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# Effects of Intracoronary Administration of Bradykinin on the Impulse Activity of Afferent Sympathetic Unmyelinated Fibers with Left Ventricular Endings in the Cat

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**SUMMARY** **In anesthetized and artificially ventilated cats, we recorded the impulse activity of 23 afferent sympathetic unmyelinated fibers with left ventricular endings, dissected from the left sympathetic rami T3 and T4. All fibers displayed a spontaneous discharge at a rate of 0.79 ± 0.2 (mean ± SE) impulses/sec. During constriction of the thoracic aorta, the discharge increased to 1.92 ± 0.2 impulses/sec. During myocardial ischemia, produced by interruption of left main coronary artery perfusion, supplied through an extracorporeal pump, the impulse activity increased to 1.73 ± 0.3 impulses/sec. The mean latency for this excitation was 16.5 ± 1.5 sec. The intracoronary administration of bradykinin (5 and 10 ng/kg) elicited a marked increase in impulse activity that, following 5 ng/kg, reached 2.06 ± 0.2 impulses/sec, after a latency of 18 ± 2 sec and in absence of significant hemodynamic changes. Myocardial ischemia and bradykinin never revealed the existence of silent afferent fibers included in the split nerve strand. The results obtained with this experimental model indicate that the ventricular endings of these afferent sympathetic unmyelinated fibers act as "polymodal" receptors. We hypothesize that the peripheral mechanism for cardiac nociception involves intensive excitation of fibers discharging spontaneously and not recruitment of silent fibers which are purely nociceptive in function.** ***Circ Res 48: 69-75, 1981***



IT generally is accepted that the sympathetic nerves are essential to the perception of cardiac pain (Jonnesco, 1921; Leriche and Fontaine, 1927; Sutton and Lueth, 1930; Lindgren and Olivecrona, 1947; White, 1957; Brown, 1967). However, it has never been tested directly whether noxious events, likely to be algesic, induce only an intensification in the tonic discharge of the sympathetic sensory nerve fibers (Malliani et al., 1975) or recruit instead silent fibers possessed of a specific nociceptive function (Perl, 1971).

In a recent study (Casati et al., 1979) we found that afferent sympathetic unmyelinated fibers with left ventricular endings were tonically active and responsive to normal mechanical stimuli. Coronary occlusion, an abnormal event, increased the discharge of the active fibers but did not recruit silent fibers.

We now report experiments in which the left coronary artery, in the cat, was perfused artificially while electrical recordings were obtained from minute nerve strands containing one spontaneously active afferent sympathetic unmyelinated fiber with a left ventricular ending. The impulse activity of these fibers increased during interruption of coronary perfusion leading to myocardial ischemia and after the injection into the coronary circulation of bradykinin, an algesic substance (Guzman et al., 1962; Burch and De Pasquale, 1963; Lim, 1970). On

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the basis of these experiments, we conclude that this population of cardiac sympathetic unmyelinated afferents display "polymodal" (Burgess and Perl, 1973) receptive properties, a fact that may be relevant to the genesis of cardiac pain.

## Methods

Twenty-three cats (2.8–4.0 kg) were anesthetized by intraperitoneal injection of pentobarbital sodium, 35 mg/kg. The trachea was cannulated and polyethylene catheters were inserted into (1) the thoracic aorta through a carotid or a femoral artery, (2) a femoral vein, (3) the left ventricle through the ventricular apex. The animals were paralyzed with gallamine triethiodide (Flaxedil), 2 mg/kg, and artificially ventilated. The respirator was adjusted to maintain arterial $Po_2$, $Pco_2$, and pH within normal limits as tested with a Radiometer blood gas analyzer (BMS 3 MK2). Blood samples were collected in 15 animals during recordings of neural activity.

The thorax was opened through the 4th left interspace and the 4th, 5th, and 6th ribs on the left side were removed. The heads of the 2nd and 3rd ribs were removed retropleurally on the left side to expose the stellate ganglion and its branches. The pericardium was opened and the left main coronary artery was dissected from the surrounding tissues without damaging the pericoronary nerve.

A thread was passed loosely around the distal portion of the descending thoracic aorta and the ends of the ligature were pulled through a rigid polyethylene tube whenever the vessel had to be occluded.

