Sympathetic Control of Coronary Circulation

By Eric O. Feigl, M.D.

ABSTRACT

The sympathetic control of left circumflex coronary blood flow was studied by stellate ganglion and hypothalamic stimulation. Flow was measured acutely in dogs under chloralose or pentobarbital anesthesia by an electromagnetic flowmeter. Coronary vasoconstriction was observed when the left stellate ganglion was stimulated after blocking beta receptors with propranolol or INPEA. The possibility of coronary sympathetic cholinergic vasodilation of the type found in skeletal muscle was examined in three types of experiments in which vasodilation occurred in skeletal muscle: (1) peripheral sympathetic nerve stimulation after chronic catecholamine depletion with reserpine, (2) peripheral sympathetic nerve stimulation after acute block of alpha and beta receptors, (3) hypothalamic stimulation to give a defense reaction after acute block of alpha and beta receptors. Within the limits of these experiments, skeletal muscle cholinergic vasodilation was demonstrated but coronary sympathetic cholinergic vasodilation was not, even as part of the defense reaction elicited by hypothalamic stimulation.

ADDITIONAL KEY WORDS sympathetic cholinergic vasodilation coronary blood flow propranolol defense reaction active vasodilation hypothalamic stimulation stellate stimulation coronary vasoconstriction alpha and beta receptors

Transient coronary vasoconstriction can be demonstrated by intracoronary arterial injections of norepinephrine or epinephrine in fibrillating or arrested hearts. This has been interpreted as a direct adrenergic effect on the coronary arteries and has been reviewed by Berne (1). More recently, Granata and co-workers (2) have observed transient decreases in coronary blood flow during electrical stimulation of the stellate ganglion in unanesthetized animals. Berne, DeGeest and Levy (3) observed the same transient decrease in coronary flow following stellate stimulation in unanesthetized animals. According to the classification proposed by Ahlquist (4) these effects may be due to stimulation of alpha receptors supplied by adrenergic sympathetic nerves.

Klocke and associates (5) observed coronary vasodilation after the intracoronary injection of isoproterenol in potassium-arrested hearts. Since isoproterenol is known to stimulate beta receptors, they concluded that beta-adrenergic (vasodilator) receptors are present in the coronary circulation.

Zuberbuhler and Bohr (6), using isolated strips from small coronary arteries, demonstrated relaxation resulting from epinephrine and norepinephrine. This relaxation was blocked by a beta-receptor blocking agent. In contrast, strips from large coronary arteries occasionally contracted in response to catecholamines and this could be blocked by an alpha-receptor blocking agent. Most recently, direct coronary artery injection of isoproterenol in unanesthetized animals resulted in a very prompt coronary vasodilation which was attributed to stimulation of beta receptors (7).

With the demonstration of both vasoconstrictor (alpha-receptor) and vasodilator (beta-receptor) adrenergic effects, the coronary vascular bed resembles the vascular bed of skeletal muscle. However, the latter has an additional sympathetic mechanism, the so-called sympathetic cholinergic vasodilators which have been extensively studied by Folkow (8), Uvnäs (9) and others.

The purpose of this investigation was to
determine if the coronary vascular bed has sympathetic cholinergic innervation. Skeletal muscle cholinergic vasodilation is demonstrable by peripheral sympathetic stimulation after catecholamine depletion or during adrenergic blockade. The first two parts of this report are the results of stellate ganglion stimulation after catecholamine depletion and during adrenergic blockade. The third part reports the results of hypothalamic stimulations that elicit a "defense reaction," including sympathetic cholinergic dilation in skeletal muscle— a situation in which sympathetic cholinergic dilation in the coronary bed might be anticipated.

