Analysis of the Pressor Sympathetic Reflex Produced by Intracoronary Injections of Bradykinin in Conscious Dogs

Massimo Pagani, Paolo Pizzinelli, Raffaello Furlan, Stefano Guzzetti, Ornella Rimoldi, Giulia Sandrone, and Alberto Malliani

From Istituto Ricerche Cardiovascolari, CNR; Patologia Medica, Ospedale "L.Sacco"; Università Milano, Italy

SUMMARY. The reflex hemodynamic effects of intracoronary bradykinin were tested in 20 conscious instrumented dogs. When the experiments were performed after full recovery from surgery and anesthesia, graded doses (10–300 ng/kg) of bradykinin always produced graded pressor responses, in the absence of any pain reaction. At the maximum pressor response obtained with 100 ng/kg, mean arterial pressure rose 28 ± 3% from 89 ± 4 mm Hg, left ventricular pressure 20 ± 3% from 121 ± 2 mm Hg, heart rate 30 ± 4% from 88 ± 5 beats/min, rate of change of left ventricular pressure 18 ± 3% from 2812 ± 65 mm Hg/sec (P < 0.01). Higher doses of bradykinin did not produce greater responses. The magnitude of the response was similar when the injection was performed in either the left anterior descending (change in mean arterial pressure 29 ± 3%) or circumflex (change in mean arterial pressure 27 ± 2%) coronary artery. The reflex nature of the response was proved by its disappearance after appropriate pharmacological blockades; moreover, after vagotomy, the pressor rise was maintained, the heart rate response was reduced (change in heart rate 10 ± 2%), and the inotropic response was enhanced (rate of change of left ventricular pressure 24 ± 3%). This suggested that the afferent pathway of the pressor reflex was in the sympathetic nerves and that a subordinate vagal depressor reflex was also operative. No pain reaction was obtained even when injecting very large amounts (1000–2000 ng/kg) of bradykinin, which, instead, induced arterial hypotension. Pain reactions (as inferred by agitation and vocalization) were observed in three out of nine dogs studied during the first week after surgery. This reaction was no longer present when the same animals were tested later on, at the time of complete recovery. In five of the nine dogs studied during the first week after surgery, the intracoronary injection of bradykinin produced a depressor (change in mean arterial pressure -31 ± 6%) response, which, however, reverted to a pressor effect (change in mean arterial pressure 22 ± 4%) later, when recovery was complete. In five additional dogs, the pressor response observed after full recovery from surgery was no longer present when the injection of bradykinin was repeated under anesthesia. The present experiments in conscious dogs show that the chemical stimulation of the fully innervated heart with intracoronary bradykinin can initiate pressor reflexes independent of pain and in the presence of intact buffering mechanisms. (Circ Res 56: 175–183, 1985)

BRADYKININ is a natural compound capable of exciting both vagal (Kaufman et al., 1980) and sympathetic (Uchida and Murao, 1974; Nishi et al., 1977; Baker et al., 1980; Lombardi et al., 1981) cardiac sensory endings. In anesthetized dogs, epicardial administration of bradykinin induced only excitatory reflex cardiovascular responses (Staszewska-Barczak et al., 1976; Staszewska-Barczak and Dusting, 1977) or either excitatory or inhibitory responses in sinoaortic denervated vagotomized dogs (Felder and Thames, 1982). On the other hand, intracoronary injections of bradykinin in anesthetized cats elicited either excitatory or inhibitory reflex responses, the former being mediated by cardiac sympathetic afferent fibers and the latter by cardiac vagal afferents (Reimann and Weaver, 1980; Lombardi et al., 1982).

It is likely that the differences in the "central excitatory state" (Sherrington, 1929) of various circuits, as affected by anesthesia and by the specific experimental conditions or animal model, might explain these contrasting observations.

Thus, the primary goal of this study in conscious dogs was to assess the effects of the simultaneous stimulation with bradykinin of the vagal and sympathetic sensory supply of the heart in the absence of anesthesia and recent surgery.

Next, we assessed the effects of anesthesia and recovery from surgery, as well as the effects of vagotomy on the observed responses.

Finally, we examined the effects of different pharmacological blockades on the hemodynamic responses to intracoronary bradykinin.

