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The Nervous Control of the Coronary Circulation

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I. INTRODUCTION

In the diagnosis and treatment of cardiac and coronary diseases which have been attracting many attentions in modern medicine, it is greatly important for the physicians to think over the problems in relation to the nervous control of the coronary circulation. However, among these problems there are many complicated matters which can not be resolved clinically. Therefore we tried to this problem mainly by the experimental research using dogs.

Since the middle of the nineteenth century many investigations have been reported on the innervation of coronary vessels, but still many problems are left unsolved. The reasons of it were mainly due to difficulties in the methods of the experiments and due to that coronary vessels are influenced very much by conditions of vasodynamics and metabolism due to modification of the vigor of cardiac contraction and being covered with those responses, changes due to the activity of the coronary vasomotor nerves by itself are difficult to separate.

The experiments described below were undertaken with these problems in mind and the responses experimentally produced were analysed and summarized.

II. NERVOUS PATHWAYS TO THE CORONARY ARTERY SYSTEM AND THESE NERVOUS STRUCTURES

Coronary arteries are innervated with both sympathetic and vagal nervous systems. (Fig. 1) The sympathetic nerves originate from the centers

DISTRIBUTION OF THE HEART NERVES

Fig. 1 C. V.: Cervical Vagus.
G. N.: Ganglion Nodosum
G. Sp.: Ganglion Superius
G. St.: Ganglion Stellatum

of the upper thoracic spinal cord via the stellate ganglia to the heart as the cardiac branches. The vagal nerves originate from the center of the medulla via the cervical vagal nerves to the heart as the cardiac branches. Among the cardiac branches we can find nervous fibers which have several functions i. e. chronotropic, inotropic, bathmotropic, dronotropic etc. At the cardiac branches only the coronary vasomotor nerves can not be separated from the other nerves to the heart.

Within the heart numerous bundles are observed at the circumference of coronary arteries and also many small nervous bundles are in the adventitia of them laying in various directions. Some of them terminate at the adventitia and the media of these arteries. In the vicinity of small arteries and arterioles small groups of nervous

fibers are also observed and most of them are running along these vessels and some of them terminate to the vessels (Fig. 2). Distribution of the nerves can be observed also by the histochemical stain of cholinesterase (true and pseud). (Fig. 3)

Fig. 2 (Bilshowsky's Silver Stain).
A: Arteriole N: Small group of nervous fibers

Fig. 3 Non-Specific Cholinesterase in Small artery.
(Koelle's Method)
A: Small artery Arrow: Cholinesterase activity

III. PHYSIOLOGY ON THE NERVOUS CONTROL OF THE CORONARY CIRCULATION

(1) Methods

Young dogs, weighing from 10 to 15 kg were anaesthetized with thiopental sodium (from 0.04 to 0.06 g per kilogr. intravenously) and under artificial respiration the chest was opened. The left coronary artery was perfused with own blood from the femoral artery, that is, the arterial blood from one femoral artery was conducted with vinyl tube and the curved glass canula with a expanded tip was connected with the vinyl tube at its end and the canula was inserted into the orifice of the left coronary artery from the right subclavian artery via the aorta (Fig. 4). Selecting a suitable one among the glass canules with tips of various sizes, the side flow from the aorta into the coronary

Fig. 4 Methods of the experiment.

artery was preserved. Coronary inflow was measured with a rotameter inserted in the perfusion circuit between the femoral artery and the coronary canula. Blood pressure was recorded from another femoral artery with a mercury manometer and in some cases an electric pressure meter was inserted in the perfusion circuit. Coronary blood flow, electrocardiogram and electric blood pressure were recorded synchronously on an oscillograph. The nervous structures were stimulated electrically with the spiky waves produced by a thyatron. About 10 mg per kg of Heparin sodium solutions were given intravenously as anticoagulant.

