The effects of sympathetic nerve stimulation on coronary flow have been investigated repeatedly in dogs under the influence of anesthesia and surgery. The experiments to be described were performed with the intent of studying coronary inflow changes elicited by sympathetic stimulation in conscious, trained dogs. This has been made possible through the development of electromagnetic flowmeters which can be mounted chronically around the main left coronary artery or one of its main branches.1

Methods

Successful studies were performed on 11 dogs weighing from 19 to 24 kg. These animals were in excellent health and had been trained to lie quietly on a table. Sine wave electromagnetic flowmeters of the Kolin type, modified by Khouri and Gregg,1 were used to record phasic arterial flows.

Surgery was performed under clean but not sterile conditions. Every animal received 300,000 units procaine penicillin and 1 g streptomycin daily for the first seven days after operation. Postoperatively, all the animals appeared to be free of infection, ate and exercised well, and, at autopsy the thoracic viscera showed only pleural and pericardial adhesions. Under sodium pentobarbital anesthesia (approximately 30 mg/kg), the left chest was opened in the third or fourth intercostal space during artificial respiration. Following a wide incision of the pericardium, the left circumflex coronary artery was carefully dissected free for a length just sufficient for implantation of an electromagnetic flowmeter. A plastic snare2 was loosely passed around the artery 3 to 5 mm beyond the flowmeter. The snare allowed the momentary occlusion of the artery in order to obtain mechanical flow zero. In some animals, the flowmeter was implanted on the main left coronary artery. In this case, snares were placed around both the descending and the circumflex branches close to their origin. Thus, flow through the septal artery branch was not measured. This has been estimated by Eckstein et al.3 to be 10%, and by Sevelius (unpublished experiments from this laboratory) to be 9% of total left coronary inflow in the open-chest dog. In some experiments, an additional flowmeter was implanted around the ascending aorta.

The left stellate ganglion was exposed together with its cardiac branches, and bipolar platinum electrodes mounted in an acrylic plastic holder were placed around either the ganglion, the common ansa subclavia or its anterior limb. In three of the eleven dogs, the stellate ganglion was separated from the sympathetic chain, and all rami of the connecting spinal nerves were cut, care being taken to avoid injury to the cardiac branches. The cables of the flowmeters and stimulating electrodes were led out through the skin of the back or the dorsal surface of the neck.

A plastic catheter filled with heparin for the measurement of blood pressure was inserted into the aorta to the level of the origin of the brachiocephalic artery via a common carotid artery. The end of the catheter was connected to a light plastic stopcock and was led out through the skin of the back or the neck. Occasionally, the catheter for blood pressure recording was inserted under local anesthesia into the descending aorta via a femoral artery, at the time when the effects of sympathetic stimulation were studied.

In some animals, a plastic sampling catheter4 was implanted in the coronary sinus. In some experiments with these animals, coronary sinus oxygen content was monitored continuously by withdrawal through a Colson cuvette densitometer at a rate of 7.6 ml/min.5 This densitometer was fitted with a thin spacer, and preliminary experiments showed that this withdrawal rate gave
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In order to prevent deposits on the cuvette surfaces, a single dose of 1000 IU heparin/kg was administered prior to the experiments. In other experiments, serial blood samples were withdrawn directly into oiled syringes containing degassed heparin. Oxygen was measured by the method of Van Slyke and Neill. These animals were not given heparin.

The effects of nerve stimulation were studied from two to eight days after surgery and only when the dogs appeared healthy and active. Stimulation was performed with the dog lying quietly on its right side. Rectangular impulses were delivered by a Grass stimulator. The duration of the impulses was 8 to 15 msec, the frequency and voltage being 15 to 30/sec and 1 to 10 volts, respectively. The stimulation voltage was observed on an oscilloscope occasionally, and the dial readings of the stimulator calibrated; however, it was not monitored during all experiments. The voltages indicated were as read on the instrument and do not necessarily represent the current applied to the nerves since the extent of current spread cannot be measured. A Statham strain gauge was used to record systemic pressure. Recordings of phasic coronary arterial flow, aortic flow, and blood pressure were made with an Electronics for Medicine DR-8 cathode ray recorder.

