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Sawatari,Hisayuki
Ueba,Yasuyuki

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KOBE UNIVERSITY

Effects of Indomethacin on Sympathetic Nerve Activity during Myocardial Ischemia

Kenichi Kujime[1], Jyunko Sasaki[2], Hisayuki Sawatari[3] and Yasuyuki Ueba[1]

Myocardial ischemia induces various changes on hemodynamics. This changes partly depends on loss of myocardial contractility and partly on autonomic reflex. In the acute ischemic heart, pain and autonomic reflexes are developed by production of bradykinin or prostaglandins. As we reported before, bradykinin which was given intravenously decreased renal symathetic nerve activity reflexly. Because vagotomy diminished this response, vagal afferent pathway participated in this reflex. Furthermore, because indomethacin could block this reflex, prostaglandins might be an acting substance. However,it is not clear how this mechanism plays a role in ischemic myocardium. In this report, we used indomethacin as an inhibitor of prostaglandins synthesis. In anesthetized rabbits, cardiac sympathetic nerve activity was recorded simultaneously with arterial blood pressure and heart rate. From the relationship between arterial blood pressure and cardiac nerve activity, gain of baroreflex was measured. During myocardial Ischemia which was developed by ligation of left anterior descending coronary artery, cardiac sympathetic nerve activity and the gain of baroreflex was reduced. However, after indomethacin was given intravenously, the reduction was diminished. Thus, prostaglandins may stimulate nerve endings in myocardial ischemia. By neural reflex mechanism cardiac sympathetic nerve activity was reduced and baroreflex was desensitized. This mechanism may play an important role in cardiogenic shock by slowing heart rate or reducing cardiac contractility.

Key words
Myocardial ischemia,
Cardiac sympathetic nerve activity,
Rabbit,
Prostaglandins,
Indomethacin.

INTRODUCTION

Cardiogenic shock is one of important factors which participate in the prognosis for myocardial infarction (1). Although loss of contractility by ischemia must play an important role, neural mechanism should play a role in this phenomenon as well.

Bradykinin has a hypotensive effect by several means. As we reported before (3), bradykinin had two different mechanisms in hypotensive effect, which consisted of the direct effect on vascular smooth muscle and the suppressive effect on sympathetic nerve activity. The latter effect was considered to be develoned through an increased vagal afferent impulse in case of intravenous administration. In contrast to this, the afferent pathway may be the spinal cord when administered intra-arterially.

Bradykinin and prostaglandins are released from ischemic myocardium (5, 6). This may reduce arterial blood pressure

School of Allied Medical Science, Kobe, University[1], Kobe, Kobe Mitsubishi Hospital[2], Kobe, and Takasago Municipal Hospital[3], Takasago, Japan.

by relaxing blood vessels directly. However very little is known the role of prostaglandins related to the neural mechanism. Because indomethacin has an inhibitory effect on the synthesis of prostaglandins by bradykinin, the administration of indomethacin may clarify the role of prostaglandins in myocardial ischemia.

Autonomic neural mechanism on cardiac rhythm, resulting from myocardial infarction, have been extensively studied in human subjects and in animals.According to these results, vagal afferent pathway played very important role (4). However, the relationship between the production of prostaglandins and sympathetic nerve activity has not been cleared yet.

Therefore, the purpose of this study was to supply useful information about the influences of bradykinin or prostaglandins on sympathetic nerve activity and baroceptor reflex.

MATERIALS AND METHODS

1. Surgical Procedures

Adult rabbits of unselected as to sex and ranging from 2.5 to 3.0 kg in weight were used. They were anesthetized with urethane (1200mg/kg) administered intraperitoneally. After a tracheotomy was performed, each rabbit was ventilated on mixture of oxygen and room air using a Harvard respirator pump. Gallamine (0.2mg/kg, i. m.) was injected initially to prevent movement and was repeated during the course of the experiment as required. Blood gas was measured on occasion and kept within the physiological range with supplement of bicarbonate or oxygen as necessary.

The right femoral vein was cannulated for intravenous administration of drugs. Blood pressure was recorded through a cannula inserted into the left femoral artery. The rectal temperature was also monitored and maintained at 38°C with a heat pad.

In order to develop myocardial ischemia, a snare was applied around the left anterior descending coronary to the development of myocardial ischemia. During the procedure great care was taken not to give damage to the nerve fibers which ran along.

A balloon catheter was introduced from the right femoral artery for the purpose of measuring baroreflex (7). The gain of baroreflex was measured from the relationship between arterial blood pressure and cardiac sympathetic nerve activity. The figure was depicted on a XY recorder.