**Methods**

Dogs weighing 10 to 20 kg were anesthetized with chloralose, 80 to 100 mg/kg iv, or with pentobarbital, 25 mg/kg iv. The reserpinized dogs were given an initial dose of 12.5 mg/kg pentobarbital or 50 mg/kg chloralose because of their sensitization to general anesthetic agents. Blood flow was measured using a 400 cycle/sec sine wave, phase sensitive demodulator, electromagnetic flowmeter, with Helmholtz coil probes (Statham K 4000). Phasic flow patterns were always recorded initially to be sure of a true recording. Averaged flows were used during the experimental runs. Zero flow baselines were determined by repeated occlusions with a cotton snare distal to the flow probe. Blood pressure was measured in the thoracic aorta with a polyethylene catheter and a strain gauge manometer (Statham P 23D4). Heart rate was determined by counting the pulse from the oscillograph record or in some experiments using a cardio-tachometer (10). Recording was on an oscillograph (Brush 1707).

Coronary blood flow was measured in the circumflex coronary artery using a noncannulating flow probe. The heart and stellate ganglion were approached through a left thoracotomy in the fifth intercostal space. Artificial positive pressure respiration was carefully adjusted to just suppress spontaneous respiration before thoracotomy. Atelectasis was prevented by maintaining an expiratory pressure of 3 cm H2O with a trap. Femoral artery blood flow was measured in the femoral triangle. Blood flow to the foot was prevented by a very tight wire ligature at the ankle. The remaining femoral blood flow was predominantly to skeletal muscle.

Catecholamine depletion was accomplished by giving reserpine 0.5 mg/kg im per day for 2 days before the experiment; this dosage has been shown to give 98% depletion (11). Beta-adrenerg-
Peripheral Sympathetic Stimulation with Beta-Receptor Blockade

Table 1

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Sys. = systolic; Diast. = diastolic; prop. = propranolol.

*Dog 6 not included because Dibenzyline was given first.

gic effects were blocked with propranolol (In- dernal, Ayerst Laboratories), in doses of 0.1 mg/kg to 1.0 mg/kg iv. In a few experiments, a different beta-blocking drug, INPEA (Selvi), was used with comparable results. Phenoxycbenzamine (Dibenzyline, Smith Kline & French) was used for alpha-adrenergic blockade in doses of 1.0 mg/kg to 10 mg/kg iv.

The left stellate ganglion and its major branches were stimulated with rectangular waves using bipolar platinum electrodes; the duration of stimuli varied from 0.1 to 5 msec, the frequency from 1 to 20 cycle/sec and intensity from 1 to 15 volts. Stimulation periods were 10 to 30 sec. Stimulation characteristics were always monitored on an oscilloscope, and special precautions were taken with stimulus isolation to prevent artifact on the flow records. In some experiments the lumbar sympathetic chain was also dissected out for stimulation.

Hypothalamic stimulations were made with the aid of a stereotaxic instrument using electrolytically sharpened monopolar steel electrodes. Stimulation characteristics were: duration, 2 msec; frequency, 70 cycle/sec; and amplitude, 2 to 3 volts. Coronary and femoral blood flow were measured simultaneously. Because brain stimulations can result in the release of catecholamines from the adrenal gland (12), the results were confirmed in two animals after acute adrenalectomy.

In all experiments recorded, cholinergic mechanisms were shown to be present either by demonstrating that cholinergic dilation occurred in the femoral vascular bed or that bradycardia occurred on vagal stimulation.

Results

Stellate Stimulation After Catecholamine Depletion by Reserpine

Left stellate ganglion stimulation following catecholamine depletion by reserpine resulted in little change in pulse pressure or heart rate. The entire ganglion, as well as its major branches, was stimulated by electrical stimuli with widely different characteristics in different experiments—all with little effect.

Figure 1 shows the results of an experiment in which the stellate ganglion and the lumbar sympathetic chain were stimulated together with one stimulator and two pairs of electrodes in parallel. The difference in response between the coronary and skeletal muscle bed was immediately apparent. Vasodilation occurred promptly in the skeletal muscle but not in the coronary bed; the cholinergic nature of the skeletal muscle dilation was demonstrated by its blockade with atropine (Fig. 1, right panel).