In the analysis of data, duration of systole was used as the period between opening and closing of the aortic valves. Pressures and flows in systole and diastole were calculated by planimetry of a number of consecutive heart beats. Resistance to coronary flow at the end of diastole was calculated as $\text{PRU} = \frac{\text{end diastolic aortic pressure (mm Hg)}}{\text{end diastolic coronary flow (ml/min)}}$. According to Green and his colleagues, this resistance value is an index of caliber changes in coronary arterioles, since, at the end of diastole, extravascular compression is minimal and is undergoing minimal changes in time.

Cardiac output and stroke volume were computed in the dogs in which a flowmeter was placed around the ascending aorta.

Results

CONTROL PATTERN OF CORONARY FLOW

As shown in record A of figures 1, 2, and 3, records of aortic blood pressure (descending aorta) and phasic flow in the left circumflex coronary artery following sympathetic stimulation. A, control; B, 6 seconds after the beginning of stimulation; C, 10 seconds after the cessation of stimulation. The left common ansa subclavia was stimulated at 1.7 v, with an impulse duration of 12 msec, and a frequency of 20/sec. All rami of the left stellate ganglion were intact. Vertical intercepts, 1.0-second intervals. Numbers on the pressure and flow curves indicate, respectively, the end diastolic pressure in mm Hg and coronary flow in cc/min.

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3, the flow decreased abruptly just prior to ejection. During the ejection phase and with the rise in aortic pressure, flow tended to increase. This, however, is not well defined in figures 2 and 3. With the onset of isometric relaxation, the flow again increased and then gradually declined with the diastolic fall of blood pressure. In the figures, the position of the zero flow line indicates that forward flow occurred throughout the cardiac cycle and that systolic volume flow is a sizeable fraction of the diastolic flow per heart beat.

**SYMPATHETIC NERVE STIMULATION IN DOGS WITH STELLATE GANGLION CONNECTIONS INTACT**

The effects of cardiac sympathetic nerve stimulation are presented in figure 1. Within six seconds, as shown in record B, heart rate increased without a significant change in blood pressure. Mean coronary flow increased from 36 to 58 ml/min which was the result of the augmented heart rate and coronary flow per heart beat. Both the systolic and diastolic flows per heart beat (and per minute) increased. End diastolic resistance to coronary flow decreased to 1.8 from a control value of 2.6. The flow pattern showed a more rapid decline during isometric contraction of the ventricle and a steeper rise in early diastole. The duration of systole was slightly decreased. Ten seconds after the end of stimulation, in record C, some effects were still present. Within three minutes, all hemodynamic parameters returned to control level.

Although not shown in the sections of record chosen for figure 1, in most experiments the initial effect of sympathetic nerve stimu-
lation was a reduction of coronary flow. This is illustrated in record B of figure 2 taken two seconds after the beginning of stimulation. Mean coronary flow was reduced from 33 to 21 ml/min, the result of a decrease in both stroke systolic and diastolic flows. Systolic flow was more affected than diastolic, and end diastolic coronary resistance was increased. These changes were accompanied by a decrease of blood pressure, stroke volume, and cardiac output. In other experiments of this group, however, no appreciable changes of blood pressure were observed during the phase of reduced coronary flow. With continued stimulation, all parameters progressively increased, and in record C at 22 seconds, coronary flow increased throughout the cardiac cycle as in record B of figure 1. In addition, cardiac output was increased whereas stroke volume was essentially the same as in the control record. After the cessation of stimulation, the parameters returned to control values within 20 seconds (record D).

**SYMPATHETIC NERVE STIMULATION IN DOGS WITH LEFT STELATE GANGLION DISCONNECTED FROM SPINAL NERVES AND SYMPATHETIC CHAIN**

When the sympathetic nerves were stimulated in dogs with intact stellate ganglia, no voltages higher than 3.5 to 4 were used because they caused movements of the dog with signs of distress. In animals with the left stellate ganglion previously disconnected from the sympathetic chain and spinal nerves, the voltage could be increased to higher values without movement or evidence of distress. Changes in coronary inflow obtained with higher voltages after stellate severance are illustrated in figure 3, taken from an experiment in which the common ansa subclavia was stimulated at 6 volts. The curves in record B representing the third and fourth cardiac cycles after the beginning of stimulation, show a considerable reduction in coronary flow from 53 to 39 ml/min. Diastolic and systolic flows were almost equally affected and end diastolic resistance was increased. The change in coronary flow was not accompanied by a change in either blood pressure or heart rate. Within six seconds after the stimulation had begun, in record C, mean coronary flow increased markedly and reached 83 ml/min. This was due entirely to the increased heart rate because the stroke