(2) Analysis of the Responses to Stimulation of the Sympathetic Nerves

When the peripheral ends of the cut stellate ganglia or their cardiac branches were stimulated electrically for 15 seconds, changes of coronary flow were usually accompanied with elevation of blood pressure, tachycardia and augmentation of cardiac contraction etc. Investigating the changes of coronary flow, increased phases were noticeable. The increases of coronary flow were consisted of two phases, the initial increased response and the late one (Fig. 5).

Fig. 5

At first, analysis was made on changes of coronary flow at the early time following the stellate stimulation. The initial increased response appeared early during the stimulation and was always accompanied with elevation of blood pressure (Fig. 5). However in about one fifth of the experimental instances the decreased responses were obtained before or at the time of the initial increased response (Fig. 6). The cases with decreased response were not always accompanied with a constant change of blood pressure. Some were accompanied with elevation of blood pressure and some were with depression of it (Fig. 7).

Fig. 6

Fig. 7

The changes in the gross vasomotor state of the coronary bed were investigated by correlating as a simple ratio the mean systemic blood pressure with the corresponding mean coronary flow (coronary vascular resistance). When correlations between changes of coronary vascular resistance and that of blood pressure were investigated in the cases with initial increased responses of coronary flow, there was the group with the decrease in coronary vascular resistance probably due to elevation of blood pressure (Fig. 8), which was assumed by analysis of the pressure responses resulted following stimu-

lation of the proximal end of the cut cervical vagal nerve (Fig. 9). And it was noticed that

Fig. 8

Fig. 9

there was another group with the tendency of increase in coronary vascular resistance for elevation of blood pressure (Fig. 8). It seemed that in the cases with decreased responses of coronary flow the increases in coronary vascular resistance were expressed more remarkably with all changes of blood pressure (Fig. 10). As factors to increase

Fig. 10

coronary vascular resistance the followings are assumed: constriction of coronary arteries due to the sympathetic vasoconstrictor nerve, extravascular myocardial compression, severe tachycardia etc. But among them there were so few instances which were accompanied with severe tachycardia that all causes of the increase in coronary vascular resistance were not always due to tachycardia.

The late increased responses of coronary flow usually appeared later from the early changes and were more considerable in grade and longer in continuation than the initial increased responses. They were usually accompanied with elevation of blood pressure but not always with a remarkable one (Fig. 11). When correlations between changes of coronary vascular resistance and grades of elevation of blood pressure were investigated in the instances with the late increased responses, in all cases the decreases in coronary vascular resistance were observed with elevations of blood pressure (Fig. 12). Compared these findings with that in the instances with the initial increased response of coronary flow, in the latter the distribution of the

dots were almost above the 45° blique line (Fig. 8) whereas that in the former were almost below the oblique line (Fig. 12). From these findings it is assumed that besides elevation of blood pressure there are other factors in the late increased responses which decrease the coronary vascular resistance.

Concerning this problem investigations were advanced to humoral mechanism. The procedures were as follows. Coronary sinus blood specimens were obtained with a catheter at several intervals. The times of it were before, during, 15 seconds—1 minute—2 minutes—3 minutes after the stimulation of the sympathetic nerve. The coronary sinus blood specimen or its plasma was injected into own coronary artery from the perfusion circuit.

Intracoronary injection of the sinus blood specimens which were obtained during and 15 seconds after the stellate stimulation produced the considerable increase in coronary flow (Fig. 13). Whereas injection of the sinus blood specimens which were obtained before and at 1 minute or more after the stimulation did not produce the remarkable increase. The figure 14 shows changes in one instance. The double line in this figure

STIMULATION OF THE LEFT SYMPATHETIC NERVE

Fig. 11

INTRACORONARY INJECTION OF THE CORONARY SINUS BLOOD

Fig. 13

STIMULATION OF THE LEFT SYMPATHETIC NERVE

Fig. 12

INTRACORONARY INJECTION OF THE CORONARY SINUS BLOOD

Fig. 14

shows increased rates of coronary flow at the preceding times. The figure 15 shows the changes of increased rate of coronary flow following injection of the sinus blood specimen in all instances when the change of coronary flow following injection of the sinus blood obtained before stimulation was calculated as 1.0. The thick line indicates change of averages. On the other hand same changes following stimulation of the vagal nerve were not recognized (Fig. 16). It was certain that some

INTRACORONARY INJECTION OF THE CORONARY SINUS BLOOD

Fig. 15

INTRACORONARY INJECTION OF THE CORONARY SINUS BLOOD

Fig. 16

substances in the sinus blood which augment coronary flow are increased during the period of stimulation and at the time corresponding to the late increase of coronary flow by the stimulation of the sympathetic nerves.