Small increases in coronary flow (5 to 10%) were sometimes observed, but always in association with a small increase in cardiac rate or pulse pressure. The modest change in coronary flow was believed to result from
### SYMPATHETIC CORONARY CONTROL

#### Coronary flow (ml/min) | Femoral flow (ml/min) | Drugs and procedures
--- | --- | ---
Control | Stim. | Diff. | Control | Stim. | Diff. | prop. 0.5 mg/kg
27.1 | 24.2 | −2.9 | 15.1 | 4.4 | −10.7 | prop. 0.5
17.5 | 14.1 | −3.4 | 29.6 | 3.6 | −26.0 | prop. 0.5
27.4 | 22.9 | −4.5 | 6.8 | 1.1 | −5.7 | prop. 1.0
14.3 | 10.1 | −4.2 | 7.1 | 4.6 | −2.5 | (panel 2, Fig. 2)
7.9 | 6.2 | −1.7 | 7.5 | 2.9 | −4.6 | prop. 1.0
10.8 | 8.1 | −2.7 | 13.6 | 3.0 | −10.6 | prop. 1.0
8.5 | 6.6 | −1.9 | 16.1 | 5.1 | −11.0 | prop. 1.0
26.1 | 23.1 | −3.0 | 5.0 | 0.6 | −4.4 | prop. 0.5
14.0 | 10.1 | −3.9 | 10.9 | 2.9 | −8.0 | both vagi cut
16.07 | 13.00 | −3.07 | 13.47 | 2.98 | −10.49 | prop. 0.5
2.57 | 2.42 | 0.30 | 2.47 | 0.47 | 2.21

#### FIGURE 2

The left stellate ganglion and lumbar sympathetic chain of a 15-kg dog were stimulated simultaneously with two pairs of electrodes in parallel from the same stimulator. Stimulation characteristics were 15 cycle/sec, 4-msec duration, and 2.2 volts. The control panel illustrates the results of sympathetic stimulation; femoral bed vasoconstriction and coronary vasodilation accompanied an increase in blood pressure and pulse pressure. The second panel illustrates coronary vasoconstriction with sympathetic stimulation after beta-adrenergic blockade. The third panel shows vasodilation in the skeletal muscle bed after both beta- and alpha-receptor blockade; the cardiac response was essentially blocked. The fourth panel illustrates the blockade of the skeletal muscle cholinergic vasodilation by atropine.

Increased myocardial metabolism caused by stimulation of the incompletely depleted sympathetic nerves. Stellate stimulation after reserpine treatment was performed in 13 dogs without demonstrating coronary cholinergic vasodilation.
STELLATE STIMULATION WITH ADRENERGIC BLOCKADE

Left stellate ganglion stimulation without adrenergic blockade resulted in a marked increase in coronary blood flow accompanied by an increase in pulse pressure and heart rate. After a beta-adrenergic blocking drug was given, stimulation of the stellate ganglion produced little increase in pulse pressure and heart rate but produced coronary vasoconstriction due to stimulation of alpha receptors (second panel, Fig. 2). The results are listed in the first part of Table 1. Vasoconstriction occurred in 10 of 11 experiments. In the remaining experiment, the alpha-receptor blocking agent was given before the beta-receptor blocking agent, precluding a response from the alpha receptor. The vasoconstriction demonstrated that coronary sympathetic nerves were not destroyed during surgery or by the application of the flow probe on the coronary artery.

When alpha-receptor blockade produced by Dibenzyline was added to the beta-receptor blockade, the coronary bed became unresponsive to stellate stimulation and there was no increase in flow even though cholinergic mechanisms were still intact as demonstrated by the procedures described earlier. The results of this type of experiment are given in Table 2.