![FIGURE 3](http://circres.ahajournals.org/)

Records of aortic blood pressure (ascending aorta) and phasic flow in the left circumflex coronary artery following sympathetic stimulation. A, control; B and C, 1 and 6 seconds after the beginning of stimulation, respectively; D, 6 seconds, and E, 3 minutes after the end of stimulation. The left common ansa subclavia was stimulated at 6 v with an impulse duration of 11 msec, and a frequency of 20/sec. The left stellate ganglion was disconnected from sympathetic chain and from spinal nerves. Vertical intercepts, 0.1-second intervals. Numbers on pressure and coronary flow curves as in figure 1.
coronary flow returned only to the control level as the result of an increase in stroke diastolic flow and a decrease in stroke systolic flow. End diastolic coronary resistance was reduced from the control value by one-half. The rate of rise of aortic pressure during systole was much more rapid than before, and peak systolic pressure was elevated. The duration of ejection was considerably shortened and the fall of diastolic pressure more rapid. The changes of systolic and diastolic pressure were directionally opposite so that the mean aortic pressure was essentially unchanged. Heart rate was increased from 110 to 176 beats per minute. In the flow pattern, the slope of isometric contraction of the ventricle was greatly increased and backflow appeared during the ventricular ejection phase, being maximal at about the time of aortic valve closure. In early diastole, the increase of flow was much more rapid, and after the diastolic peak, the curve tended to reach a plateau. Six seconds after the end of the stimulation, mean coronary flow increased further from 83 to 111 ml/min, as shown in record D. This was due to a further augmentation of flow during diastole and to a rise of systolic flow which approached that in the control record. End diastolic coronary resistance was reduced still more. Backflow during systole disappeared and the flow pattern was similar to that observed during stimulation at lower voltages. In record E, three minutes after the end of stimulation, coronary flow and flow pattern were approximately the same as in the control.

The preceding account illustrates the effects most frequently obtained with nerve stimulation in this group of animals. In all experiments, the sustained effect was an increase of stroke diastolic flow and of diastolic and mean coronary flow per minute, with reduction of the systolic flow; in other particulars, the response varied. In some experiments, the initial phase of reduced coronary flow was absent. Frequently, the blood pressure rose significantly together with coronary inflow, but even in these instances, end diastolic coronary resistance was decreased. In other instances, backflow in the coronary artery occurred early in systole.

Exploratory studies of oxygen metabolism were done in three animals of this group. They all showed that the rise in flow paralleled a rise in oxygen consumption. In the experiment summarized in table 1, left circumflex coronary flow rose from 32 to 78 ml/min, while oxygen consumption rose from 3.0 to 6.9 ml/min. The coronary sinus oxygen content rose slightly from 4.1 to 4.7 ml/100 ml, so that the arteriovenous oxygen difference decreased from 9.5 to 8.8 ml/100 ml. Stroke oxygen consumption increased from 0.028 to 0.048 ml/beat as the result of a disparity between the rise in oxygen consumption and heart rate.

Discussion

The control curves of coronary inflow obtained in this type of preparation are generally similar in pattern to those obtained by Gregg and Green in the open-chest dog by means of the orifice meter. They differ from the latter in that backflow is generally not present during the isometric contraction period and the volume of flow during systole is considerably higher.

Artifacts of two types may be present in these phasic flow curves. The first is due to "noise" produced by the amplifier, a ripple of 1 to 2 mm at the gains used in three experiments. The second artifact appears to be due to cardiac action potentials. Although these may be quite large initially, they usually disappear within a week. This type of artifact did not appear to be present at the time of the experiments reported here.

In accordance with previous findings in anesthetized open-chest dogs, stimulation of the stellate ganglion or its cardiac branches in previously operated conscious dogs is found to increase the coronary inflow. This effect occurred with or without a rise in aortic blood pressure and when heart rate was only slightly increased.