It seemed that such vasodilative substances to coronary arteries were one of main factors which produced the late increased responses. Nature of the substances is not clear but it is assumed that these are metabolites due to augmentation of the vigor of cardiac contraction, because such sinus blood which increased coronary flow considerably

was obtained when the vigor of cardiac contraction was maximum.

(3) Analysis of the Responses to Stimulation of the Vagal nerve

When the peripheral ends of the cut cervical vagal nerves were stimulated electrically for 10 seconds not so strong as to produce standstill of the heart, coronary flow usually decreased, accompanied by the depression of blood pressure and by the bradycardia (Fig. 17). In some instances coronary flow increased at the early time following the stimulation and decreased later (Fig. 18). In other

Fig. 17

STIMULATION OF THE VAGAL NERVE

Fig. 18

instances the coronary flow did not show any remarkable changes with all moderate modifications of blood pressure.

When correlations between changes of coronary vascular resistance and degrees of depression of blood pressure were investigated, in most instances coronary vascular resistances decreased for all depression of blood pressure (Fig. 19). Black dots in this figure indicate the instances with the decrease in coronary flow and white dots show the instances with the increase in coronary flow. In the latter

Fig. 19

the decreases in coronary vascular resistance were especially marked. It is very interesting to compare these findings with those of depressor responses following stimulation of the proxysmal end of the cut cervical vagal nerve. The coronary vascular resistances following stimulation of the proxysmal one usually increased with depression of blood pressure (Fig. 20) but the coronary vascular resis-

Fig. 20

tances following stimulation of the peripheral one usually decreased with depression of it (Fig. 19). The decrease of coronary vascular resistances in the latter are probably due to dilatation of coronary arteries by the actions of vagal vasomotor nerve and bradycardia which prolongs the duration of diastole. Then how the bradycardia influenced coronary flow was investigated. The figure 21 shows correlations between changes of coronary flow and rates of bradycardia. The line in the figure indicates averages of changes of coronary vascular resistance to rates of bradycardia. Black dots indicate the instances with the decrease in coronary flow and white dots indicate the instances with the increase in it. The most suitable rate in the

Fig. 21

decrease of heart rate to augment coronary flow was about 30% and when the rate of it was more than 40% the effect to augment the coronary flow seemed to become weak. To interpret this in further detail it will be necessary to investigate ratio of the duration of systole to that of diastole, and variation of coronary flow in the respective durations of systole and diastole.

(4) *Sum up the Results of Stimulation of the Sympathetic and the Vagal Nerves*

When observations were made on the coronary circulation including the changes due to modification of the vigor of cardiac contraction, in most instances the excitement of the sympathetic nerves produced the increase in coronary flow and that of the vagal nerves produced the decrease in it. However these results do not indicate immediately that the innervation of coronary arteries in a narrow sense is resolved clearly.

At the present time we have several problems which were difficult to be interpreted clearly. Therefore definite statement may not be made on it. But it seems possible for us to consider as follows:—

The excitement of the sympathetic nerves brings, at the early time, constriction of coronary arteries due to the sympathetic vasoconstrictive nerves and to the extracoronary myocardial compression and produces the increase in coronary vascular resistance and the decrease in coronary flow. But in most instances, following the modification of cardiac activities i. e. increase of cardiac output, elevation of blood pressure and augmentation of the vigor of cardiac contraction etc., the increase in coronary flow occur. According to the changes of vasodynamics and to humoral regulation following augmentation of myocardial metabolism, a great deal of increase in coronary flow is produced.