### Coronary Perfusion

The main left coronary artery was perfused according to the method of Brown (1968). Blood was led from one femoral or carotid artery to a pump (Holter Co.) and thence to a stainless-steel cannula, which was passed down the left subclavian artery into the main left coronary artery and was tied in place. Flow was set at 6.5–8 ml/min and the pressure into the inflow coronary arterial line, registered with a Statham P23 De strain gauge, was 15–20 mm Hg greater than arterial blood pressure. The cats were given heparin (250 U/kg, iv, initially and 500 U/hr later).

### Variables Recorded

Afferent nerve impulses were recorded from filaments isolated under a dissecting microscope from the cut peripheral end of the 3rd and 4th left thoracic sympathetic rami communicantes. Filaments were split until impulses from a single active unmyelinated fiber with a left ventricular ending were present (Casati et al., 1979). A digital spike analyzer, with an accuracy of 1%, was used as in previous work (Recordati et al., 1976) to count the number of impulses per second. These readings provided an approximation of the instantaneous frequencies and were used to obtain the peak and to calculate the average frequencies. Arterial pressure was measured with a Statham P23 De strain gauge: the catheter-manometer system had a flat (±5%) frequency response of 15 Hz, as calculated by its response to a step input of pressure (Fry, 1960). Left ventricular pressure was measured with a Statham P23 De strain gauge connected to a high frequency dc operational bridge amplifier. The measured flat (±5%) frequency response of the ventricular catheter-manometer system was 30 Hz. We also recorded the ECG, heart rate, and respiratory movements, all details having been reported already (Lioy et al., 1974).

### Measurements of Conduction Velocity of Afferent Fibers

The left inferior cardiac nerve was isolated above the aortic arch from the surrounding tissues. This portion of the nerve was stimulated through platinum electrodes (interelectrode distance 5 mm, cathode proximal) with a Grass S4 stimulator through an isolation unit. Pulse were monophasic, 0.1–1.5 msec in duration and 10–15 V in amplitude. Conduction velocity was calculated from the distance between the proximal stimulating electrode and the closest recording electrode divided by the time from the stimulus artifact to the beginning of the evoked action potential. To ascertain that the nerve impulses elicited by electrical stimulation, as well as those occurring spontaneously, originated from the same fiber, we analyzed their configuration on photographic records with an expanded time base. Constancy of amplitude and shape of action potentials or absence of other impulses were considered safe criteria (Malliani et al., 1973; Malliani and Pagani, 1976; Casati et al., 1979).

### Location of the Receptor Endings

A preliminary left ventricular location of the sensory ending of each single fiber displaying spontaneous impulse activity was assessed by very gentle mechanical probing performed with a blunt instrument. In some cases light pressure exerted by a finger was a helpful maneuver. When no excitation of impulse activity could be obtained by local mechanical stimuli, the left ventricular location of the endings was inferred on the basis of the pattern of the impulse activity in relation to various hemodynamic stimuli, such as constriction of the aorta, of the pulmonary artery, and of the inferior vena cava (Malliani et al., 1973). However, the endings of each fiber definitely were localized to the left ventricle by mechanical probing performed after the cat had been killed and the heart opened (Coleridge et al., 1957). Therefore, not more than one fiber could be studied in each successful experiment. The destruction of the left ventricular ending always produced the disappearance of impulses in the fiber studied, confirming that no additional sensory fields were

present (Coleridge et al., 1975; Malliani and Pagani, 1976). The fibers that erroneously were considered, in the course of the experiment, to have ventricular endings and instead innervated other structures (e.g., the right ventricle or the left atrium) were not included in this report.

### Intracoronary Administration of Bradykinin

Synthetic bradykinin (BRS-640 Sandoz; mol wt, 1060.25) was dissolved in normal saline (NaCl, 9 g/l) in scalar concentrations from 100 to 1000 ng/ml. Progressive amounts of bradykinin (5, 10, and 30 ng/kg) were administered by injecting volumes from 0.05 to 0.1 ml into the main left coronary artery through the outflow line of the extracorporeal circuit. Bradykinin reached the main left coronary artery with a mean latency of 2.5 seconds from the time of injection. The interval between subsequent administrations of bradykinin was not less than 10 minutes. Similar volumes of saline also were injected.