The results indicate that, in conscious dogs, the
in vivo, using the left atrial and aortic pressures. The
recovered from the operation, as judged by their normal
behavior, body temperature, and hematocrit. While the
traphic receptor blockade was verified by the lack of a further
increase in heart rate following a booster dose of 0.1 mg/
kg of iv atropine. Ganglionic transmission was blocked
by trimethaphan (Arfonad, Roche) infused iv at a dose of
5-10 μg/kg per min.

To study the afferent limb of the reflex, we planned
experiments in which the vagi were severed in the neck,
thus leaving intact only the sympathetic portion of cardiac
afferent innervation. To minimize the problems related to
acute hypertension and respiratory depression that can
follow vagotomy, this intervention was performed in two
steps (Pagani et al., 1982). Thus, in five dogs under
thiopental anesthesia (20 mg/kg, iv), the cervical vagi
were moved to a subcutaneous position, and 3-5 days later,
the response to intracoronary bradykinin was studied.
Following this, under light transient thiopental sodium anesthesia
(5-10 mg/kg, iv) and local infiltration with Xylocaine (Byk
Gulden), both vagi were cut in the neck. The response to
intracoronary bradykinin was again determined after a
recovery period of 24-48 hours.

Statistics
The results are expressed as means ± SEM. Each individ-
ual animal underwent several (4-10) trials, the responses
in each dog were calculated at their early peak, and the
average was used to compute the group means. The
significance of the responses to intracoronary bradykinin
was assessed with the t-test for paired observations. One-
way analysis of variance was used to assess the differences
of responses obtained with and without pharmacological
blockades, using the Scheffe test for multiple comparisons.
Differences were considered significant with a P value
<0.05 (Armitage, 1971).
Results

In the conscious dog, the intracoronary (ic) injection of bradykinin at doses devoid of direct hemodynamic effects produced a cardiovascular reflex that was always pressor in nature. As shown in Figure 1, graded injections of bradykinin, in doses ranging from 10 to 100 ng/kg, into the circumflex coronary artery induced gradual increases in arterial pressure and heart rate. The pressor response begins 15 ± 1 seconds after the injection and reaches a peak in 26 ± 2 seconds, after which both pressure and heart rate slowly return to baseline levels.

Moreover, it is important to notice that pressor responses of the same magnitude were obtained from injections into either the left anterior descending or circumflex coronary artery. In fact, 100 ng/kg of bradykinin into the left anterior descending coronary artery (n = 7) increased mean arterial pressure 29 ± 3% from 86 ± 6 mm Hg and heart rate 31 ± 8% from 86 ± 2 beats/min, while a similar injection into the circumflex coronary artery (n = 13) increased mean arterial pressure 27 ± 2% from 92 ± 3 mm Hg and heart rate 31 ± 4% from 88 ± 2 beats/min. Hence, in the following sections of the paper, the results of the experiments will be presented together, irrespective of the specific site of the injection.

Dose-Response Analysis

As shown in Figure 2, a clear dose-response curve was detectable starting from a threshold dose of 10 ng/kg. With increasing doses of ic bradykinin, the response rose up to a maximum, which was obtained with 100 ng/kg, after which, even the use of greater doses produced no further increase in the response.

At the peak of the response to 100 ng/kg, the increase in mean arterial pressure was 28 ± 3% from 89 ± 4 mm Hg, in left ventricular dP/dt maximum 18 ± 3% from 2812 ± 65 mm Hg/sec.

It should be noticed that, when injected iv, the vasodilatory properties of the drug became apparent only with high doses. For instance, whereas 10 ng/kg was the approximate threshold dose for intracoronary effects, 100 ng/kg was the smallest dose which consistently caused a transient hypotension (−21 ± 2%) and tachycardia (41 ± 11%) when injected iv (Fig. 1).

During the experiments, the animals remained calm or somnolent on the recording table, and did not manifest any discernible pain reaction (vocalization, struggling) to the intracoronary injections of bradykinin; however, they could show an increase in depth of respiration.

Since the absence of a pain reaction was surprising (Guzman et al., 1962), we planned experiments to elicit behavioral reactions in a limited number of animals. In seven dogs, we injected very large amounts of bradykinin into the cannulated coronary artery (1000–2000 ng/kg) to excite the afferent fibers from the corresponding area of myocardium maximally. Even with this dose, no reaction was observed which could be attributed to pain, whereas the vasodilatory action of the drug induced hypotension (−38 ± 3%) and tachycardia (47 ± 8%).