2. Recording Nerve Activity

Effect sympathetic nerve activity was recorded from a branch of the right cardiac nerve which mainly controls heart rate. The nerve was exposed under binocular microscope and placed on silver-silver bipolar electrode. The nerve activity was recorded using a high gain amplifier and measured in arbitrary unit of integrated amplitude. These were recorded on chart paper simultaneously with arterial blood pressure and heart rate.

3. Protocol for Myocardial Ischemia

1) Experiment 1

After all parameters were stabilized, each control level was recorded. By constriction of the coronary artery with the snare, myocardial ischemia was developed. Changes in arterial blood pressure, heart rate and cardiac nerve activity were recorded simultaneously. After 10 minutes continuous recording, the con-

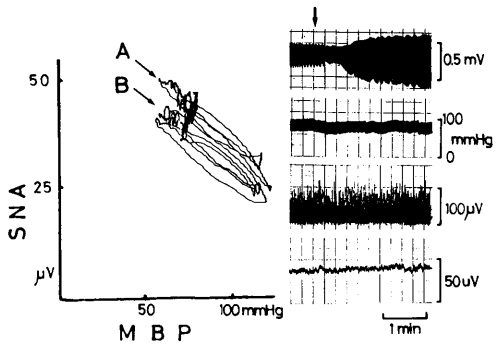


Figure 1. Typical changes during myocardial ischemia.
On the left panel, the relationship between mean cardiac sympathetic nerve activity (mSNA) and mean blood pressure (MBP) are shown. Line A is the correlation obtained before myocardial ischemia and line B is one obtained after constriction. On the right panel, changes of EKG, blood pressure, sympathetic nerve activity and mean sympathetic nerve activity are shown from top to bottom.

striction was released. Before and 10 minutes after the development of myocardial ischemia, baroreflex gain was measured by a chage in arterial blood pressure.

2) Experiment 2

After indomethacin was given intravenously at a dose of 15mg/kg, myocardial ischemia was developed by the same method as the experiment 1. The results were compared with ones of experiment 1.

4. Data Analysis

The results are graphed in terms of mean ±S.E.M. Analysis of data was performed using Student's test or ANOVA test (8). The criterion for statistical significance was $P<0.05$.

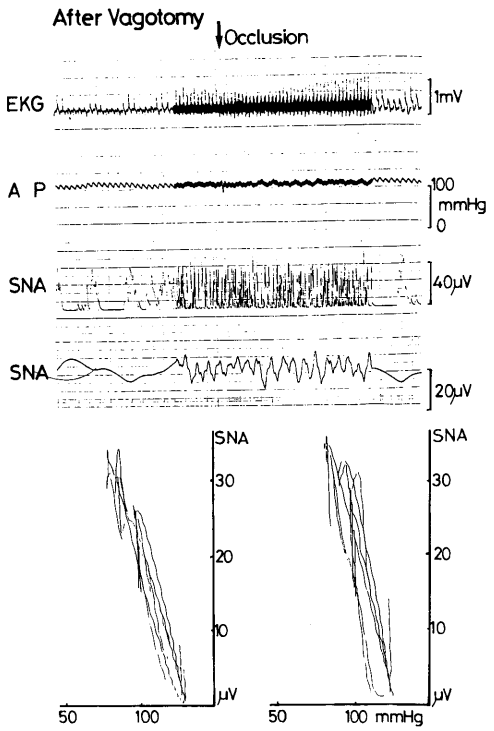


Figure 2. Typical changes after vagotomy.
The top of the panel shows the changes of EKG, ABP (arterial blood pressure, SNA (cardiac symathetic nerve activity) and SNA (mean cardiac sympathetic nerve activity) after vagotomy. As shown in the bottom panel, the left line is the result obtained before myocardial ischemia and the right line is the results 10 minutes after myocardial ischemia.

5. Materials

The drugs used in this experiment were as in the following.: Indomethacin (Sumitomo Pharm. Co.), Gallamine (Teikoku Sangyo Co), Urethane (Wako Chem. Co.)

