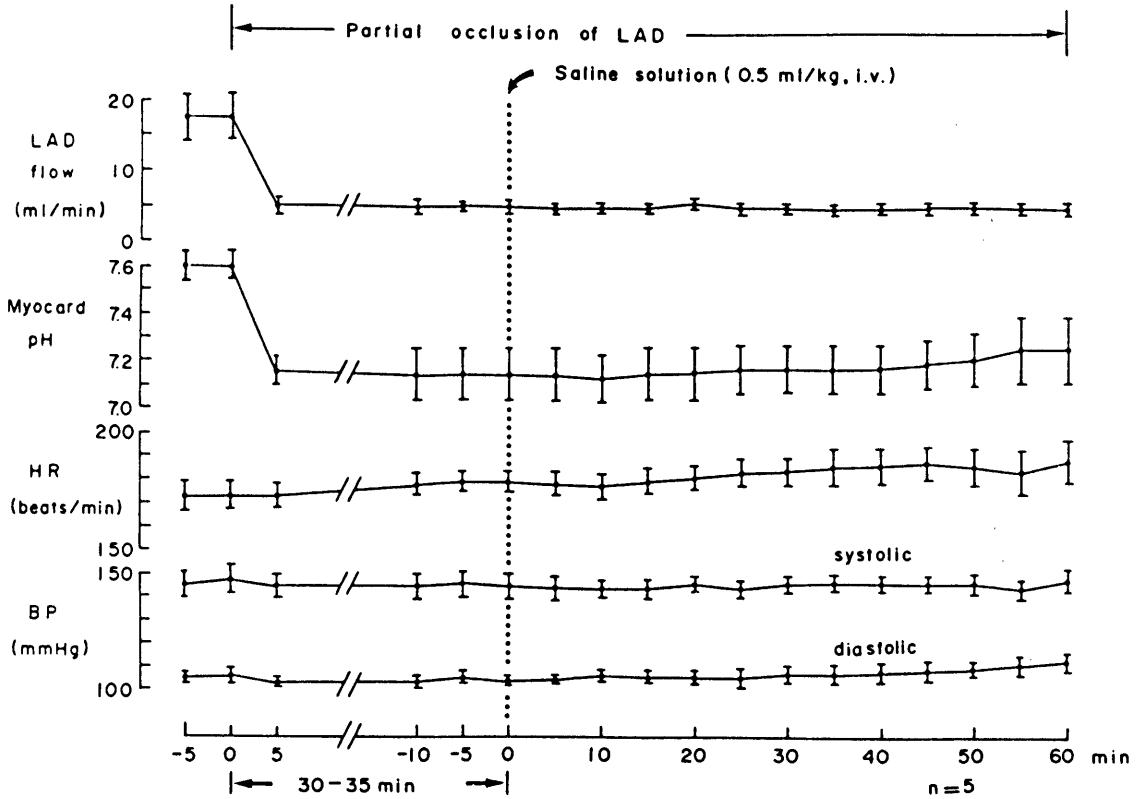


Fig. 9 The effect of saline on the ischemic myocardial pH. From top, blood flow in the LAD (LAD flow), myocardial pH (Myocard pH), heart rate (HR), and blood pressure (BP). Each point represents mean ± SE (vertical bar).

clusion reduced myocardial pH from about 7.6 to 7.1, but it did not affect heart rate and blood pressure. Saline injection did not modify myocardial pH that had been decreased by partial occlusion, and also did not modify heart rate and blood pressure. Fig. 10 shows an example of the saline control experiment.

Fig. 11 illustrates the effect of nitroglycerin (20 μg/kg). It can be seen from the figure that nitroglycerin increases myocardial pH that has been reduced by partial occlusion, without an increase in myocardial pO_2. Blood pressure decreased transiently after the nitroglycerin injection. The reason why nitroglycerin has increased the myocardial pH is unclear, however. One possibility is that the pH effect of nitroglycerin is due to the decrease of blood pressure, because a decrease in blood pressure leads to a reduction on oxygen requirement of the heart. The effect of nitroglycerin to inhibit anaerobic carbohydrate-metabolism must be related also to the pH effect of nitroglycerin (8). Other possibility is that nitroglycerin decreases myocardial contractile force only in the ischemic area (Fig. 12) (9). Nevertheless, it is not quite sure what is the most important cause of the pH increase induced by nitroglycerin.

