A sympathetic reflex elicited by experimental coronary occlusion

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Malliani, Alberto, Peter J. Schwartz, and Alberto Zanchetti. A sympathetic reflex elicited by experimental coronary occlusion. Am. J. Physiol. 217(3): 703–709. 1969.—The effects of transient coronary occlusion on a sympathetic outflow presumably directed to the heart have been studied on cats. Single preganglionic fibers and a few multifiber strands have been isolated from the left third thoracic ramus communicans (T3). Coronary occlusion quickly induced an increased discharge of most of the fibers tested. A very few fibers decreased their discharge, whereas some were apparently unaffected by coronary occlusion. Increased firing neither depended on direct anoxic stimulation of preganglionic neurons nor on sinoaortic or vagal reflexes and was observed in spinal preparations. A sympathetic cardio-cardiac reflex is proposed, the afferent and efferent pathways of which are both in sympathetic nerves.

METHODS

The results reported here have been obtained in 19 successful experiments on cats. Five animals were anesthetized with pentobarbital sodium (35 mg/kg intraperitoneally) and seven with chloralose-urethan (60 mg/kg and 250 mg/kg intraperitoneally, respectively). Two of the latter received additional intravenous doses of thiopental sodium (10 mg at a time). Four animals were decerebrated under transient ether anesthesia, and three others had the spinal cord sectioned at the first cervical level after receiving fully anesthetic doses of pentobarbital sodium. In three spinal preparations the brain rostral to the section was left intact.

In every preparation, the trachea was cannulated, and the left side of the pericardium incised longitudinally. A segment of the left coronary arterial tree (left main artery, left descending or circumflex ramus) was freed from the surrounding tissues, using a dissecting microscope and avoiding damage to pericoronary nerves. A thread slipped around the artery and passed through a polyethylene or glass tubing was pulled whenever the artery was to be occluded. To avoid excessive myocardial damage, each occlusion lasted from 20 to 90 sec, and subsequent occlusions were spaced at intervals of at least 20 min. In a control experiment a similar occlusion was performed on the main left coronary vein.

A bilateral pneumothorax was produced by widely opening the chest. A segment of the pleura close to the heart. The preparation was placed with the left side up and firmly fixed by vertebral clamps. The stellate ganglion was exposed retropleurally by removing overlying muscles and ribs, covered by a pool of mineral oil maintained at body temperature by thermal radiation. The thoracic sympathetic rami communicantes entering the left stellate ganglion were identified and T3 was then dissected clear to its entrance into the ganglion. The external connective sheath was removed and filaments for recording were prepared by cutting portions of the rami. All fibers from which recordings were to be made were distally disconnected from the ganglion and could carry only afferent impulses. In most experiments the rami filaments were split until only discharges from a single active fiber were present. In some cases, recordings were obtained from filaments containing up to ten active fibers in order to assess the responsiveness of a small population of neurons. Recordings of nerve impulses were obtained by a bipolar silver electrode coupled with a Tektronix 122 preamplifier (band-pass filter, usually between 8 cycles/sec and 10 kc/sec); signals were then fed into one beam of a Tektronix 565 oscilloscope. A
slave cathode-ray tube was arranged in parallel and its screen was photographed on moving film. We also measured the arterial pressure with a Statham P23Dc strain gauge, the first lead of the electrocardiogram (amplified by a Tektronix 122 preamplifier), the average heart rate with a Grass 7PM4 tachograph, and the respiratory movements with a transducer connected to the tracheal cannula. These variables were recorded on a multichannel ink-writer polygraph (Grass P7) and one of them was also displayed on the second beam of the oscilloscope. The nerve action potentials were used to trigger electric pulses corresponding to each action potential (see Fig. 4), and these pulses were continuously recorded on the polygraph. Firing rates were measured by counting the numbers of action potentials, usually for 4 sec periods, and reporting these sums in histograms (see Figs. 2, 3, 5). For fibers discharging with the respiratory rhythm, histograms were commonly calculated using as a time basis one-third of the duration of the respiratory cycle (see Fig. 4). For all fibers, mean firing rates per second were also separately computed for periods of 20 sec to several minutes both preceding and following coronary occlusion, as well as for the entire period during coronary occlusion. These data appear in Figs. 2-5, above the histograms.

Results as described were collected from preparations (except for those with spinal cord section) having systolic arterial pressure above 120 mm Hg and with a rectal temperature between 37 and 38.5 C. Spinal preparations had systolic arterial pressures between 80 and 100 mm Hg.