Figure 2 shows an experiment in which the effects of adrenergic blockade were contrasted in the skeletal and cardiac muscle beds. Both the stellate and lumbar sympathetic chain were stimulated with the same stimulator with two pairs of electrodes in parallel. The first panel shows the increased coronary flow and decrease in skeletal muscle flow resulting from sympathetic stimulation. In the second panel,
SYMPATHETIC CORONARY CONTROL

<table>
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<th>Coronary flow (ml/min)</th>
<th>Femoral flow (ml/min)</th>
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after beta-adrenergic blockade with propranolol, there was coronary vasoconstriction followed by vasodilation after the stimulation. The secondary vasodilation after stimulation was presumably compensatory for the decreased flow during the stimulation. The femoral bed continued to show vasoconstriction after beta-receptor blockade.

The third panel of Figure 2 shows the effects of combined alpha- and beta-receptor blockade. The coronary bed was essentially unresponsive to sympathetic stimulation, but the skeletal muscle bed showed vasodilation. The cholinergic nature of this vasodilation was demonstrated, since it was blocked by atropine (last panel). This experiment demonstrates that stimulation of the stellate ganglion, which could elicit beta- and alpha-adrenergic effects on the heart, did not result in a cholinergic vasodilator effect. The same stimulation characteristics from the same stimulator at the same time clearly revealed cholinergic vasodilation in the skeletal muscle vascular bed.

HYPOTHALAMIC STIMULATION

A defense alarm reaction can be elicited by electrical stimulation in the hypothalamus. As a part of this overall preparation for “fight or flight,” cholinergic vasodilation occurs in the skeletal muscle bed (13). The possibility that this response also might involve cholinergic vasodilation in the coronary bed was tested. The cardiac effects of hypothalamic stimulation which gave simultaneous skeletal muscle vasodilation were similar to stellate ganglion stimulation. An increase in heart rate and pulse pressure accompanied an increase in coronary blood flow. These effects could be blocked by a beta-adrenergic blocking agent. Repeated anterior hypothalamic stimulation in seven animals failed to reveal cholinergic coronary
vasodilation. The results of these experiments are given in Table 3. Since stimulation of the central nervous system can result in the release of catecholamines from the adrenal gland which might confuse the response, the results were confirmed in two animals after acute adrenalectomy.

Figure 3 illustrates the response to anterior hypothalamic stimulation in an adrenalectomized dog. In the control stimulation, heart rate, pulse pressure, and coronary flow increased together with cholinergic vasodilation in the skeletal muscle. The cardiac effects, including coronary vasodilation, were essentially absent after administration of propranolol, while the femoral dilation was maintained.

Discussion

The experiments in this study using beta-receptor blocking drugs with stimulation of the stellate ganglion resulting in an alpha-adrenergic coronary vasoconstriction, confirm the results of similar experiments by Granata and co-workers (2) as well as those of Berne, DeGeest and Levy (3).

The presence of beta-adrenergic coronary vasodilation which is separate from the well-known beta-adrenergic effects of myocardial contractility and heart rate was not examined in this study. These results have no bearing on the presence or absence of beta-adrenergic receptors in the coronary artery wall.

Folkow and co-workers (14) stimulated the sympathetic nerves of an eserinized isolated heart preparation and examined the perfusate for acetylcholine-like activity using a bioassay. Acetylcholine-like activity was found during sympathetic nerve stimulation. Further, small amounts of injected acetylcholine caused coronary vasodilation (15). It was presumed that the sympathetic cholinergic fibers innervated the coronary vascular bed and were capable of causing cholinergic vasodilation. The results of the present study do not support this view. The results of Folkow and co-workers might be explained by the existence of sympathetic synapses displaced from the ganglion to the vicinity of the heart. Presynaptic sympathetic fibers release acetylcholine which could appear in the perfusate of an eserinized preparation.