The excitation of the vagal nerves produces in some instances the marked depression of blood pressure and brings the decrease in coronary flow. However, by the activity of the vagal vasodilative nerves to coronary arteries and the effect of bradycardia which prolongs relative length of a diastolic duration, in some cases the decrease in coronary flow due to depression of blood pressure is covered or the coronary flow rather tends to increase.

(5) *Reflexes from the Gallbladder to Coronary Vessels*

It has been well known that we had often experienced a fit of anginal pain in case of abdominal diseases, i. e. cholelithiasis, cholecystitis, gastrointestinal diseases etc. To investigate the reflex mechanism arising from one of these abdominal organs to coronary vessels the following procedures were carried out. A balloon was inserted into the gallbladder and when this balloon was inflated changes of the coronary flow were measured.

In most instances following inflation of the gallbladder coronary flow decreased with depression of blood pressure (Fig. 22). The coronary vascular resistances usually increased both in the cases with depression and with elevation of blood pressure (Fig. 23). There were a few cases in which the

decrease in coronary flow with little changes of blood pressure and heart rate (Fig. 24). These

Fig. 24

findings indicated that the decreases in coronary flow following stimulation of the gallbladder were due not only to the reflexive depression of blood pressure but also to the reflexive vasoconstriction directly to coronary arteries. In case of the aged who have organic disorders in their coronary arteries i. e. coronary atherosclerosis, the decrease of coronary flow due to such reflex mechanism may be evoked more markedly and accompanied with a relative oxygen deficiency in their heart muscle and it will become a cause which give rise to a fit of angina pectoris.

(6) *Circulation Regulating Reflexes arising from the Coronary Artery*

It was well known that with changes of blood pressure in the carotid sinus and the aortic arch the regulation of systemic blood pressure and heart rate were made reflexly (according to pressoreflex) and also the circulation of important organs i. e. the cerebral circulation etc. were regulated and as chemoreflexes the carotid and aortic bodies were reported. Besides these reflexes several pressoreflexes and chemoreceptors in blood vessels and heart were reported. As far as reflexes arising from coronary vessels are concerned, investigations had been made with particular reference to angina pectoris and myocardial infarction. However at the present time it seems best to refer these reflexes by the experiments i. e. coronary arterial occlusion, embolization and perfusion etc. but there is no positive assurance that the origin of these reflexes are limited to the coronary arterial wall.

In our experiment we have noticed accidentally that when the glass canula was inserted into the orifice of the left coronary artery the systemic blood pressure rose and when the canula was pulled out

Fig. 22

Fig. 23

from the coronary orifice the systemic blood pressure fell without any exceptions (Fig. 25). These pressor

Fig. 25

and depressor responses were mediated mainly by the left cervical vagus and were eliminated after cutting both cervical vagi. According to these findings it seems that these phenomena are due to reflex mechanism which arises from the pressoreceptors at the orifice of the left coronary artery and are mediated by the cervical vagi. When the changes of the intracoronary perfusion pressure were measured with a mercury manometer inserting in the perfusion circuit, at the time of insertion of the canula into the left coronary orifice the coronary perfusion pressure fell immediately 10 to 40 mm Hg lower than that in the aorta and then the systemic blood pressure rose (Fig. 26).

Fig. 26 S. P.: Systemic blood pressure.
C. P.: Coronary Perfusion Pressure.

Just at the time of extraction of the canula the coronary perfusion pressure which now indicates the pressure in the aorta in reality rose immediately compared with that at the time of being inserting the canula and then the systemic blood pressure fell (Fig. 26). The intracoronary pressure measured

from the anterior descending branch with a mercury manometer indicated that the intracoronary pressure truly fell in case of insertion of the canula and rose to the former level in case of extraction of it (Fig. 27). Therefore it seems that rapid change

Fig. 27

of the intracoronary pressure is one of the factors which stimulate the occurrence of these reflexes.