RESULTS

Background Activity and Types of Effects Evoked by Coronary Occlusion

We report here results obtained from 22 single preganglionic sympathetic fibers and 8 multifiber strands. In agreement with previous descriptions (4, 19) the spontaneous activity of single fibers usually consisted of a few action potentials ("spikes") per second, but some fibers had nearly no spontaneous discharge, whereas others had a high level of background activity (exceptionally up to 50 impulses/sec). As described by previous authors (1, 5, 19, 26, 31) there were fibers (5 in our sample) discharging with the respiratory rhythm, synchronous either with deflation or inflation. The cardiac rhythm sometimes observed by Bronk et al. (5) and by Iggo and Vogt (19) was never found for the fibers we isolated.

Coronary occlusion was tested several times for each fiber (average four times). Most of the fibers consistently increased their firing rate, whereas only very few of them showed a decreased discharge. Some of the fibers did not react to occlusion. The results for the three groups of fibers will be presented separately below.

Fibers Responding with Increased Firing Rate

Pattern of response. This pattern was the most frequently found, and equally observed after occlusion of the left coronary artery or of either of its main branches. During coronary occlusion 13 of 22 single fibers and 5 of 8 multifiber strands clearly increased their discharge. As shown in Table 1, where the mean discharge rates for each of the 13 excited fibers are indicated, this increase in firing varied from fiber to fiber. Though seldom marked, it was consistent from trial to trial, and was easily discernible because of the low level of activity preceding coronary occlusion. In a few cases coronary occlusion evoked a low discharge frequency in a fiber previously silent for a prolonged time. An instance of the latter is shown in Fig. 1. The latency of the response was variable from fiber to fiber. Sometimes it was several seconds, as in Fig. 1 (about 5 sec), though often it was shorter. In Fig. 2, C and D the increased discharge started almost immediately after occlusion, the latency being less than a heart cycle. Although in several fibers the response showed a peak during the first few seconds (Figs. 2 and 3), the discharge remained elevated throughout the period of occlusion, quickly returning to basal levels at its termination (Fig. 2) or shortly thereafter (Fig. 1).

Cardiovascular concomitants. Occlusion of the left coronary artery or one of its main branches (anterior descending or circumflex) was always accompanied within a few seconds by clear electrocardiographic changes, which, however, usually appeared after the increased sympathetic discharge had started (Figs. 1 and 2). Such changes could often involve the S-T segment and the T wave, leading to the picture known electrocardiographically as acute ischemia and lesion (Fig. 1). At times only the T wave was altered, becoming either higher or inverted, sharp and symmetrical. Arrhythmias were also observed, especially at the beginning of occlusion, usually consisting of supraventricular or ventricular ectopic beats.

During coronary occlusion there was a moderate decrease in heart rate in five animals, and a small increase in one.
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Heart rate was unaffected in seven preparations. Likewise, arterial pressure decreased in the five cats in which bradycardia occurred; the pressure fall was moderate, except in one cat, and always involved both systolic and diastolic values. No change in arterial pressure was observed in eight animals during coronary occlusion leading to increased sympathetic discharge.

Effects of vagotomy. The increase in sympathetic activity induced by coronary occlusion did not necessarily depend upon afferent impulses transmitted along the vagi. In four fibers in which coronary occlusion was tested both before and after bilateral cervical vagotomy (see Table 1), the increase in sympathetic discharge to coronary occlusion still occurred after both vagi were severed (Fig. 4). Furthermore, coronary occlusion induced a definite increase in the firing rate of other five fibers tested only after bilateral vagotomy had been performed (Table I and Fig. 2).

Transsection of spinal cord. In three vagotomized cats the spinal cord was transected at the first cervical level. In these animals single fiber and multifiber preparations were found to increase their discharge during coronary occlusion (Table 1). Figure 3 shows excitation of a single preganglionic fiber. No change in systolic and diastolic pressure and in heart rate was observed during this and other coronary occlusions in spinal preparations.

Effects of anesthesia and of different background discharges. Increased sympathetic activity after coronary occlusion was observed both in animals anesthetized with pentobarbital sodium and in animals under chloralose-urethan. It was also found in unanesthetized decerebrate animals. Moreover, the response was not dependent on a particular type of brain transection, inasmuch as it appeared both in decerebrate and in spinal cats.

Changes in background activity sometimes occurred during prolonged recording from a fiber, but they were never such as to influence qualitatively the response to coronary occlusion. For instance, the fiber in which activity is sampled in Fig. 2 promptly discharged, upon coronary occlusion, both when there was practically little background firing (A, C) and when this was induced by moderate bleeding (about 20 ml) (B, D).

Subtler interactions between background and evoked activities were observed in fibers discharging with the respiratory rhythm. In Fig. 4, one of the two fibers simultaneously recorded discharged only during positive-pressure inflation of the lungs (B). During coronary occlusion the discharges were still inflation locked, but their association with the respiratory cycle became more regular, a spike occurring practically at each inflation (A). After cervical occlusion...
vagotomy, this fiber lost its respiratory rhythmicity (D), but could still be excited by coronary occlusion (C).

