A Positive Feedback Sympathetic Pressor Reflex during Stretch of the Thoracic Aorta in Conscious Dogs

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SUMMARY The role of pressor sympathetic reflexes in circulatory control was investigated in conscious dogs. Animals were previously instrumented with a 6- to 8-cm rigid core cannula covered by an inflatable rubber cylinder in the thoracic aorta, a pressure catheter implanted in the aorta above the cannula, and a second catheter inserted into the aorta below the cannula through a femoral artery. Two piezoelectric crystals were positioned at opposing adventitial sites to measure aortic distension with ultrasound techniques. After recovery from surgery, the diameter of the aortic segment surrounding the cannula was increased by 9.6 ± 0.4% from 16 ± 1 mm by inflating the rubber cylinder, without obstructing blood flow. Mean aortic pressure rose 31 ± 3% from 100 ± 3 mm Hg and heart rate 20 ± 3% from 81 ± 3 beats/min (P < 0.01). The pressor response was abolished by α-adrenergic blockade (phenolamine 1 mg/kg, iv) or muscarinic blockade (atropine 0.2 mg/kg, iv) and abolished by their combination. During aortic stretch, the sensitivity of the baroreflex was reduced 57 ± 7% from 18 ± 2 msec/mm Hg (P < 0.01). The pressor response was increased to 49 ± 8% after bilateral carotid sinus nerve section and vagotomy. These excitatory reflex responses were obtained in absence of any pain reaction. Thus, in the conscious dog, aortic distension within physiological ranges induces a potent pressor sympathetic reflex with positive feedback characteristics. Such a pressor reflex not only occurs in the presence of functioning baroreflexes, but is also capable of reducing their sensitivity. Circ Res 50:125-132, 1982

THE observation that arterial blood pressure measured in resting humans or in anesthetized animals is remarkably constant and that powerful reflexes tend to counteract any of its changes has given a major impetus to the concept of circulatory homeostasis. Accordingly, the sino-aortic negative feedback reflex system has been regarded for decades as the indisputable leader of this strategy. Only recently, however, it began to be appreciated that inhibitory influences on baroreceptor function must be present when an organism maintains an elevated heart rate in the face of an increased systemic arterial pressure, as happens during periods of stress or exercise (Bristow et al., 1971; Coote et al., 1971; Smith, 1974; Vatner and Pagani, 1976). The subsequent progressive investigation into the hemodynamic events characterizing exercise or emotion (Rushmer et al., 1960; Bergamaschi and Longoni, 1973; Vatner and Pagani, 1976) revealed that the negative feedback baroreflexes could change to such an extent as to become permissive bystanders in those circulatory "storms" (Lewis, 1931). Although it is felt that central and peripheral influences can interact within the central nervous system depressing baroreflex function, the exact mechanisms responsible for this modulation remain elusive. Possibilities include influences from the suprabulbar structures (Hilton, 1966; Smith, 1974) or from the periphery through vagal (Vatner et al., 1975) or somatic (Kumada et al., 1975) afferent nerve fibers.

An additional, yet unexplored, possibility is that cardiovascular reflexes with negative and positive feedback characteristics participate in these regulatory functions. Such an interaction would facilitate both the drastic changes and the fine tuning necessary to the multifarious cardiovascular performances. Indeed, experiments on anesthetized cats, in which supraspinal baroreflexes were made inoperable by bilateral vagotomy and carotid sinus denervation, provided evidence of the existence of cardiovascular sympathetic reflexes with positive feedback characteristics (Lioy et al., 1974; Malliani et al., 1975). In those experiments, the stretch of a segment of the thoracic aorta—a stimulus likely to mimic the effects of an increased pressure on aortic walls—elicited through the activation of aortic sympathetic afferents (Malliani and Pagani, 1976) a reflex excitation of the sympathetic outflow, with a consequent rise in arterial blood pressure, heart rate, and myocardial contractility (Lioy et al., 1974).