Fig. 13 shows the effect of propranolol (1 mg/kg). It is evident that propranolol increased myocardial pH that had been reduced by partial occlusion of the LAD. Propranolol also increased myocardial pO_2 and decreased heart rate. The pH effect of propranolol may be due to an increase in collateral flow induced by the drug, leading to an increase in myocardial pO_2, and/or due to a decrease of cardiac work

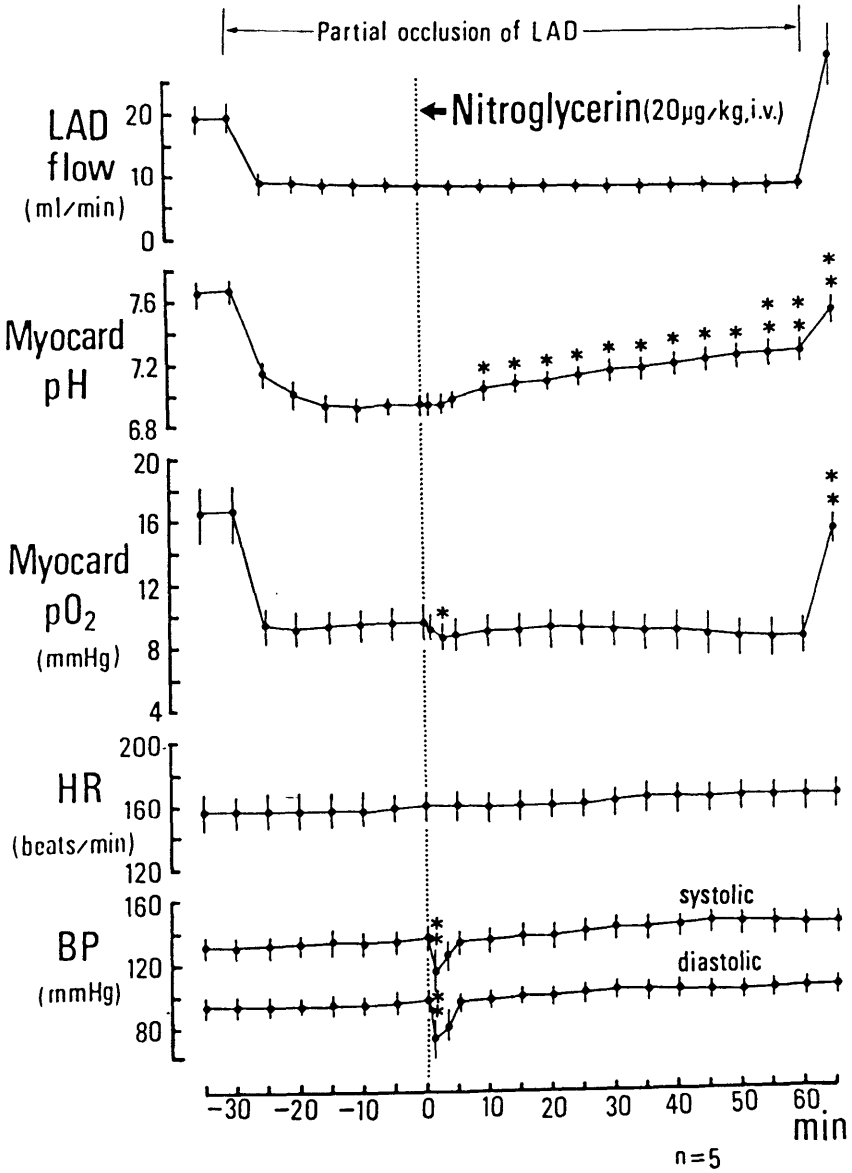


Fig. 11 The effect of nitroglycerin on the myocardial pH and myocardial pO_2. At "-30 min" the LAD was occluded partially, and at "0 min" nitroglycerin was injected.