The augmentation of coronary inflow following sympathetic nerve stimulation resulted chiefly from an increased flow during diastole, systolic flow changes being smaller and
TABLE 1

<table>
<thead>
<tr>
<th>Effect of Sympathetic Nerve Stimulation on Myocardial Oxygen Metabolism</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
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<tr>
<td>Mean aortic pressure, mm Hg</td>
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<tr>
<td>Circumflex flow, ml/min</td>
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<tr>
<td>Coronary sinus oxygen, ml/100 ml</td>
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<td>A-V oxygen difference, ml/100 ml</td>
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<tr>
<td>Oxygen consumption, ml/min</td>
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<tr>
<td>Stroke coronary flow, ml/beat</td>
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<tr>
<td>Stroke oxygen consumption, ml/beat</td>
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<td>Stroke oxygen consumption, ml/beat</td>
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variable in direction according to the strength of stimulation. When the latter was relatively low, coronary inflow increased in systole though to a lesser extent than it did in diastole. When the voltage of stimulation was raised above a certain level, coronary inflow was depressed during systole with evidence of backflow. The significance of these different changes in systolic coronary inflow may possibly be that at low strength of stimulation, the reduction of intravascular resistance is greater than the increase of extravascular compression during myocardial contraction, whereas the opposite may happen at higher strength of stimulation, the positive inotropic effect then becoming dominant.

In previous studies dealing with stimulation of cardiac sympathetic nerves, either with intact ganglia or after their central connections had been severed, the only change in systolic coronary inflow observed was a reduction. This was probably due to the use of only high strengths of stimulation in these studies.

According to Denison and Green, the increase of mean coronary inflow following sympathetic nerve stimulation is due mainly to a relative lengthening of diastole and to a more rapid increase of flow during isometric relaxation of the ventricles, the dilatation of coronary arterioles being a minor effect. The latter conclusion was reached through the observation that end diastolic coronary resistance did not decrease significantly in their experiments. In the present study, however, sympathetic nerve stimulation was followed by a constant and often remarkable reduction in end diastolic resistance to coronary inflow. Therefore, it seems probable that an active vasodilatation plays a role in augmenting coronary inflow during sympathetic nerve activation. Furthermore, the existence of such a vasodilatation is supported by the increase of systolic coronary flow occurring at low-strength stimulation.

At the beginning of sympathetic nerve stimulation, an initial phase of reduced coronary inflow with an increase in end diastolic resistance to flow was often observed. During this phase, aortic blood pressure, i.e., coronary perfusion pressure, was decreased in some experiments whereas, in others, no changes in this parameter were observed. In the latter instance, the reduction of coronary flow could be attributed to a direct vasoconstrictor effect on coronary arterioles, this being subsequently overcome by the dilatation resulting presumably from enhanced myocardial metabolism. Results obtained by other authors support this view. Moreover, our data on oxygen consumption suggest that the rise of coronary flow is associated with an increase of cardiac metabolism.

According to Juhasz-Nagy and Szentivanyi, preganglionic coronary vasomotor fibers are present in cardiac sympathetic nerves of dogs and cats. Using low parameters of stimulation, they reported pure constrictor or dilator effects, i.e., without concomitant metabolic changes. The activation of such fibers may be responsible for the initial reduction of coronary flow observed in our experiments although no studies were done to test this possibility.

In the experiment represented by the records in figure 3, the left stellate ganglion, at
the time of electrode implantation, was severed from the spinal nerves and sympathetic chain to obtain a cardiac response only. Artificial (electrical) stimulation of its cardiac fibers would not necessarily be expected to produce cardiac effects similar to those which follow naturally occurring stimulation. Despite this, the changes of coronary flow pattern observed with this intense sympathetic stimulation are strikingly similar to the responses observed following spontaneous excitement in the resting dog.

**Summary**

The effects of cardiac sympathetic nerve stimulation on coronary inflow were studied in previously operated conscious dogs, using electromagnetic flowmeters. Stimulation caused an increase of coronary inflow which was due mainly to an augmentation of flow during diastole. In systole, inflow changes were smaller and variable according to the strength of stimulation. The data presented indicate that an arteriolar dilatation may play a role in augmenting coronary inflow.

In several instances, the increase of coronary inflow was preceded by a phase of reduction which suggested the possibility of coronary vasoconstriction as a primary direct effect of cardiac sympathetic activation.

**References**

Coronary Inflow and Oxygen Usage Following Cardiac Sympathetic Nerve Stimulation in Unanesthetized Dogs
LINO GRANATA, RAY A. OLSSON, Maj., ANDREW HUVOS and DONALD E. GREGG

_Circ Res_. 1965;16:114-120
doi: 10.1161/01.RES.16.2.114

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1965 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/16/2/114

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