However, preliminary experiments (Malliani et al., 1979; Pagani et al., 1979) showed that in conscious dogs this excitatory sympathetic reflex is operative also in the presence of intact vagi and carotid sinus nerves. The goal of the present investigation was to analyze this reflex by determining the magnitude of aortic distension, as assessed by

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ultrasound techniques, necessary to elicit it, the afferent pathway, the autonomic efferent mechanisms, and the interaction with baroreceptive reflexes.

The results favor the hypothesis that positive feedback sympathetic reflexes participate in normal cardiovascular regulation.

Methods

Surgical Procedure

Under aseptic conditions and pentobarbital Na anesthesia (30 mg/kg, iv), 24 mongrel dogs (20–30 kg body weight) underwent thoracotomy in the 6th left intercostal space. A heparin-filled Tygon catheter was implanted in the proximal descending thoracic aorta through a puncture and secured with a suture. This catheter was connected to a pressure transducer (Statham Instruments) throughout the remainder of the surgical procedure to monitor arterial blood pressure. During transient aortic crossclamping, a 6- to 8-cm stainless steel (10 dogs) or Teflon (14 dogs) stiff cannula (Fig. 1), covered by an inflatable rubber cylinder, was introduced into the descending aorta through a longitudinal opening. The length of the inflatable cylinder corresponded to approximately two intercostal spaces. The diameter of the aortic cannula was chosen so as to fit snugly within the vessel. The arteriotomy was closed with a continuous suture, using 5-0 silk. In the 14 dogs instrumented with the Teflon cannula, a pair of piezoelectric crystals was positioned at opposing adventitial sites (Fig. 1), to measure aortic diameter with an ultrasound technique. In the 10 dogs instrumented with the stainless steel cannula, in which aortic diameter could not be assessed with ultrasound technique, the volume of saline needed to inflate the implanted cylinder so as to distend the aorta by ~10% was determined at surgery and was verified later at autopsy.

After the thoracotomy was closed, a second pressure catheter was advanced into the abdominal aorta by way of a femoral artery (eight dogs). The pressure and cannula catheters and dimension wires then were exteriorized at the base of the neck.

Recorded Variables

Aortic blood pressure proximal and distal to the cannula were measured with the catheters implanted respectively in the thoracic and abdominal aorta, using pressure transducers (Statham Instruments). Mean pressure was obtained with an R-C filter with a 2-second time constant. Heart rate was measured continuously with a cardiac tachometer, triggered by the R wave of the electrocardiogram (lead II), obtained with an AC amplifier.

Aortic distension was assessed by measuring instantaneously and continuously aortic diameter at the site of the implanted cannula with a modified ultrasound technique (Pagani et al., 1978). This technique measures the transit time of ultrasound impulses between the implanted transmitter and receiver crystals. The transit time is converted to distance by substituting for the speed of ultrasound in blood and tissues, i.e., 1.5 mm/μsec. Repeated calibrations can be obtained throughout the experiments with a calibrated crystal clock (Pagani et al., 1978; Patrick et al., 1974). The presence of the Teflon cannula between the crystals was always compatible with an adequate received ultrasound signal (>0.5 V), although a 30–50% increase in voltage was observed in postmortem controls when the cannula was withdrawn.

Protocol

Experiments were performed 1–3 weeks postoperatively, when the dogs were apparently well and had recovered from operation, as judged by normal behavior, body temperature, and hematocrit. While the trained dogs were lying quietly on a recording table, proximal and distal aortic blood pressure, external aortic diameter, and heart rate were recorded continuously before, during, and after aortic distensions, produced by inflating the implanted cylinder with warm (37°C) saline without obstructing aortic blood flow. Distensions usually lasted from 30 to 60 seconds; sometimes they were maintained as long as 5–10 minutes.

At the autopsy, the gross anatomy of the tract of aorta surrounding the cannula was always verified. Scarring of the aortic wall was minimal. A thin thrombotic jacket was always observed in the virtual space between the cannula and the aortic wall; this jacket extended into the ostia of the corresponding intercostal arteries that were thus permanently occluded.