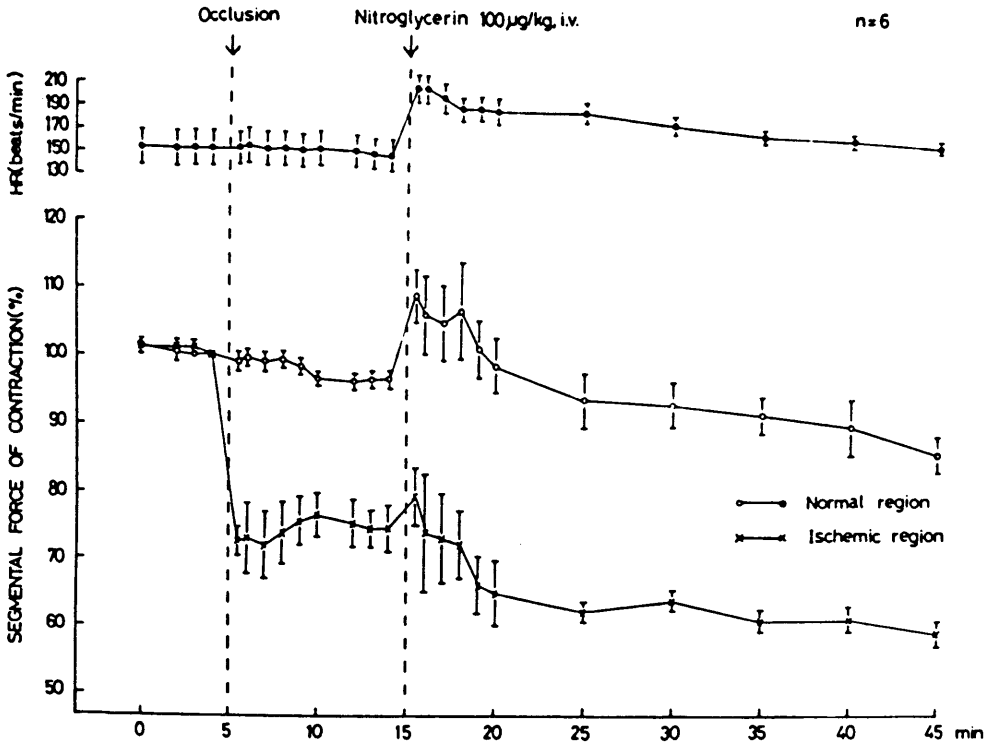


Fig. 12 Effect of nitroglycerin on regional myocardial contractile force (determined by a Walton-Brodie strain gauge arch) in both normal (circumflex) and ischemic (LAD) regions. At "5 min" LAD was occluded completely, and at "15 min" nitroglycerin was injected.

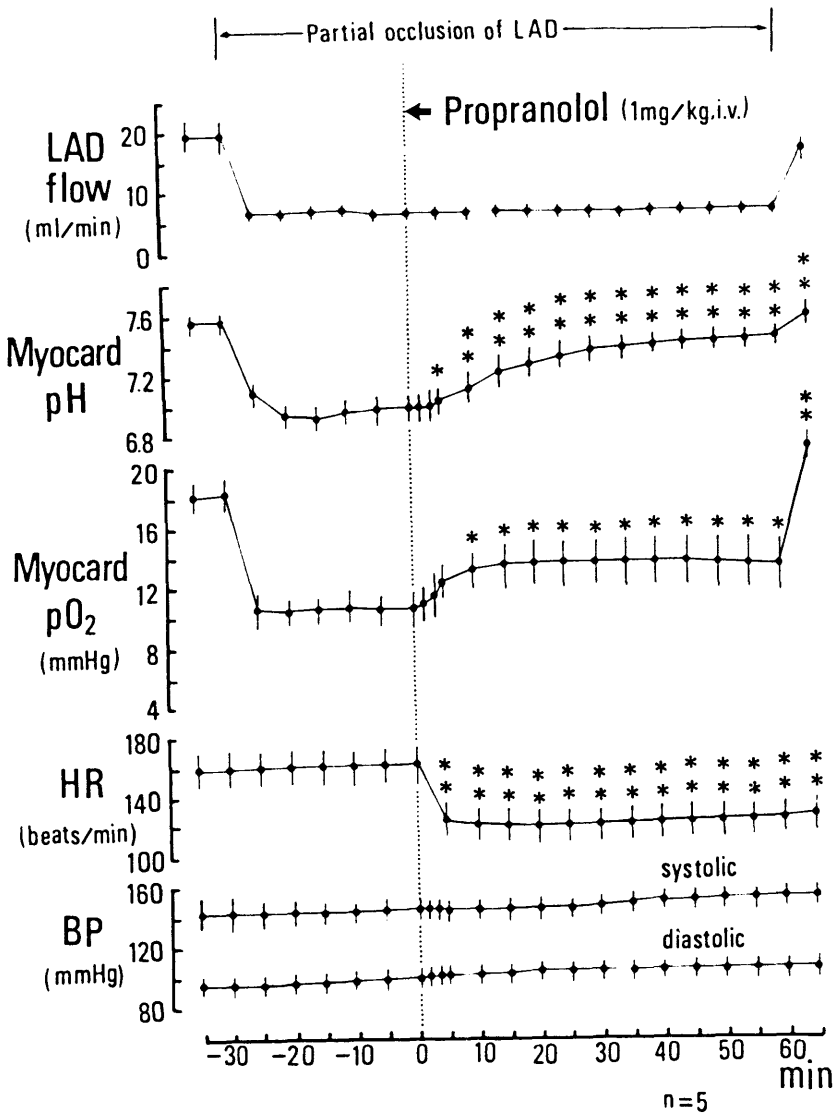


Fig. 13 The effect of propranolol on the ischemic myocardial pH. Symbols are those given in Fig. 9.

resulted from decrease in heart rate. There is a question, however, whether membrane stabilizing effect of propranolol is responsible for its pH effect. Therefore, soltalol, a beta-adrenoceptor antagonist without having membrane stabilizing effect, was used in the next experiments. Fig. 14 shows that sotalol (5 mg/kg) also increases myocardial pH that has been reduced by partial occlusion. Even in the paced heart, in which heart rate was kept constant, sotalol increased the ischemic myocardial pH effectively (Fig. 15). On the contrary, sotalol was ineffective on the non-ischemic myocardial pH (Fig. 16). These results indicate that beta-adrenoceptors are involved in the changes in myocardial pH, under ischemic conditions (10).