### Statistical Analysis

Values reported in the Results are mean ± SE. One-way analysis of variance was employed to test the significance of the observed changes using the Scheffé method (Armitage, 1971).

## Results

We studied the impulse activity of 23 afferent sympathetic unmyelinated fibers (type C) with left ventricular endings.

### Spontaneous Impulse Activity

All nerve fibers had a spontaneous impulse activity the mean of which was 0.79 ± 0.2 impulses/sec at an arterial systolic pressure of 127 ± 9 mm Hg, a left ventricular end-diastolic pressure of 4.25 ± 0.4 mm Hg, and a heart rate of 176 ± 8 beats/min.

As already reported (Casati et al., 1979), the spontaneous discharge consisted of not more than a single action potential per cardiac cycle (Fig. 1, upper part), each cycle not necessarily being accompanied by a nerve impulse. Most often (19 fibers) a fixed temporal correlation between impulses and ventricular dynamics was not detectable (Fig. 1, upper part).

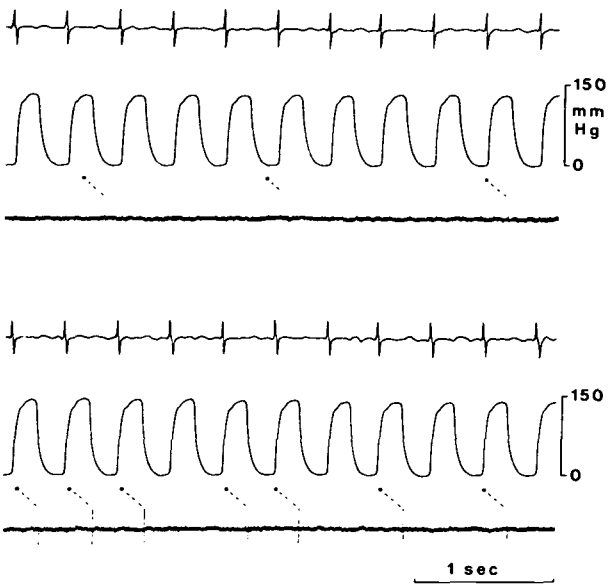


FIGURE 1 *Impulse activity of an afferent sympathetic unmyelinated nerve fiber with a left ventricular sensory field. Tracings represent, from top to bottom, the ECG, left ventricular pressure (polygraph recordings) and neural activity (cathode-ray oscilloscope recording). Upper part of the figure, spontaneous activity; lower part, 21 seconds after the intracoronary administration of bradykinin, 5 ng/kg. The fiber conduction velocity was 0.54 m/sec; the measured conduction distance from the receptive field to the recording electrode was 8.6 cm. Dots indicate the approximate relation between impulses and cardiac cycles, taking into account a conduction time of 160 msec.*

### Effects of Various Stimuli

The mechanoreceptive properties of the receptors were tested with increases in aortic pressure lasting 9.8 ± 0.8 sec, produced by constriction of the thoracic aorta (Table 1). The impulse activity of the fibers was significantly increased (Fig. 2), after a latency of 1.7 ± 0.2 sec.

The interruption of perfusion of the left main coronary artery (for brevity indicated as left coronary occlusion, LCO) for a period of 30–45 seconds caused a significant increase in the discharge of the

TABLE 1 *Hemodynamic Variables under Control Conditions and during Interventions*

| | Control | AO | LCO | BK, 5 | BK, 10 |
|---|---|---|---|---|---|
| Systolic arterial pressure (mm Hg) | 127 ± 9<br>*n* 23 | 203 ± 8<br>*n* 23* | 90 ± 7<br>*n* 23* | 121 ± 4<br>*n* 23 | 118 ± 4<br>*n* 16 |
| Mean coronary pressure (mm Hg) | 142 ± 6<br>*n* 23 | 171 ± 6<br>*n* 23† | —<br>*n* 23 | 140 ± 5<br>*n* 23 | 134 ± 5<br>*n* 16 |
| Left ventricular end-diastolic pressure (mm Hg) | 4.25 ± 0.4<br>*n* 23 | 9.8 ± 1.7<br>*n* 23* | 12.3 ± 1.5<br>*n* 23* | 4.42 ± 0.4<br>*n* 23 | 4.52 ± 0.4<br>*n* 16 |
| Heart rate (beats/min) | 176 ± 8<br>*n* 23 | 162 ± 7<br>*n* 23 | 173 ± 8<br>*n* 23 | 174 ± 7<br>*n* 23 | 175 ± 8<br>*n* 16 |

Values significantly different from control. AO = occlusion of thoracic aorta, LCO = occlusion of left coronary; BK, 5 and BK, 10 = intracoronary administration of bradykinin, 5 and 10 ng/kg, respectively.
*$P < 0.01$; †$P < 0.05$.