Effects of Recovery from Surgery

In a second series of experiments, we injected bradykinin into the coronary bed of nine dogs during the first week after surgery, hence, before a complete recovery. Five of these dogs exhibited an early depressor response (Fig. 3, III day) which reverted to the usual pressor effect at a time of complete recovery from surgery (Fig. 3, XX day; Table 1).
Effects of Brachykinin

Out of the nine dogs, three animals exhibited vocalization and agitation, suggesting a pain reaction, in response to the brachykinin injection performed during the first week after surgery: this reaction was no longer present when the animals were tested during the course of the third week. The presumable pain reactions were accompanied in two cases by hypertension and tachycardia, and in one case by hypotension and bradycardia (Fig. 3, III day).

Effects of Anesthesia

The acute effects of barbiturate anesthesia were tested in a group of five animals by comparing the hemodynamic response to ic brachykinin obtained in the conscious state, after full recovery from surgery, with that observed, in a following day, under anesthesia (see Methods). Thus, the pressor (20 ± 4% from 96 ± 7 mm Hg) and heart rate response (28 ± 4% from 90 ± 3 b/min) were drastically reduced in the anesthetized state, as mean arterial pressure was no longer significantly increased by ic brachykinin (8 ± 6% from 98 ± 8 mm Hg) and the tachycardia response was reduced (9 ± 2% from 138 ± 8 beats/min).

Effects of Various Blockades (Table 2, Fig. 4)

\(\alpha\)-Adrenergic receptor blockade with phentolamine (1 mg/kg, iv) reduced mean arterial pressure to 77 ± 3 mm Hg and increased heart rate to 139 ± 11 beats/min and left ventricular dP/dt to 3016 ± 291 mm Hg/sec. Under these conditions, the pressor response to ic brachykinin (100 ng/kg) was virtually abolished, while the heart rate response was preserved and the increase in left ventricular dP/dt was slightly enhanced.

The increase in heart rate was reduced either by \(\beta\)-adrenergic receptor blockade with propranolol (1 mg/kg, iv) or by muscarinic blockade with atropine (0.2 mg/kg, iv) and was abolished by their combination, while the pressor response was preserved. The dP/dt response was abolished by \(\beta\)-adrenergic receptor blockade. In a group of four conscious dogs, the effects of intracoronary brachykinin were tested during ganglionic transmission blockade obtained with an infusion of trimethaphan 5–10 \(\mu\)g/kg/min, iv. Under these conditions (Fig. 4; Table 2), the pressor and heart rate response was no longer observed.

Effects of Intrapericardial Brachykinin

In a group of three conscious dogs, we obtained a consistent pressor (20 ± 5% from 97 ± 8 mm Hg) and heart rate response (18 ± 2% from 113 ± 7 beats/min) when injecting brachykinin (150–300 ng/kg) into the pericardial sac. This response was maintained for periods of 5–10 minutes until the injected brachykinin was washed from the pericardial sac with warm saline. 

Effects of Vagotomy

The role of the vagi was assessed in five animals in which the effects of intracoronary brachykinin was examined before and 1–3 days after vagotomy.

As shown in Figure 5, the pressor response was
TABLE 1
Contrasting Effects of Intracoronary Bradykinin (100 ng/kg) in Five Conscious Dogs when Examined Early and Late in the Postoperative Period

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Left ventricle pressure (mm Hg)</th>
<th>Left ventricle dP/dt (mm Hg/sec)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>87 ± 3</td>
<td>118 ± 10</td>
<td>2115 ± 220</td>
<td>96 ± 8</td>
</tr>
<tr>
<td>%Δ</td>
<td>-31 ± 6*</td>
<td>-16 ± 3*</td>
<td>-17 ± 4*</td>
<td>-34 ± 9*</td>
</tr>
<tr>
<td><strong>Late response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>85 ± 5</td>
<td>109 ± 3</td>
<td>3119 ± 404</td>
<td>93 ± 4</td>
</tr>
<tr>
<td>%Δ</td>
<td>22 ± 4*†</td>
<td>11 ± 2†</td>
<td>17 ± 2*†</td>
<td>49 ± 9*†</td>
</tr>
</tbody>
</table>