**Control procedures.** In a number of experiments, when a fiber was unequivocally excited by coronary occlusion, we also tested the effects of various mechanical stimuli to the heart such as gentle displacement of the heart, light pinching of the myocardium, touching the coronary region with the polyethylene tubing used for tying the snare around the coronary artery, and (in one case) occlusion of a main coronary vein. In no instance was the background discharge of a preganglionic sympathetic fiber modified by any of these experimental procedures.

**Fibers Responding with Decreased Firing Rate**

Only 2 of 22 single fibers and none of 8 multifiber strands were found to decrease their firing rate during coronary occlusion. In 1 of the 2 fibers recordings were made before and after vagotomy. It will be noted in Fig. 5a that a progressive reduction in firing during occlusion was associated with progressive hypotension and bradycardia, suggesting a rather widespread reduction in sympathetic activity. After bilateral vagotomy (B) the background discharge of the fiber and arterial pressure were somewhat higher. Coronary occlusion neither induced a decrease in the firing of the sympathetic fiber after vagotomy nor produced hypotension and bradycardia. However, it should not be concluded that decreased sympathetic activity induced by coronary occlusion is necessarily mediated by vagal afferents, as the other fiber in our population which responded with a decrease in discharge was observed in a vagotomized animal.

**Fibers not Responding to Coronary Occlusion**

No response to coronary occlusion was noted in 7 of 22 fibers and 3 of 8 multifiber strands. However, 1 multifiber strand was studied in a preparation in which a small peripheral branch of the left coronary artery was occluded, and no electrocardiographic change was observed. In other instances, unresponsive single fibers were characterized by very high background firing (up to 50 spikes/sec). In these cases, though the conditions of the animals were apparently good, spinal or cerebral anoxia could have acted as a tonically stimulating agent (2, 6). Other unresponsive fibers, however, had a low rate background discharge, and some...
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FIG. 5. A: fiber responding with decreasing firing rate to coronary occlusion. B: response disappeared after vagotomy. Chloralose-urethane anesthesia. All other explanations as in Fig. 2.

were studied in the same preparation at the same time or shortly after other fibers, which were excited by coronary occlusion. Although some of the fibers not responding to coronary occlusion might be of somatic origin (12), it should be noted that they could be affected by other visceral stimuli such as baroceptive stimulation or inactivation, chemoceptive stimulation, etc. (23).

DISCUSSION

Our experiments show that an increased discharge is the most common response of preganglionic sympathetic neurons in T3 to transient coronary occlusion. The following discussion will be mainly centered on this type of response and will try to answer four major questions: 1) whether the changes in sympathetic efferent activity produced by coronary occlusion were reflex in nature and 2) what were the afferent pathways of the reflex; 3) whether the fibers we studied were part of the efferent innervation of the heart; 4) what may be the significance of this response.

Reflex nature of the response. Before defining the increased sympathetic discharge during coronary occlusion as a reflex response, it is necessary to rule out the possibility of a direct anoxic stimulation of the preganglionic neurons in the spinal cord (2, 6). It is extremely unlikely that anoxia played a role in the excitatory reactions to coronary occlusion because, in most experiments, no change in arterial pressure and heart rate was observed during coronary occlusion. In the cases showing hypotension, only one drop in arterial pressure was of a degree compatible with the hypothesis of spinal or cerebral anoxia.

Afferent pathways of the reflex. Three of the most likely sources of afferent activity causing the increase in preganglionic sympathetic discharge are: 1) baroceptive and chemoceptive sinoaortic receptors; 2) vagal afferent fibers from the heart, and 3) afferent fibers in cardiac sympathetic nerves.

Studies of previous authors, showing increased vascular resistance after human myocardial infarction (14, 16, 17, 21, 30, 33) or experimental coronary occlusion (18, 22, 34), had suggested that in these conditions the sympathetic vasoconstrictor system might be reflexly excited through a deactivation of baroceptive sinoaortic afferents. The latter would be brought about, in its turn, by an arterial pressure fall consequent to a primary reduction in cardiac output. A similar interpretation cannot apply to our results, since the activity of thoracic sympathetic neurons could increase in absence of any change in arterial pressure and heart rate. Furthermore, sympathetic activation still occurred in the spinal animal, when pathways from receptors with afferent fibers in cranial nerves were interrupted. Of course, these conclusions on the role of sinoaortic reflexes do not necessarily extend to the vasoconstricting response reported by others, although our results suggest caution in ascribing this phenomenon to sinoaortic mechanisms only.