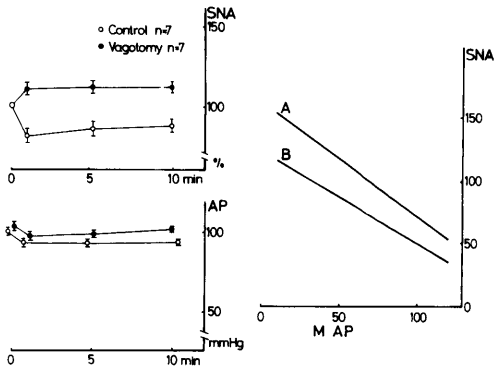


Figure 3. Summarized results without and with vagotomy.
Figure 3 demostrates the summarized results of SNA, mAP on the left panel and the correlation between the two on right panel. The line A was obtained after vagotomy in 7 rabbits. The line B was obtained in 7 rabbits without.

RESULTS

1. EFFECTS OF MYOCARDIAL ISCHEMIA ON CARDIAC NERVE ACTIVITY AND BAROREFLEX

Figure 1 represents the typical changes in electrocardiogram (EKG), arterial pressure (AP), Cardiac sympathetic areve activity (SNA) and mean cardiac nerve, activity (mSNA) during myocardial ischemia. On the left panel, the relationship between mSNA and mean blood pressure (MBP) are shown. Line A is the correlation obtained before constriction and line B is one after constriction. It is clear that the curve is shifted to left. This indicates the desensitization of baroreflex.

Figures 2 shows effects of vagotomy on this reflex. After bilateral vagotomy, the shift of the curve was diminished.

Figure 3 demonstrates the summarized results of SNA, mAP and the correlation between the two parameters. As clearly shown in the left panel, SNA and mAP were diminished in the control (intact) group with statistical significance. In contrast, vagotomy prevented myocardial ischemia from inducing the decrease in SNA. The decrease in mABP was minimized as a result.

As for the baroreflex shown in the right panel, the curve was shifted after (A) vagotomy in comparison with the result obtained before (B) vagotomy. This result may indicate the desensitization of baroreflex.

2. EFFECTS OF INDOMETHACIN

Figure 4 shows the results before and after indomethacin treatment. Without indomethacin (control) the curve was shifted to left as is shown in panel A (before) and B (after) and SNA was reduced. After indomethacin treatment, the shift of the curve and decrease in SNA were not observed.

Figure 5 represents the summarized results before and after indomethacin treatment. After indomethacin treatment the decrease in SNA was changed to increase above the control value. The decrease in mBP was also minimized. The curve of the correlation was inverted after indomethacin treatment in the same manner as was observed in vagotomized group.

DISCUSSION

1. PRODUCTION OF PROSTAGLANDINS IN THE ISCHEMIC MYOCARDIUM

Thus, myocardial ischemia suppressed cardiac nerve activity and desensitize baroreflex. Furthermore, this response