* Results are expressed as mean ± SEM. Note that the depressor response observed in these animals during the first week after surgery reverted to a pressor one, later, at the time of complete recovery.
† Early response significantly different from late response (P < 0.05).

essentially unmodified by vagotomy: mean arterial pressure increased 23 ± 1% from 98 ± 4 mm Hg before vagotomy and 20 ± 1% from 88 ± 3 mm Hg after vagotomy. The heart rate response was reduced: 25 ± 4% from 90 ± 4 beats/min before vagotomy and 10 ± 2% from 120 ± 1 beats/min after vagotomy. Finally, the increase in left ventricular dP/dt maximum was enhanced: 13 ± 2% from 2547 ± 308 mm Hg/sec before vagotomy and 24 ± 3% from 2728 ± 271 mm Hg/sec after vagotomy.

TABLE 2
Effects of Various Blockades on the Reflex Response to Intracoronary Bradykinin in Conscious Dogs

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Left ventricle pressure (mm Hg)</th>
<th>Left ventricle dP/dt (mm Hg/sec)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>89 ± 4</td>
<td>121 ± 2</td>
<td>2812 ± 65</td>
<td>88 ± 5</td>
</tr>
<tr>
<td>%Δ</td>
<td>28 ± 3*</td>
<td>20 ± 3*†</td>
<td>18 ± 3*†</td>
<td>30 ± 4*†</td>
</tr>
<tr>
<td>n = 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α-Blockade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>77 ± 3</td>
<td>106 ± 2</td>
<td>3016 ± 291</td>
<td>139 ± 11</td>
</tr>
<tr>
<td>%Δ</td>
<td>-5 ± 3†</td>
<td>-1 ± 5†</td>
<td>22 ± 6*</td>
<td>17 ± 3*</td>
</tr>
<tr>
<td>n = 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β-Blockade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>94 ± 5</td>
<td>125 ± 5</td>
<td>2199 ± 197</td>
<td>86 ± 2</td>
</tr>
<tr>
<td>%Δ</td>
<td>19 ± 2*</td>
<td>15 ± 1*</td>
<td>4 ± 3†</td>
<td>11 ± 2*†</td>
</tr>
<tr>
<td>n = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Muscarinic blockade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>93 ± 6</td>
<td>116 ± 7</td>
<td>2890 ± 234</td>
<td>168 ± 7</td>
</tr>
<tr>
<td>%Δ</td>
<td>21 ± 4*</td>
<td>17 ± 3*</td>
<td>16 ± 4*</td>
<td>9 ± 2*†</td>
</tr>
<tr>
<td>n = 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β-plus muscarinic block</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>98 ± 8</td>
<td>123 ± 11</td>
<td>2385 ± 286</td>
<td>125 ± 3</td>
</tr>
<tr>
<td>%Δ</td>
<td>16 ± 3*†</td>
<td>13 ± 3†</td>
<td>4 ± 2†</td>
<td>1 ± 4†</td>
</tr>
<tr>
<td>n = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ganglionic blockade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61 ± 9</td>
<td>85 ± 10</td>
<td>2675 ± 395</td>
<td>126 ± 6</td>
</tr>
<tr>
<td>%Δ</td>
<td>-2 ± 2†</td>
<td>-3 ± 5†</td>
<td>-5 ± 5†</td>
<td>1 ± 2†</td>
</tr>
<tr>
<td>n = 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Significantly different from control (P < 0.05).
† Significantly different from control response (P < 0.05).
‡ n = 4.
Discussion

In the conscious dog, the chemical stimulation with bradykinin of the sensory supply of the heart elicits a pressor sympathetic reflex characterized by a rise in arterial blood pressure, in left ventricular pressure and dP/dt, and in heart rate. When the animals were studied after full recovery from surgery, the pressor response was constantly obtained, in absence of any pain reaction. After vagotomy, a similar pressor reflex could still be elicited and its inotropic component was even enhanced.

Reflex Nature of the Response

The reflex nature of the response to the ic injection of bradykinin was proved by its disappearance after appropriate pharmacological blockades. Pretreatment with phentolamine, which blocks α-adrenergic receptor-mediated responses, abolished the rise in arterial pressure, while maintaining the increase in heart rate and left ventricular dP/dt. Pretreatment with propranolol, which blocks β-adrenergic receptor-mediated responses, maintained the pressor, reduced the heart rate, and abolished the inotropic response to ic bradykinin.