There is another question as to whether beta 1- or beta 2-adrenoceptors are involved in the ischemic myocardial pH changes. Because both propranolol and sotalol block beta 1- and beta 2-adrenoceptors, the results of these experiments do not suggest which receptors are more important in changes in ischemic myocardial pH. In the next experiments, therefore atenolol that blocks beta 1-adrenoceptors selectively was used. As seen in Fig. 17, atenolol (1 mg/kg) increased myocardial pH that had been reduced by partial occlusion of the LAD. Accordingly, it can be concluded that at least beta 1-adrenoceptors are involved in pH changes in the ischemic myocardium. It is not certain that a small decrease in blood pressure is responsible for the pH effect of beta-adrenoceptor antagonists (Fig. 15), but there is a possibility that metabolic effect of beta-adrenoceptor antagonists is also responsible for the pH effect of the drugs.

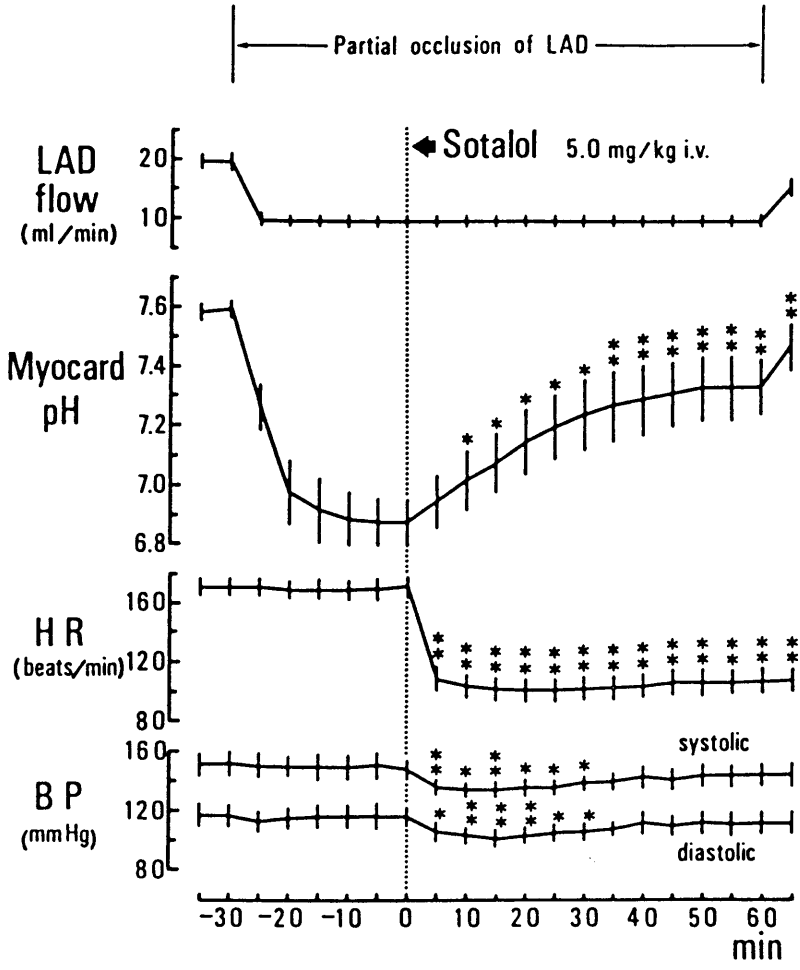


Fig. 14 The effect of sotalol on the ischemic myocardial pH. Symbols are those given in Fig. 9.