On the other hand, even when using the special canula which has several holes at its side and through the holes of which the pressure within the canula was easy to be influenced directly with the aortic pressure, the preceding pressor and depressor responses could also be recognized by insertion and extraction of the canula without any changes of intracoronary pressure (Fig. 28). Consequently as

Fig. 28

one of mechanisms bringing these reflexes, it will be assumed that the arterial wall in the vicinity of the left coronary orifice receives mechanical stimuli with insertion or extraction of the tip of the canula and changes in distensibility of the arterial wall are produced and then these reflexes are provoked.

According to the histological investigations at

the adventitia and the media of the arterial wall in the vicinity of the left coronary orifice distinctly differentiated from the aortic wall, thick nervous fibers which arborized into thin branches and some of them terminated in the form of a ring or a nodule were observed (Fig. 29).

Fig. 29 Bilshowsky's Silver Stain.

Thus, we suggested that changes of the intracoronary pressure is one of the factors which stimulate the occurrence of the reflexes due to insertion and extraction of the canula. Concerning this matter further investigations were intended. Ten cc of arterial blood was injected from the perfusion circuit into the coronary artery in the time from 4 to 6 seconds and then immediately closing the circuit from the femoral artery, the added pressure to the coronary artery was recorded with a mercury manometer in the perfusion circuit. With these procedures the perfusion pressure rose to as high as 150 to 200mmHg and then the depressor reflex was elicited (Fig. 30). When after

Fig. 30

preparation of the parts in the left coronary trunk which is divided into the anterior descending branch and the circumflex branch carefully not

to injure the nerves around them and again ascertaining the occurrence of this intracoronary pressoreflex the nerves were blocked by plastering 20 per cent of carbol solution on the parts, this reflex weakened very much and sometimes almost abolished (Fig. 31). But in this case the

Fig. 31

reflexes following insertion and extraction of the canula were remained intact in spite of elimination of the intracoronary pressoreflex. These findings indicate that there is a mechanism which differs in origin from the intracoronary pressoreflex in the reflex mechanisms following insertion and extraction of a canula. The intracoronary pressoreflex was also eliminated entirely after cutting both cervical vagi. The pathways of the nerves in the vicinity of the left coronary trunk were investigated macroscopically in full detail. The left vagal cardiac branches formed the anterior plexus with the right cardiac branches on the heart wall between the base of the pulmonary artery and the left coronary trunk. As the anterior ventricular branches the nerves from the plexus or through it innervated mainly the front of the left ventricle. A thin nerve from the anterior plexus or in some cases

DISTRIBUTION OF THE VENTRICULAR BRANCHES

Fig. 32

distinctly from a left vagal branch innervated the bifurcation parts of the left coronary trunk along it and drawing to the side of the anterior descending artery (Fig. 32). After cutting this thin nerve the intracoronary pressoreflex was eliminated. Serial histological investigations by silver stain at the parts demonstrated that several thick nervous fibers were found at the adventitia and the out layer of the media in the arterial wall localized in the anterior foot of the anterior descending artery. These nervous fibers were arborized suddenly into thin branches, some of which connected with each other in their course and some of them formed their terminal endplates like a ring, a brush, a nodule or a basket (Fig. 33) (Fig. 34). These nervous

Fig. 33 Bilshowsky's Silver Stain.

Fig. 34 Sketch of Fig. 33.

structures were assumed to be the afferent receptors of the intracoronary pressoreflex.

It has been already known that Bezold-Jarisch reflex is the one which have origin in the ventricle and produces reflexly the effects of depression of blood pressure and bradycardia. But it has not been clear where the origin is, in myocard or in coronary vessels. Up to now this reflex had been taken notice as a chemoreflex produced by

veratrum alkaloid etc. Recently it has been paid attention as a pressoreflex provoked by such changes of volume of the heart or of stroke volume. And now investigation was made concerning the relationship between Bezold-Jarisch reflex and the above mentioned pressoreflex.