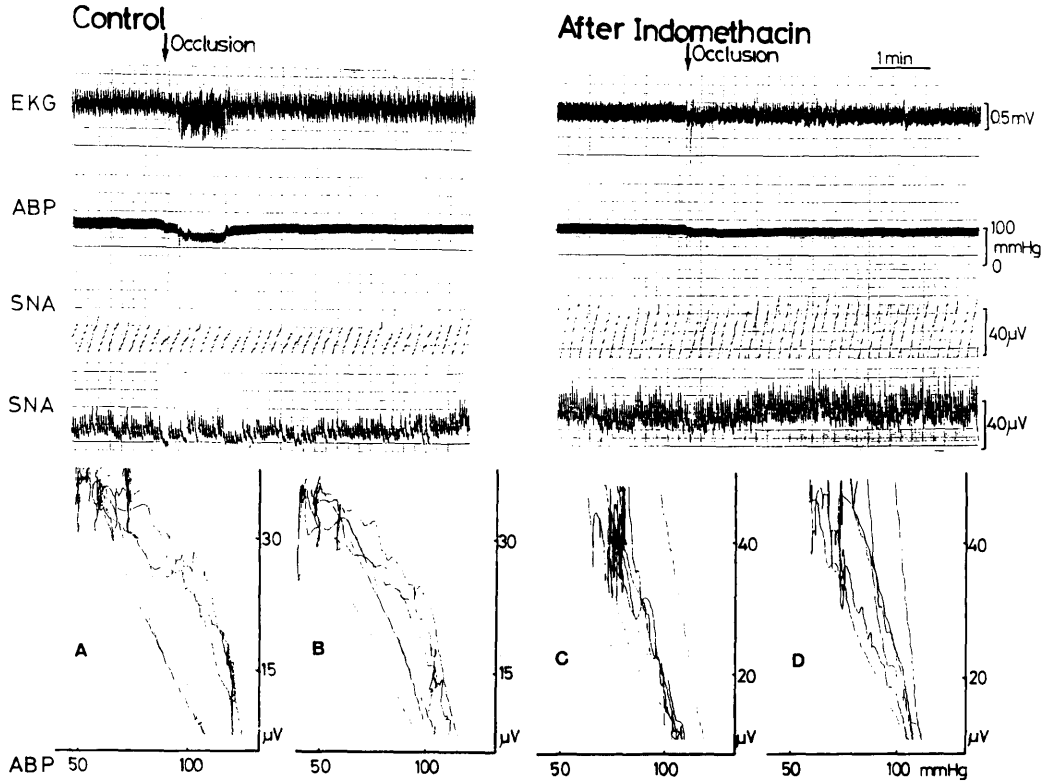


Figure 4. Typical results without and with treatment of indomethacin.
On the left panel the results of the rabbit without indomethacin treatment were shown. On the right panel the results with indomethacin treatment were shown.
In the lower half, the relationships between the nerve activity and arterial blood pressure were shown. Line A was obtained before occlusion in a control rabbit. Line B was obtained after occlusion in a control rabbit. Line C was obtained before occlusion in an indomethacin-treated rabit. Line D was obtained after occlusion in the indomethacin-treated rabbit.

was blocked by indomethacin (10).

Indomethacin is a substance to inhibit prostaglandins synthesis. There are numbers of prostaglandins which have different action. PG A, PG E and PG F have inotropic effects. PG A and PG E have an action to increase of coronary blood flow. PG A and PG E have vasodilating action (11). During myocardial ischemia, PG E and PG F are released from ischemic area in dogs and patients (12, 13). In these prostaglandins, PG E is speculated to induce ischemic pain (angina pectoris) (14).

Although during some shocks prostaglandings are released into blood (15), there is no remarkable evidence of an increase of prostaglandins in blood. However this may be due to short life span of prostaglandins or due to intramyocardial regional

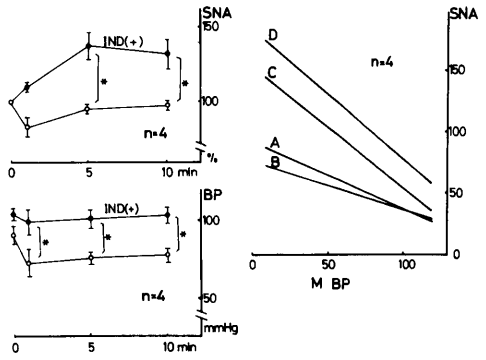


Figure 5. Summarized results with (+) and without (−) indomethacin.
On the right panel shows the relationship of the nerve activity and arterial blood pressure with (+) and without (−) indomethacin treatment in 4 rabbits.
On the left panel shows the relative % change of SNA and BP with and without indomethacin treatment in 4 rabbits.

metabolism.

Thus, prostaglandins may be produced in the regional myocardial and affect on the autonomic nervous system. Because indomethacin can block the neural reflex, bradykinin is a major substance to produce prostaglandins.

2. INFLUENCE OF PROSTAGLANDINS ON THE AUTONOMIC NERVOUS SYSTEM

Because suppression of sympathetic nerve activity was possible to be eliminated by vagotomy, the vagus nerve might be an important afferent pathway. In this reflex, the stretch receptor is reported to be an important one in myocardial ischemia (16).

Neither the atrial nor the ventricular stretch receptors are sensitive to changes in the normal chemical constituents of the blood, but they can be activated by certain substances foreign to the body (17). For example, stimulation of the cardiac receptors by veratrine derivatives produces reflex bradycardia and vasodilatation. This sequence of events is called the Bezold-Jarisch reflex and seemed to play no significant part in normal cardiovascular control. However, our present results indicate that this receptor may be stimulated by prostaglandins and play a part in myocardial ischemia. The afferent pathway is through the vagus nerve because the vagotomy eliminated the reflex.

Desensitization of baroreflex was produced by myocardial ischemia. This might exaggerates the fall in arterial blood pressure because of poor responded symathetic nerve activity. Thus, the suppression of cardiac symathetic nerve activity was produced by this mechanism. This must play an important role in cardiogenic shock.

CONCLUSION

Thus, myocardial ischemia suppressed cardiac sympathetic nerve activity by desensitized baroreflex. The vagus nerve participated in this phenomenon as an afferent pathway.

Because indomethacin could block this neural loop, prostaglandins must play an important role. Although prostaglandins are one of the substances which are released from the damaged myocardium, the present results suggested the participation of this neural mechanism in cardiogenic shock.

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