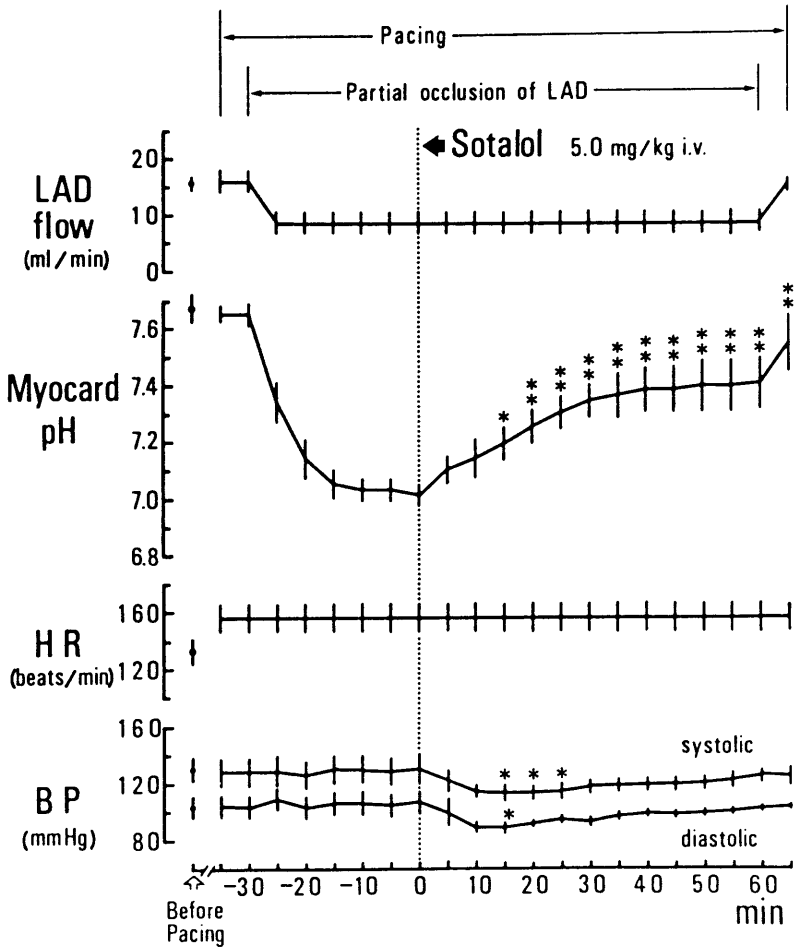


Fig. 15 The effect of soltalol on the ischemic myocardium that was paced by an electric stimulator. Symbols are those given in Fig. 9.

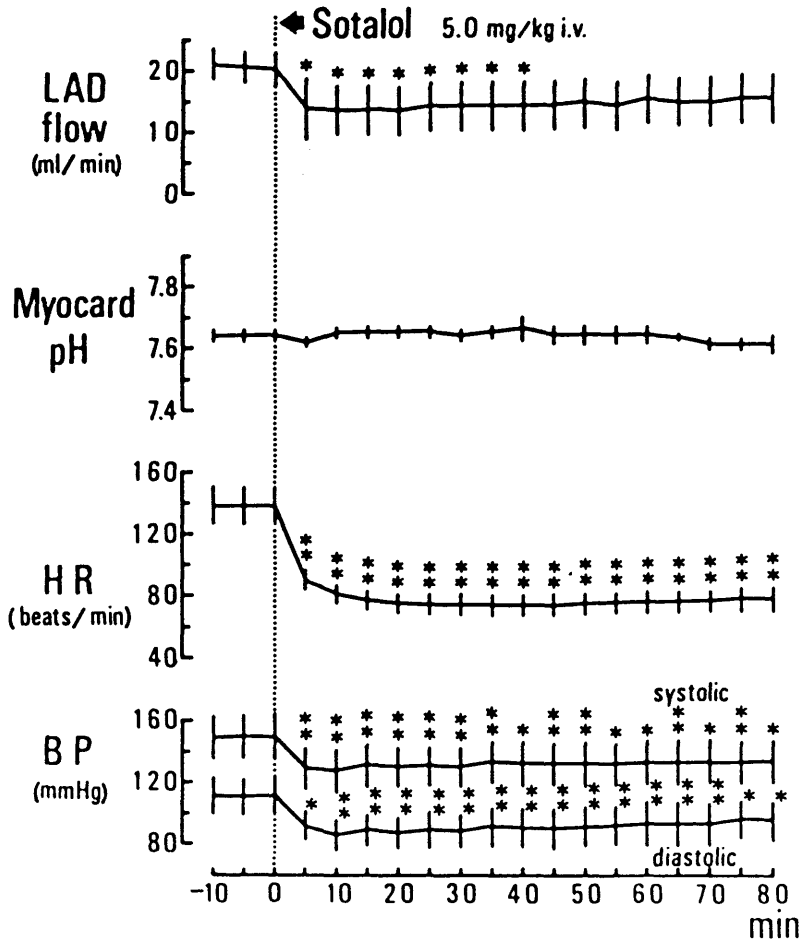


Fig. 16 The effect of sotalol on the non-ischemic myocardial pH. Symbols are those given in Fig. 9.

