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

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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
intracoronary injection of bradykinin consistently initiates a dose-dependent pressor sympathetic reflex, requiring as the most crucial factor a full recovery from surgery. In the latter circumstances, signs of pain never accompanied the pressor reflex.

**Methods**

Under aseptic conditions and pentobarbital anesthesia (30 mg/kg, iv), 28 mongrel dogs of either sex (24–32 kg body weight) underwent thoracotomy in the 5th left intercostal space. A heparin-filled Tygon catheter was implanted in the descending thoracic aorta through a puncture and secured with a suture. In a first group of 25 dogs, after the pericardium had been opened, either the left anterior descending (eight dogs) or circumflex coronary artery (17 dogs) was carefully dissected 2–3 cm from its bifurcation so as to avoid any damage to the pericoronary nerves, and a small silicone (Dow Corning) catheter was implanted by the technique described by Herd and Barger (1964). In 14 of these dogs, a miniature pressure transducer (Konigsberg) was implanted within the left ventricle with a purse string suture. After the thoracotomy had been sutured, the catheters and the wire were exteriorized at the base of the neck.

**Recorded Variables**

Aortic and left atrial pressures were measured with the catheters implanted in the aorta and the left atrium, respectively, using pressure transducers (Statham Instruments). Aortic mean pressure was obtained with an RC filter with a 2-second time constant. Left ventricular pressure was measured with the implanted miniature pressure gauge, which was calibrated statically in vitro and dynamically in vivo, using the left atrial and aortic pressures. The time derivative of left ventricular pressure (LVP) (i.e., dP/dt) was obtained from the LVP signal with an operational amplifier with a frequency response of 0.5–700 Hz.

A triangular signal with known slope was used to calibrate the differentiator. Heart rate was measured continuously with a cardiotachometer, triggered by the R wave of the ECG (lead II) obtained with an AC amplifier.

Data were recorded on a multichannel FM-type recorder (Racal Store 7) and played back on a direct writing recorder (Brush Gould).

**Protocol**

Experiments were performed 2–3 weeks postoperatively, when the dogs were apparently well and had recovered from the operation, as judged by their normal behavior, body temperature, and hematocrit. While the trained dogs were lying quietly on a recording table, aortic blood pressure, left ventricular pressure and dP/dt, and heart rate were recorded continuously before, during, and after the intracoronary injection of graded doses of bradykinin (BRS 640 Sandoz, molecular weight 1060.25). This substance was freshly prepared for every experiment, with normal saline. Doses injected were 10–300 ng/kg in a volume of 0.5–1.0 ml. In seven dogs, larger doses 1000–2000 ng/kg were also employed. To assess the role of incomplete recovery from surgery on animal responsiveness, we also studied nine dogs the first week postoperatively. As the animals during this period could easily exhibit life-threatening arrhythmias, they were studied only once, until complete recovery.

The role of anesthesia was assessed in a group of five dogs that were studied first after complete recovery from surgery, and, later, on a different day, under thiopental sodium anesthesia (20 mg/kg, iv, followed by booster doses 5 mg/kg, iv, every 30 minutes).

At the autopsy, the intracoronary position of the catheter, the patency of the coronary artery and the lack of infarction of the myocardium perfused by it were verified.

The role of the route of administration of bradykinin was assessed in a group of three conscious dogs with an intrapericardial catheter. In these animals, doses of bradykinin of 150–300 ng/kg (in 2–3 ml of saline) were injected through the implanted catheter, into the pericardial sac. After 5–10 minutes, the drug was washed away with repeated (3–4 times) injections and withdrawals of 20 ml of 37°C saline.

α-Adrenergic receptor-mediated responses were blocked with phentolamine, 1 mg/kg, iv; β-adrenergic receptor-mediated responses were blocked with propranolol 1 mg/kg, iv; and muscarinic receptor mediated responses were blocked with atropine 0.2 mg/kg, iv. The completeness of α-adrenergic receptor blockade was verified by the abolition of a pressure response to a test injection of 0.1–0.3 μg/kg norepinephrine, iv; β-adrenergic receptor blockade was verified by the lack of heart rate or dP/dt response to 0.08 μg/kg of iv isoprenaline. Muscarinic 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 with 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 individual 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 Scheffé 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).
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 bradykinin 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 bradykinin (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)

α-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 bradykinin (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 β-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 β-adrenergic receptor blockade. In a group of four conscious dogs, the effects of intracoronary bradykinin were tested during ganglionic transmission blockade obtained with an infusion of trimethaphan 5-10 μg/kg/min, iv. Under these conditions (Fig. 4; Table 2), the pressor and heart rate response was no longer observed.

Effects of Intrapericardial Bradykinin

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 bradykinin (150–300 ng/kg) into the pericardial sac. This response was maintained for periods of 5–10 minutes until the injected bradykinin 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 bradykinin 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>
</tbody>
</table>

* Significantly different from control (P < 0.05).
† Significantly different from control response (P < 0.05).
‡ n = 5.
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
Ammons et al., 1983.
depressed by the stimulation of afferent vagal fibers
sympathetic afferent activation from the heart is
scious dogs. Indeed, the present study suggests the
artery occlusion (Peterson and Bishop, 1974) in con-
induced by injections of veratridine in the coronary
Brown, 1971) and chronic conditions (Barron and
1982; Lombardi et al., 1982). The inhibitory reflexes have been in-
terpreted as mediated by cardiac vagal (Reimann
Weaver, 1980; Lombardi et al., 1982) or by
cardiac sympathetic afferent fibers (Felder and
1982).
Finally, it should be pointed out that no differ-
ences were noticed, whether the drug was injected
into the left anterior descending or circumflex coro-
ary 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 de-
scribed 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 re-
flex is more commonly associated with inferior wall

Adequacy of the Stimulus
Although it has been proved that bradykinin is
released into the coronary venous blood during ex-
perimental myocardial ischemia (Kimura et al., 1973)
and that doses of comparable magnitude adminis-
tered ic can excite cardiac sympathetic sensory end-
ings (Lombardi et al., 1981), admittedly, the abrupt
stimulation used in the present experiments cannot
be considered as duplicating a natural pathophysi-
ological condition.

However, our specific purpose was to analyze, in
the conscious state, the result of the simultaneous
stimulation of vagal and sympathetic cardiac affer-
ent fibers, and to explore the mechanisms underly-
ing 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 depres-
sor reflexes (Staszewska-Barczak et al., 1976; Stasz-
wska-Barczak and Dusting, 1977; Reimann
Weaver, 1980; Felder and Thames; Lombardi
et al., 1982). The inhibitory reflexes have been in-
terpreted 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. How-
ever, an inhibitory response was elicited in a small
group of animals during the early phase of their
recovery from the operation: response which re-
verted 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 (Vat-
nr 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 sur-
gery 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 differ-
ences were noticed, whether the drug was injected
into the left anterior descending or circumflex coro-
ary 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 de-
scribed 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 re-
flex 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 buildup 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 pain 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 electrophysiologic 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 electrophysiologic alterations can precede pain or occur in the absence of it. These circulatory changes suggest a various participation of pressor, depressor, and baroreceptor 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.

We wish to thank U. Boccaccini for his technical help and Y. Stewart for typing the manuscript.

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Received November 28, 1983; accepted for publication October 3, 1984.

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Circ Res. 1985;56:175-183
doi: 10.1161/01.RES.56.2.175

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