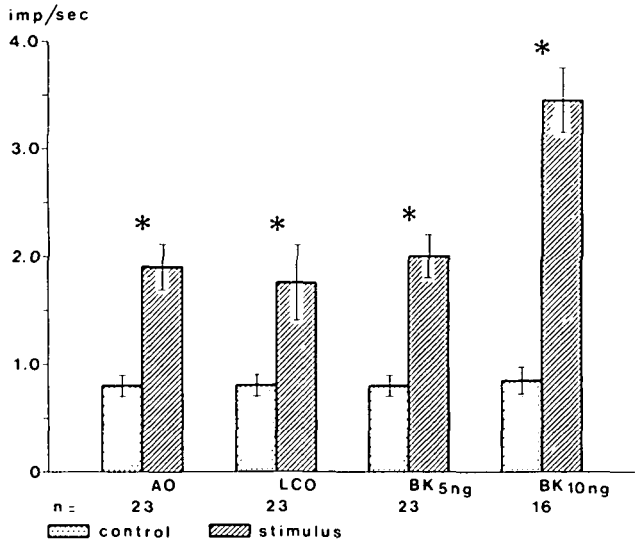


FIGURE 2 *Responses of afferent fibers to the experimental interventions. AO, aortic occlusion; LCO, interruption of the perfusion of the left main coronary artery; BK 5 ng and BK 10 ng, intracoronary administration of bradykinin, 5 ng/kg and 10 ng/kg. n = number of fibers studied; * P < 0.001.*

fibers (Fig. 2). The mean latency for this excitation was 16.1 ± 1.5 sec (about 18 seconds in the example shown in Fig. 3a).

No silent fiber became active during coronary occlusion.

Intracoronary administration of bradykinin (at doses of 5 and 10 ng/kg) did not produce significant changes in systolic arterial pressure, mean coronary perfusion pressure, left ventricular end-diastolic pressure or heart rate (Table 1 and Fig., 4 a and b). The same doses, however, induced a significant increase in the nerve discharge (Fig. 2). After a dose of 5 ng/kg, the impulse activity increased for 35 ± 3.3 sec with a mean frequency of discharge of 2.06 ± 0.2 impulses/sec and a mean peak frequency of 5.15 ± 0.6 impulses/sec.

After a dose of 10 ng/kg, the impulse activity increased for 65 ± 5.5 sec with a mean frequency of 3.44 ± 0.3 impulses/sec and a mean peak frequency of 8.6 ± 0.8 impulses/sec. When peak frequencies of discharge were attained, more than one action potential per cardiac cycle could be present. Taking into account the transit time from the site of injection to the main left coronary artery (see *Methods*), the mean latency for the excitations was 18 ± 2 sec