Bezold-Jarisch reflex could be produced reflexly by injection of 10 γ per cc solution of verilloid into the left coronary artery via the perfusion circuit with the effects of depression of blood pressure and bradycardia (Fig. 35). These responses were also

Fig. 35

eliminated after cutting both cervical vagi. They were also eliminated after cutting both the anterior ventricular branches which mainly innervated the front of the left ventricle and the posterior ventricular branches which dominantly innervated the back of the left ventricle on the heart wall (Fig. 32) (Fig. 36). From these results this reflex seems

Reflexes From Left Coronary Artery

	Localization of the receptor	Cutting both anterior and posterior vagal nerves	Cutting both anterior and posterior ventricular branches	Cutting of posterior ventricular branch	Cutting of anterior ventricular branch or branch
pressoreflex on insertion or extraction of the canula	orifice of the left coronary artery	(-)	(+)	(+)	(+)
intracoronary pressoreflex	Foot of the anterior descending artery	(-)	(-)	(+)	(-)
Veratrine reflex	Heart muscle or peripheral coronary vessels	(-)	(-)	(+)	(+)

Fig. 36

to originate mainly from the left ventricle. In case of cutting both ventricular branches the intracoronary pressoreflex was also eliminated but the reflexes due to insertion and extraction of a canula were remained (Fig. 32) (Fig. 36). Accordingly it is certain that the reflexes due to insertion and extraction of a canula have the different origin from verilloid reflex. After cutting only the posterior ventricular branches these three kinds of reflexes

were remained intact or some of them were remained slightly weakened (Fig. 36). After cutting only the anterior ventricular branches the intracoronary pressoreflex was eliminated, but the reflexes due to insertion and extraction of a canula were remained intact and the verilloid reflex was remained slightly weakened (Fig. 36). Therefore it is certain that the intracoronary pressoreflex has different origin from the other reflexes. From the findings that the afferent pathways of the verilloid reflex consist in both the anterior and posterior ventricular branches, the distribution of the afferent receptors of this reflex seems to be in the wide range of the left ventricle. The structures of the terminal nervous endplate could not be demonstrated.

As mentioned above, the pressoreflexes arising from the orifice of the left coronary artery and from the anterior foot of the anterior descending artery were different in origin from the verilloid reflex (Bezold-Jarisch reflex). Figure 37 shows the

Fig. 37

distribution of the circulation regulating reflexes arising from the left coronary artery and the left ventricle. What is the physiological significance of these pressoreflexes? It will be considered as follows. When systemic blood pressure rises and burden of the heart increases, these pressoreflexes are provoked and regulate to depress the blood pressure. When the intracoronary pressure falls accompanied with the decrease in coronary flow and the supply of nourishes to the heart muscle becomes insufficient, the pressoreflexes are provoked to increase the coronary flow by the elevation of blood pressure. These pressoreflexes are interpreted as a teleological and a defensive mechanism for the body as well as that of the carotid sinus. It is a

very interesting problem in the field of the nervous control of the coronary circulation that the pressoreflexes arising from the left coronary artery and Bezold-Jarisch chemoreflex exist in the important organ, the heart to regulate the systemic circulation and indirectly the coronary circulation.

IV. CONCLUSION

Using dogs investigation on the nervous pathways and the structures of the nerves to coronary arteries were made and the following results were obtained.

1. Coronary flow following stimulation of the sympathetic nerves in most instances increases remarkably, influenced hard by modification of the vigor of cardiac contraction i. e. elevation of blood pressure and augmentation of myocardial metabolism etc. But it seems the action of the sympathetic vasomotor nerves is constrictive to coronary arteries with myocardial extravascular support.

2. Coronary flow following stimulating of the vagal nerves usually decreases, influenced by depression of blood pressure due to modification of cardiac activity. But it seems the action of the vagal vasomotor nerves is dilatative to coronary arteries usually accompanied by bradycardia and tends to increase coronary flow.

3. One of mechanisms which decrease coronary flow following stimulation on the gallbladder is the reflexive depression of blood pressure and another is the reflexive constriction of the coronary arteries.

4. It was demonstrated clearly that some new pressoreflexes arose from the orifice of the left coronary artery and the foot of the anterior descending artery to regulate systemic blood pressure and these reflexes differed in origin from veratrum reflex (Bezold-Jarisch reflex).

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