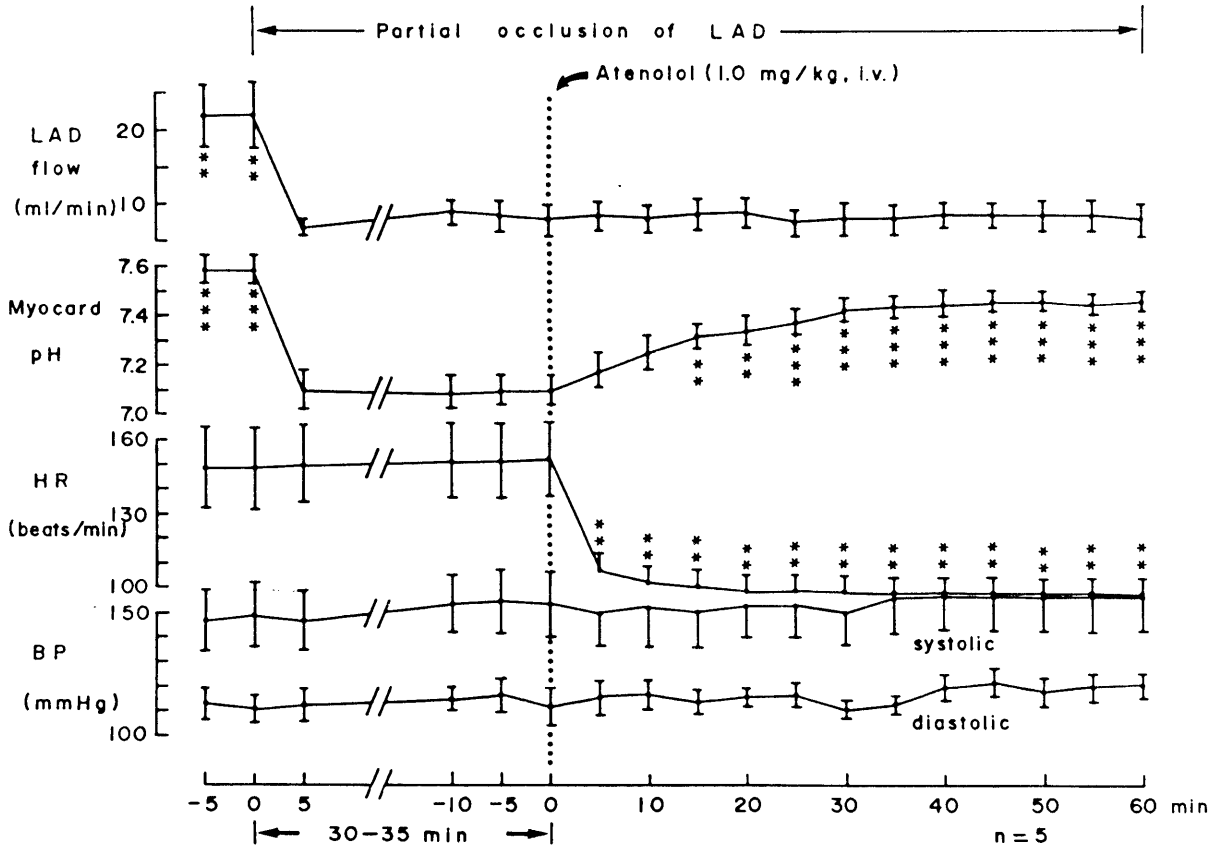


Fig. 17 The effect of atenolol on the ischemic myocardial pH. Symbols are those given in Fig. 9.

The foregoing discussion supports the view that beta-adrenoceptors are important in decreasing myocardial pH during ischemia. However, it arises a question why nitroglycerin increases the ischemic myocardial pH, and whether other coronary vasodilators are also capable of increasing ischemic myocardial pH. We examined the effect of dipyridamole (250 μg/kg), a potent coronary vasodilator, but it failed to increase the ischemic myocardial pH. SG-75 (50 μg/kg), another coronary vasodilator, however, increased the ischemic myocardial pH (Fig. 18). Therefore, there is a possibility that only coronary vasodilators that improve nutritional circulation (instead of A-V bypass circulation) to the myocardial cells can increase the ischemic myocardial pH, although it is not quite sure that nitroglycerin and SG-75 increase nutritional flow and that dipyridamole does not. It should be noted that all the coronary vasodilators increase total coronary coronary flow, but this does not necessarily mean that all the coronary vasodilators increase the nutritional circulation to the myocardial cells. In recent studies, we found that diltiazem increased the ischemic myocardial pH, but nifedipine did not. Both diltiazem and nifedipine are calcium channel blockers as well as coronary vasodilators. Therefore, it seems likely that the effect of caclcium channel blockers is not simple but complicated, and that we cannot predict which drugs are capable of increasing ischemic myocardial pH, except for beta-adrenoceptor antagonists. In this regard, it is of interest to note that pantethine, which can be converted to coenzyme A in the liver, also increased the ischemic myocardial pH without a significant increase in myocardial pO_2 (Fig. 19). The pH effect of pantethine is probably due to