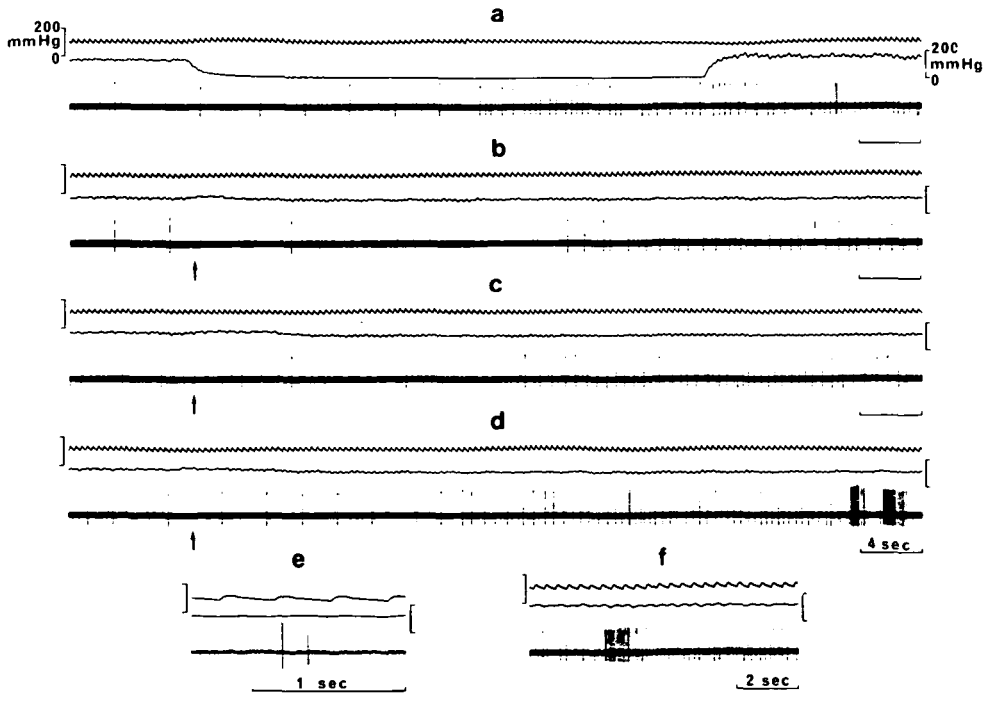


FIGURE 3 *Activity of an afferent sympathetic unmyelinated nerve fiber with a left ventricular sensory field. Tracings represent, from top to bottom, systemic arterial pressure, coronary perfusion pressure, nerve impulse activity (cathode-ray oscilloscope recordings). a: Interruption of the left main coronary artery perfusion; b: intracoronary administration, beginning at the arrow, of bradykinin, 5 ng/kg; c: intracoronary administration of bradykinin, 10 ng/kg; d: intracoronary administration of bradykinin, 30 ng/kg; e: electrical stimulation of the left inferior cardiac nerve activating the afferent fiber; the biphasic first deflection is the artifact of the stimulus, and the second biphasic deflection is the action potential of the fiber. The approximate length of the fiber was 8 cm. The conduction velocity calculated for this fiber was 0.45 m/sec; f: mechanical probing, marked by a bar, of an area of the external surface of the left ventricle; notice the after-discharge which is typical of unmyelinated afferents.*

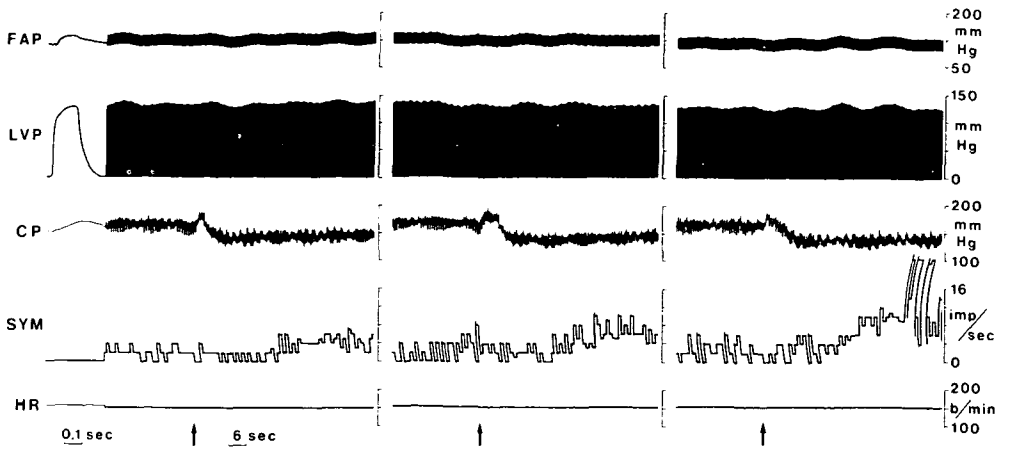


FIGURE 4 *Hemodynamic and neural responses to intracoronary injections of bradykinin. AP: arterial pressure; LVP: left ventricular pressure; CP: left coronary perfusion pressure; SYM: impulse activity of the afferent sympathetic unmyelinated fiber counted with a digital spike analyzer; HR: heart rate (polygraph recordings). Effects of intracoronary administration of bradykinin at doses of 5 ng/kg (a), 10 ng/kg (b), and 30 ng/kg (c).*

after the injection of 5 ng/kg of bradykinin and 16.2 ± 2 sec after 10 ng/kg. Examples are shown in Figure 3, b and c, and Figure 4, a and b.