Muscarinic receptor blockade drastically reduced the heart rate response, while sparing the increase in arterial pressure and in left ventricular dP/dt. As already pointed out (Pagani et al., 1982), it is difficult to ascertain the relative contribution of an efferent sympathetic excitation and of a parasympathetic withdrawal in determining the tachycardia component of an excitatory reflex in the intact conscious animal. Apart from the complexity of the interaction between vagal and sympathetic neurotransmitters.
(Levy, 1971; Vatner et al., 1979), it has been proved that the ic bradykinin, being capable of exciting vagal (Kaufman et al., 1980) and sympathetic (Uchida and Murao, 1974; Nishi et al., 1977; Baker et al., 1980; Lombardi et al., 1981) cardiac sensory endings, can simultaneously activate reflexes mediated by cardiac vagal and sympathetic afferent fibers (Reimann and Weaver, 1980; Felder and Thames, 1982; Lombardi et al., 1982). In terms of neural circuits, this corresponds, at the very least, to vagovagal, vago-vagal, vago-sympathetic, sympatho-sympathetic and sympatho-vagal reflexes (Malliani, 1982), in addition to possible baroreceptive modulatory influences. An additional complication in interpreting the results following atropine administration consists of the fact that, in such experimental conditions, the baseline heart rate is greatly elevated and, hence, it might be difficult for it to increase further. Yet a small heart rate response to intracoronary bradykinin could still be observed during muscarinic blockade, together with a significant increase in arterial blood pressure and myocardial contractility.

The absence of hemodynamic effects of ic injections of bradykinin during ganglionic blockade gives greater support to the conclusion that the observed responses are reflex in nature and are not dependent upon direct effects of bradykinin on the efferent nerve endings or on the myocardium.

As to the afferent limb of the reflex, the observation that the pressor, the heart rate, and the inotropic responses were maintained after vagotomy, i.e., when the only innervation to and from the heart is via the sympathetic nerves, strongly suggests that the afferent pathway is in the sympathetic nerves (Colori and Colori, 1979). This contention is supported by recent experiments in anesthetized cats by Lombardi et al. (1982) showing that the afferent pathway of the excitatory reflexes that are initiated by ic bradykinin after vagotomy is via the cardiac sympathetic afferents, as it is abolished by sympathetic deafferentation. Moreover, excitatory reflexes mediated by cardiac sympathetic afferent fibers have been described in acute (Malliani et al., 1969, 1972, 1973; Brown and Malliani, 1971; Peterson and Brown, 1971) and chronic conditions (Barron and Bishop, 1982) in the absence of functioning vagi.

Finally, it should be pointed out that our results are not in contrast with experiments showing cardio-cardiac depressor reflexes mediated by the vagi, induced by injections of veratridine in the coronary artery (Barron and Bishop, 1982) or by coronary artery occlusion (Peterson and Bishop, 1974) in conscious dogs. Indeed, the present study suggests the operation of a subordinate vagal depressor reflex, modulating the inotropic response. This modulation might well occur at the level of spinal interneurones, as the excitation of spinothalamic cells induced by sympathetic afferent activation from the heart is depressed by the stimulation of afferent vagal fibers (Ammons et al., 1983).

Adequacy of the Stimulus

Although it has been proved that bradykinin is released into the coronary venous blood during experimental myocardial ischemia (Kimura et al., 1973) and that doses of comparable magnitude administered ic can excite cardiac sympathetic sensory endings (Lombardi et al., 1981), admittedly, the abrupt stimulation used in the present experiments cannot be considered as duplicating a natural pathophysiological condition.

However, our specific purpose was to analyze, in the conscious state, the result of the simultaneous stimulation of vagal and sympathetic cardiac afferent fibers, and to explore the mechanisms underlying the prevailing type of the reflex response, i.e., inhibitory or excitatory.

The results showed that fundamental differences characterize the anesthetized and the conscious state. In fact, ic administration of bradykinin in anesthetized animals elicits either pressor or depressor reflexes (Staszewska-Barczak et al., 1976; Staszewska-Barczak and Dusting, 1977; Reimann and Weaver, 1980; Felder and Thames, 1982; Lombardi et al., 1982). The inhibitory reflexes have been interpreted as mediated by cardiac vagal (Reimann and Weaver, 1980; Lombardi et al., 1982) or by cardiac sympathetic afferent fibers (Felder and Thames, 1982).