Conclusions of the present study conflicts with those of Szentiványi and his co-workers. Szentiványi and Kiss (16) used a modified Langendorff preparation with constant coronary perfusion pressure to study coronary blood flow in cat hearts. They found that selective stimulation of very small terminal branches of the stellate ganglion resulted in coronary vasodilation. This effect was blocked by atropine. These fibers were thought to be analogous to the sympathetic
cholinergic fibers found in the skeletal muscle vascular bed. These investigators stimulated only small branches of the stellate ganglion in their study to obtain a nerve filament that did not contain sympathetic adrenergic fibers. In the present study large branches or the whole ganglion were stimulated and adrenergic effects blocked pharmacologically.

The experimental evidence of Szentiványi and co-workers for cholinergic fibers (Fig. 4 in references 16 and 17) shows that during stimulation the heart beat completely stopped. Heart rates were not reported, but it is clear from their Figure 4 that there was a regular cardiac rate which stopped in diastole during the stimulation. A portion of the resistance to coronary blood flow is the result of compression of the coronary circulation by the con-

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**FIGURE 3**

The supraoptic region of the anterior hypothalamus of a 14-kg adrenalectomized dog was stimulated at 70 cycle/sec, 2 msec duration, 2.0 volts. The control panel illustrates an increased coronary flow accompanying an increased pulse pressure, heart rate, and blood pressure simultaneous with skeletal muscle vasodilation. The second panel shows that the cardiac effects were blocked by a beta-adrenergic blocking agent, while cholinergic vasodilation remained in the skeletal muscle bed.
traction of the beating myocardium. Changes in heart rate and the proportion of time occupied by systole can thus affect coronary blood flow by this mechanical factor. Sabis-ton and Gregg (18) demonstrated average increases of 50% in coronary blood flow when the heart was arrested. The 20% increase in coronary blood flow observed by Szentiványi and Kiss during cardiac arrest can easily be accounted for by the arrest and the absence of compression by the myocardium.

Szentiványi and Juhasz-Nagy (17) present the same experimental evidence in a second paper with an identical Figure 4. Juhasz-Nagy and Szentiványi (19) in a later study using dogs, state that sympathetic cholinergic coronary vasodilation was found. The demonstration in dogs was more difficult because the dog has fewer small stellate ganglion fibers for dissection. No experimental record was illustrated and no heart rates were reported.

In the present study no attempt was made to dissect out the very small fibers described by Szentiványi. The major branches of the stellate ganglion were individually stimulated or the entire ganglion was stimulated. However, the stimulation characteristics of frequency, duration, and strength reported by Szentiványi were used repeatedly in this study, and there is no reason to doubt that all sympathetic fibers can be stimulated in this way.

Coronary flow during a defense reaction elicited by hypothalamic stimulation has not been reported previously. The cardiovascular components of a defense reaction include augmented cardiac contraction and tachycardia (20), vasoconstriction in the skin (21), and skeletal muscle vasodilation (8, 9, 13, 20, 21, 23). The increase in coronary blood flow observed with hypothalamic stimulation before beta blockade is probably due to the increased cardiac metabolism resulting from the tachycardia and augmented contraction. The possibility of a direct beta-adrenergic coronary vasodilation resulting from hypothalamic stimulation cannot be ruled in or out by the present experiments. The results indicate that coronary sympathetic cholinergic vasodilation is not a part of the defense reaction.

In conclusion, cardiac sympathetic nerves were stimulated in three types of experiments in which skeletal muscle cholinergic vasodilation was clearly demonstrated; under the experimental conditions used, coronary sympathetic cholinergic vasodilation analogous to that found in skeletal muscle was not observed.

Acknowledgment

I am indebted to Professor Bjorn Folkow for suggesting the possibility of synapses near the heart for interpreting his work and to Mr. William Bedka for his technical assistance. Dr. Alex Sahagian-Edwards of Ayerst Laboratories generously provided Inderal. Dr. Walter Murmann of Selvi and Company kindly provided the INPEA. Dr. Murray G. Smyth of Smith Kline & French generously provided the Dibenzyline.

References


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