During the excitation consequent to administration of bradykinin, 7 of 19 nerve fibers that under control conditions had a discharge unrelated to the cardiac cycle (Fig. 1, upper part), displayed their impulses during ventricular systole (Fig. 1, lower part; an appropriate correction for the fiber conduction time is indicated (Casati et al., 1979)), suggesting a phenomenon of "sensitization" (Iggo, 1974; Perl et al., 1976) to ventricular contraction in absence of significant changes in ventricular pressures (Table 1).

In four cats, bradykinin was injected in a dose of 30 ng/kg. The nerve discharge, besides a marked excitation, showed bursts of impulses at very high frequency (mean peak values of 16.22 ± 2.2 impulses/sec; Figures 3d and 4c).

Administration of bradykinin, at all doses tested, never revealed the existence of silent afferent fibers included in the split nerve strand.

### Nerve Fibers Conduction Velocity

The 23 nerve fibers included in this report had a mean conduction velocity of 0.62 ± 0.14 m/sec (range 0.30–0.90) (Fig. 3e). Therefore they were all likely to be unmyelinated (type C) (Grundfest and Gasser, 1938; Burgess and Perl, 1973). Electrical stimulation of the left inferior cardiac nerve never elicited the appearance of action potentials from additional fibers not discharging spontaneously.

## Discussion

This study was restricted to *unmyelinated* afferent sympathetic nerve fibers with left ventricular endings. As described in a previous report (Casati et al., 1979), these afferents display spontaneous impulse activity and respond to a variety of mechanical stimuli. In the present and in the previous study, the absolute values of the spontaneous discharge and of the responses to an increased pressure load were remarkably similar. This suggests that the additional experimental procedures which had to be adopted, that is opening of the pericardium and cannulation of the main left coronary artery, did not alter the background discharge and the responsiveness of the ventricular afferents.

The excitation of *unmyelinated* sympathetic afferents induced by bradykinin, although reported for the first time, was not an unexpected finding. Afferent sympathetic fibers, with an unspecified conduction velocity, innervating the heart and the great thoracic vessels (Baker et al., 1978) and the left ventricle (Uchida and Murao, 1974a) were found to be excited after topical applications of bradykinin. Similar observations were made on myelinated cardiac sympathetic afferents (Nishi et al., 1977) and on unmyelinated cardiac and vascular vagal afferents (Kaufman et al., 1979). In addition, a vast population of somatic afferents also can be excited by bradykinin: this is the case for cutaneous afferents (Fjallbrant and Iggo, 1961; Burgess and Perl, 1973) and for skeletal muscle afferent fibers of small diameter (Mense, 1977). The endings of all of these fibers act as "polymodal" (Burgess and Perl, 1973) receptors, the term indicating that the receptive zone is considered to be sensitive to both mechanical and chemical stimuli, although a transducer mechanism to account for such dual sensitivity has not been characterized yet (Leek, 1977).

Bradykinin is an algogenic substance (Guzman et al., 1962; Lim, 1970) which is released during experimental myocardial ischemia (Kimura et al., 1973) and suspected (Burch and De Pasquale, 1963) to take part in the genesis of cardiac pain. The rapid intracoronary administration of doses that did not

produce general vascular effects was considered most appropriate to provide consistently sufficient concentrations of drug in the extracellular space [where pain-producing substances are likely to be released (Vane, 1969)]. Furthermore, bradykinin was injected in concentrations of 0.2–0.3 μM that, considering the dilution in the perfusion circuit, might approximate the concentrations of about 0.05 μM that were found in the coronary sinus blood after experimental coronary occlusion (Kimura et al., 1973). In addition, these doses should excite only sensory endings and not the preterminal fibers; the latter should require higher concentrations of bradykinin (Khayutin et al., 1976).

In the experiments reported here, bradykinin markedly increased the activity of all spontaneously active unmyelinated afferents. At times, the drug also appeared capable of increasing their mechanosensitivity (as in Fig. 1), suggesting a phenomenon of "sensitization" (Iggo, 1974; Perl et al., 1976).

Alternatively, intracoronary administration of bradykinin never recruited silent afferents.