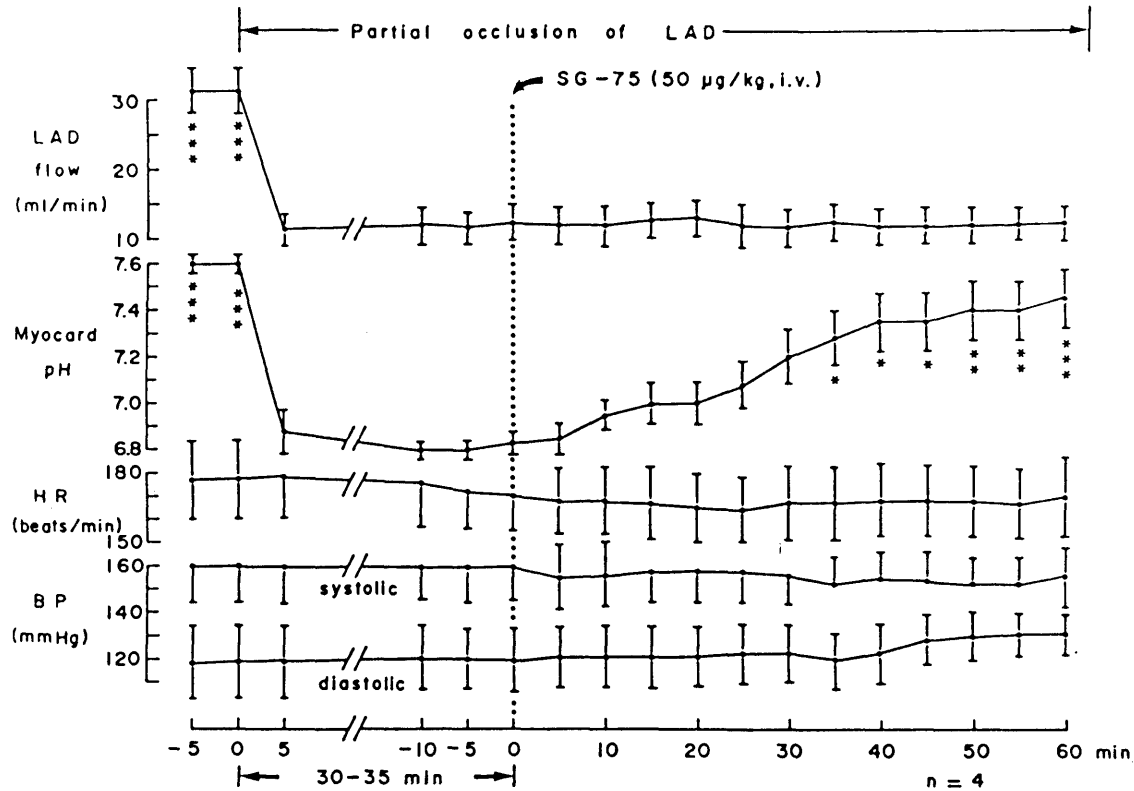


Fig. 18 The effect of SG-75 on the ischemic myocardial pH. Symbols are those given in Fig. 9.