In the experiments on conscious dogs reported here, only pressor responses were observed. However, an inhibitory response was elicited in a small group of animals during the early phase of their recovery from the operation: response which reverted to a pressor one, in the same animals, later, when the recovery from surgery was complete. Moreover, the importance of anesthesia in altering the normal cardiovascular control mechanisms (Vatner and Braunwald, 1975) is further emphasized by the near abolition during anesthesia of the pressor response to ic bradykinin. Hence, it would appear that the acute effects of anesthesia and recent surgery emphasize the efficacy of depressor reflexes. These alterations in responsiveness might be less important in other species, such as the cat, where excitatory cardio-cardiac reflexes may be easier to obtain, even during anesthesia.

Finally, it should be pointed out that no differences were noticed, whether the drug was injected into the left anterior descending or circumflex coronary artery, an observation which is in keeping with data obtained in conscious animals subjected to either anterior or posterior experimental myocardial infarction (Karlsberg et al., 1979) but which does not parallel the preferential ventricular distribution of sources for inhibitory or excitatory reflexes described on anesthetized dogs (Walker et al., 1978). However, the pathophysiology of the hyperacute phases of myocardial infarction indicate that a hemodynamic picture suggestive of a depressor reflex is more commonly associated with inferior wall...
infarcts, whereas pressor reflexes are more commonly observed during anterior wall infarcts, (Webb et al., 1972; Pantridge, 1978). Although it is difficult to compare the reflex effects of the chemical stimulation of the intact heart with those observed in the course of acute experimental ischemia (Peterson and Bishop, 1974), one could suggest that, from the healthy heart, the prevalence of excitatory reflex mechanisms initiated by intracoronary bradykinin might be capable of masking possible opposite influences.

Excitatory Reflexes and Pain

The evidence against the possibility that pain, as a conscious experience, contributed to the pressor reflexes observed is 3-fold. First, dose-response curves were obtained, indicating a progressive build-up of excitation. Second, behavioral changes indicating a pain reaction were never observed. Third, in the few instances in which a pain reaction was obtained during recovery from surgery, it could be associated with either a pressor or depressor response, as in the case of Figure 5. In short, the simple coupling between hypertension and pseudoaffective reactions (Woodsworth and Sherrington, 1904) may not apply to the complexity of the conscious state. On the other hand, in previous experiments, we had already observed that an intense stimulation of aortic sympathetic mechanoreceptors leading to pressor reflexes was not associated with pain reactions (Pagani et al., 1982).

Moreover, our observations, whatever may be the peripheral algogenic neural code from the heart (Malliani and Lombardi, 1982; Malliani et al., 1984), seem to refute the existence of specific cardiac nociceptors (Baker et al., 1980). In such a case, we should have confirmed the findings by Guzman et al. (1962), obtained on animals recovering from surgery and anesthesia, indicating a constant relationship between intracoronary bradykinin administration and pain reactions.

Pathophysiological Implications

It has been increasingly recognized that electrocardiographic changes typical of ischemic episodes can occur in concomitance of (1) increases in arterial pressure and heart rate (Lewis, 1931; Roughgarden, 1966; Guazzi et al., 1971, 1975; Littler et al., 1973; Maseri et al., 1978; Figueras et al., 1979; Chierchia et al., 1980), (2) decreases in arterial pressure and rises in heart rate (Guazzi et al., 1971, 1975; Maseri et al., 1978), (3) decreases in arterial pressure and in heart rate (Guazzi et al., 1971). In each of these cases, hemodynamic and electrocardiographic alterations can precede pain or occur in the absence of it. These circulatory changes suggest a various participation of pressor, depressor, and baroreceptive reflex mechanisms (Peterson and Bishop, 1974) associated with the direct striking depressing effects of ischemia on ventricular function (Pagani et al., 1978).

The present experiments in dogs, in which the depressant action of ischemia was avoided, show the potentiality of pressor reflexes arising from the intact heart and how they can manifest, in the conscious state, independently of pain and in the presence of functioning buffer mechanisms.

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Address for reprints: Dr. Massimo Pagani, Istituto Ricerche Cardiovascolari, Via Bonfanti 214, 20138 Milano, Italy.

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