## Experimental Coronary Occlusion and Hypotheses for Cardiac Pain

During experimental reduction of coronary blood flow leading to myocardial ischemia, most of the afferent nerve fibers with cardiac endings become excited. Thus afferent nerve fibers running in the vagi, with their endings in the various cardiac chambers, myelinated (Recordati et al., 1971) or unmyelinated (Thorén, 1979), increase their impulse activity. Cardiac sympathetic afferents (Brown, 1967; Brown and Malliani, 1971), myelinated (Malliani et al., 1973; Uchida and Murao, 1974b) and unmyelinated (Uchida and Murao, 1974b; Casati et al., 1979) are excited similarly. The nature of the stimulus leading to this excitation is likely to vary for the different receptors according to their properties and locations, and would include mechanical factors such as enlargement of the cardiac chambers or release of chemical substances. This increased afferent vagal and sympathetic nervous activity is known to be the basis for complex reflex mechanisms from the heart (Schwartz et al., 1978; Brown, 1979).

On the other hand, sympathetic nerves are the only nerves that are considered essential to the perception of cardiac pain (Jonnesco, 1921; Leriche and Fontaine, 1927; Sutton and Lueth, 1930; Lindgren and Olivecrona, 1947; White, 1957) and this nociceptive function probably involves both myelinated (Brown, 1967) and unmyelinated afferents. However, it is still unknown whether nociception from the heart is subserved by a recruitment of silent fibers possessed of a specific nociceptive function (Perl, 1971) or, rather, by an intensification in the discharge of tonically active fibers.

The first possibility seems consistent with various reports (Ueda et al., 1969; Uchida and Murao, 1974a, 1974b, 1975) describing a large population of afferent fibers normally silent and excited during coronary occlusion or by chemical substances. However it should be noted that in these studies most of the fibers also were sensitive to mechanical stimuli and yet devoid of a spontaneous discharge (Ueda et al., 1969). Therefore, the doubt exists that in those experimental conditions the mechanical factors were below the threshold for some mechanosensitive endings, thus causing their fibers to remain with no background discharge. This was probably the case for some silent fibers found to be excited during coronary occlusion by Brown and Malliani (1971) in experiments in which recordings were obtained in spinal animals with a lower than normal arterial pressure.

Besides the problem concerning the presence or absence of a background discharge, most of the fibers in the reports of Uchida and Murao (1974a, 1974b, 1975) seem to have "polymodal" receptors. These authors, in addition, described some fibers with specifically chemosensitive endings. However, this finding should be evaluated with caution. In fact there is the possibility that the topical application of substances like bradykinin to the epicardial surface at concentrations of 0.5–1 μg/ml directly excited the fibers "en passage" (Khayutin et al., 1976), and a superficial probing of the beating heart (Uchida and Murao, 1974a, 1974b, 1975) was not an adequate procedure to assess the existence of mechanosensitive fields if these were located deeply in the ventricular mass (Casati et al., 1979). Thus one could consider as an experimental failure either the inability to detect this type of normally silent fiber with purely chemosensitive endings, or the lack of identification of some mechanosensitive fields. Although the matter still remains open for discussion, the following additional few points should be considered.

Split nerve strands, small as they may be, obviously are made up of many fibers. If silent fibers truly constituted a significant population in the cardiac sympathetic nerves, it seems highly improbable that none of them was ever revealed in any of the 23 nerve strands we studied during electrical stimulation of the left inferior cardiac nerve, coronary occlusion, or after the injection of bradykinin. On the other hand, afferent cardiac sympathetic nerve fibers, myelinated and unmyelinated, are likely to be only a few tens in number in a single ramus communicans (Oldfield and McLachlan, 1978) and a few hundreds in all (Emery et al., 1978). It is conceivable that, to subserve the unbearable cardiac pain, the majority of them should be excited.

In conclusion, the stringent evidence for a specific neural channel subserving somatic pain, with peripheral sensors purely nociceptive in function, and hence with no background discharge (Perl, 1971; Burgess and Perl, 1973), would not apply to the large majority of cardiac sympathetic afferents with

"polymodal" receptors that, under our experimental conditions, have a spontaneous impulse activity. Accordingly, it is our opinion that the "intensity" mechanism appears the most appropriate to account for the properties of the neural substratum subserving cardiac nociception.

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