Our observations in spinal and vagotomized preparations also rule out vagal afferent fibers as an essential link. Moreover, those four fibers which were found to be excited to about the same degree by coronary occlusion before and after vagotomy indicate that vagal afferents contributed little to reflex sympathetic activation.

On the other hand, our study suggests that the vagi may sometimes play a role in evoking a decreased sympathetic activity as a response to coronary occlusion. It should be recalled, in this connection, that Costantin (10) has observed regularly decreased activity in the inferior cardiac nerve during coronary occlusion which depended upon the vagi. However, in our cats with intact vagi, only 1 of 15 single preganglionic fibers and none of 8 multifiber strands responded to coronary occlusion by decreased firing.

If both sinoaortic and vagal afferents are not required for the reflex increase of thoracic sympathetic activity, it should be concluded that this effect is evoked from the afferents in cardiac sympathetic nerves which Brown found to be excited by coronary occlusion (8). The type of receptor from which these fibers originate is unknown. Coronary occlusion may act through ischemic or anoxic excitation of specific or unspecific receptors in the myocardium, a possibility supported by those experiments in which the latency of the reflex was of several seconds, or through activation or deactivation of coronary chemo- or mechanoreceptors (7), a possibility supported by those experiments in which the latency of the reflex was extremely short.

At least in the spinal and vagotomized animal afferent fibers in sympathetic nerves of the heart can act as the only afferent limb of the reflex. Therefore, we have demonstrated that coronary occlusion cliffs a sympathetic reflex which can be integrated at a purely spinal level. A segmental organization of this spinal reflex is suggested by the fact that some of the afferents excited by coronary occlusion in Brown’s experiments enter the spinal cord at the third thoracic segment. Of course, in the intact animal, supraspinal mechanisms may also be involved (9).

Destination of recorded impulses. As we have recorded from T3, it is possible only to say that the fibers studied were distributed to postganglionic cells in sympathetic ganglia, presumably the stellate ganglion. The unknown destination of preganglionic impulses beyond their relay in the ganglion is a major limitation inherent in recording from preganglionic fibers, but this limitation is balanced by distinct advantages. Only when recording from a ramus communicans can one be sure to have a purely sympathetic...
population of fibers. Contamination with somatic (12) axons is unlikely when recording from filaments entering the stellate ganglion (4), whereas vagal axons, absent in these rami, are numerous in all cardiac nerves (25). Moreover, there is good evidence that T3 is importantly involved in the efferent control of the heart. Sectioning of this ramus considerably decreases the activity in cardiac nerves (5). Its electrical stimulation induces in the dog a remarkable cardiac augmentor effect with little or no tachycardia (28), an observation we have also confirmed in the cat (unpublished data). Undoubtedly, a great many fibers in T3 participate in the efferent innervation of the heart, and it seems likely that the spinal sympathetic reflex we have described represents a cardio-cardiac reflex.

Our lack of precise information on the destination of the preganglionic sympathetic fibers makes it impossible to say whether the neurons which behaved differently (increased, decreased, or unchanged firing) belonged to a common population in terms of peripheral distribution, or whether each group was connected with ganglionic neurons acting on different effectors within or near the heart. Our observations of different responses in different fibers simply support those recent studies (4, 13, 19, 35), showing that the sympathetic system is possessed of a remarkable specificity of responses. Considering this, we do not suggest that the predominant excitation induced by coronary occlusion in fibers of T3 also occurs at other levels in the sympathetic system.

Significance of the reflex. At this stage of our knowledge, one can only advance hypotheses on the significance of a cardio-cardiac spinal sympathetic reflex to coronary occlusion.

REFERENCES

24. Newman, W. H., and R. P. Walton. Alterations in left ventricular contraction. If the effect of electrical stimulation of T3, which is almost exclusively an augmentation of myocardial contraction (28), is tentatively supposed to represent the function of the sympathetic fibers excited by coronary occlusion, then one might suggest than an increase in myocardial contractility, or at least an attempt to increase it, might be the first reflex event following coronary occlusion. In fact, an increase in myocardial contraction strength has been observed after experimental coronary occlusion (21), though it has been differently explained; and an increase in cardiac output has sometimes been measured both after coronary occlusion in animals (11, 27, 36) and after myocardial infarction in man (21, 31). A reflex increase in contractility may not always be evident because of algebraic summation with the direct depressive action of myocardial ischemia on ventricular contractility (32).

A reflex like this might have two opposite consequences in the course of human disease. On the one hand, increased cardiac sympathetic activity signifies increased myocardial oxygen consumption, facilitated arrhythmias, etc. On the other hand, a reflex increase in contractility might be an important mechanism to oppose ventricular dilatation and cardiogenic shock (3, 15, 20, 29).

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