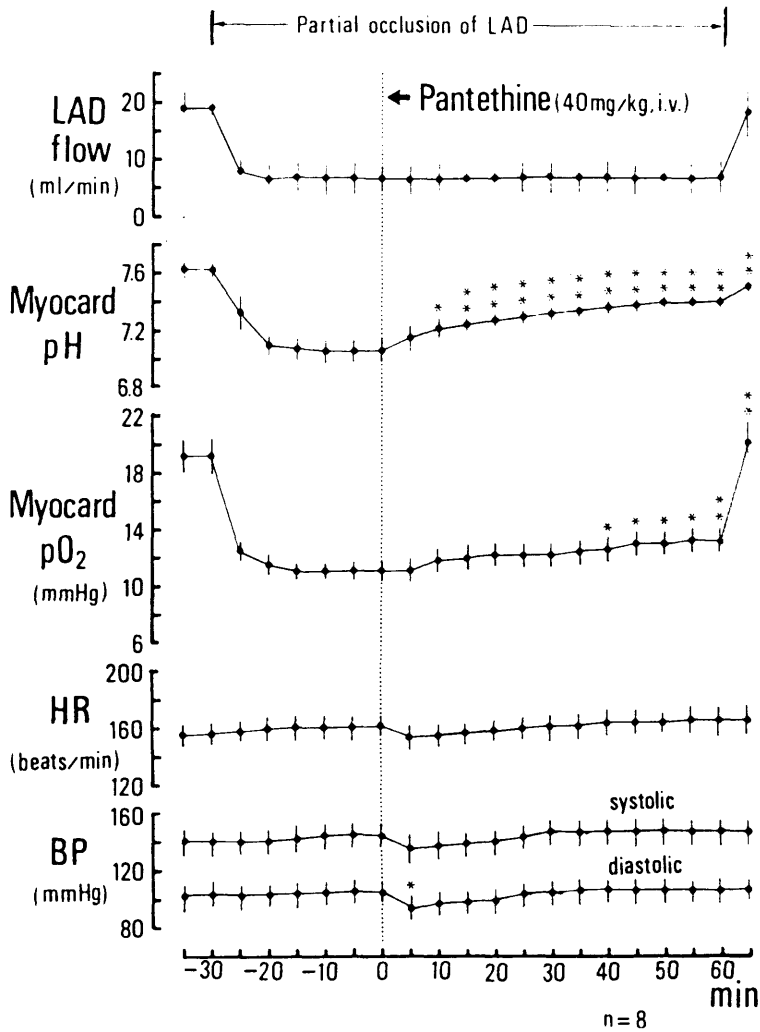


Fig. 19 The effect of pantethine on the ischemic myocardial pH. Symbols are those giben in Fig. 9.

its metabolic effect, because it prevents accumulation of lactate and decreases the levels of adenosine triphosphate and creatine phosphate during partial occlusion of the LAD (11).

III. Overview and Conclusion

Occlusion of the left anterior descending coronary artery (LAD) decreased thickening of the left ventricular wall and also decreased myocardial pH with a decrease in regional contractile force. The former results accord with those by Goldstein and De Jong (1), Sasayama et al. (2), and Komer et al. (3), and the latter with those by Ichihara et al. (4), Benzing et al. (12), Gebert et al. (13), and Pieper et al. (14). Although there are no reports regarding which parameter, wall thickness or myocardial pH, is more sensitive to ischemia, both parameters are considered useful in evaluating ischemic state of the heart. Drug effect on these parameters, however, was different; wall thickening of the ischemic myocardium did not respond to drugs, while pH of the ischemic myocardium responded well to some of the drugs used. The most typical response was obtained with beta-adrenoceptor antagonists, such as propranolol, sotalol, and atenolol. Similar evidence was obtained by Pieper et al. (14) using propranolol in the isolated guinea pig heart. Thus, beta-adrenoceptor blockade is effective intervention to attenuate the myocardial pH decrease that has been produced by partial occlusion of the LAD (15, 16). Why myocardial pH decreases after coronary occlusion, and why beta adrenoceptor antagonists attenuate the ischemia-induced pH decrease?

It has been generally believed that accumulation of lactate, resulted from acceleration of anaerobic metabolism, is responsible for tissue acidosis. According to Gevers (17), however, accumulation of lactate is not responsible for, but accelerated breakdown of adenosine triphosphate (ATP) is responsible for the pH decrease in the tissue. It is certain that propranolol inhibits accumulation of lactate as well as reduction of the ATP level in the myocardium, under ischemic conditions (18). It is known that noradrenaline is released from the myocardium during ischemia (19). Noradrenaline may in turn increase the glycogen phosphorylase activity to accelerate glycogenolysis. Therefore, beta-adrenoceptor antagonists block glycogenolysis, and hence inhibit accumulation of lactate in the tissue. This is probably a reason for that lactate does not accumulate in the ischemic myocardium when the myocardium has been treated with beta-adrenoceptor antagonists. Nevertheless, this effect of beta-adrenoceptor antagonists does not explain why the decrease in myocardial pH can be attenuated by the beta- adrenoceptor antagonists. The negative inotropic effect of the beta-adrenoceptor antagonists may be primarily responsible for the attenuation of the decrease in myocardial pH.

The fact that nitroglycerin, SG-75, diltiazem, and pantethine increase the ischemic myocardial pH, supports the view that inhibition of the glycogen phosphorylase activity itself is not the direct cause of attenutation of myocardial pH changes. It should be pointed out that dipyridamole and nifedipine did not attenuate the myocardial pH that had been reduced by partial occlusion of the LAD, suggesting that the

coronary vasodilators are not always anti-ischemic (or antianginal) drugs. Thus, although diltiazem and nifedipine are both calcium channel blockers, their effects on the ischemic myocardial pH are different. Diltiazem has been shown to inhibit an increase in anerobic carbohydrate-metabolism of the heart after coronary occlusion (21), while nifedipine has not (22). This difference in the metabolic effect between diltiazem and nifedipine may be the reason why only diltiazem attenuates ischemic myocardila pH changes. However, it is not known why inhibition of the anaerobic metabolism leads to attenuation of the ischemic myocardial pH (or inhibition of ATP breakdown during ischemia).

In conclusion, regional ischemia of the heart induced by partial occlusion of the LAD decreases wall thickening of the left ventricle, and also decreases myocardial pH. The former cannot be markedly affected by drugs, but the latter can be affected by some drugs. Nitroglycerin, propranolol, sotalol, atenolol, SG-75, and patethine attenutated the decrease in myocardial pH induced by partial occlusion, but dipyridamole and nifedipine did not.

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