α-Adrenergic receptor-mediated responses were
blocked with phentolamine, 1 mg/kg, iv; \( \beta \)-adrenergic receptor-mediated responses were blocked with propranolol 1 mg/kg, iv; and muscarinic-mediated responses were blocked with atropine 0.2 mg/kg, iv. The completeness of \( \alpha \)-adrenergic blockade was verified by the abolition of a pressor response to a test injection of 0.1–0.3 \( \mu \)g/kg norepinephrine, iv; \( \beta \)-adrenergic blockade was verified by the lack of the heart rate response to 0.08 \( \mu \)g/kg of iv isoprenaline; muscarinic 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.

To assess baroreflex sensitivity (Smyth et al., 1969) phenylephrine 50 \( \mu \)g/kg was injected iv into seven conscious dogs in the resting control state. Systolic arterial pressure during the pressure rise was plotted against the pulse intervals, and the slope of the relationship, treated as a linear function, provided an index of baroreflex sensitivity. The effects of aortic stretch on baroreflex sensitivity were determined on a separate day by similarly obtaining the slope in the presence of an aortic distension initiated 45–60 seconds before the injection of phenylephrine.

To study the afferent limb of the reflex, we planned experiments in which the carotid sinus nerves and vagi were severed, thus leaving intact only the sympathetic cardiovascular afferents. To minimize the problems related to acute hypertension and respiratory depression that can follow such a denervation, this intervention was performed in two steps. Thus, in six dogs, after the response to aortic stretch in the control state had been determined, the carotid sinus nerves were severed in the neck under thiopental Na anesthesia (20 mg/kg, iv) and the vagi were moved to a subcutaneous position. Three to five days later, under light transient thiopental Na anesthesia (5–10 mg/kg, iv) and local infiltration with xylocaine (Astra), both vagi were cut in the neck. The response to aortic stretch was again determined after a recovery period of 24–48 hours. To study the reproducibility of the reflex over time, in four animals we determined the response to aortic stretch before and 24–48 hours after a two-step sham operation. During the first step, under thiopental Na anesthesia (20 mg/kg, iv), the carotid sinus nerves were isolated in the neck but not severed, and the vagi were moved to a subcutaneous position. The second step was performed 3–5 days later and consisted simply of transiently exposing the vagi under a light thiopental Na anesthesia (5–10 mg/kg, iv), as already described, in addition to a local infiltration with xylocaine.

**Statistics**

The results are expressed as means ± SEM. Each individual animal underwent several (3–10) trials. The responses in each dog were calculated at their early plateau and the average was used to compute the group means. In the table and figures, the number of animals is indicated. The significance of the responses to aortic distension was assessed with the t-test for paired observations. One-way analysis of variance with the Scheffe test for multiple comparisons was used to assess the differences in responses obtained with and without pharmacological blockades.

Least squares techniques were used to calculate the slope of the regression of pulse interval as a function of systolic arterial pressure, and comparison between slopes was performed using analysis of variance (Armitage, 1971).

**Results**

In the conscious dogs, the distension of a segment of the descending thoracic aorta obtained by inflating the rubber cylinder covering the implanted cannula produced a cardiovascular reflex that was always pressor in nature. In the example illustrated in Figure 2 (left panel), a stretch increasing aortic diameter by about 9% elicited a marked rise in arterial pressure, both proximally and distally to the cannula, and in heart rate. The whole response reached a plateau in approximately 15 seconds: after 5 minutes of constant aortic distension, arterial pressure and heart rate were still elevated, although a slight decline towards baseline was apparent (Fig. 2, middle panel). Such a decline was never present for distensions maintained for 1–2 minutes.

During the distensions, the animals remained calm or somnolent, lying on their right side, and did not manifest any discernible pain reaction.

**Figure 2** Pressor and heart rate responses to stretch of the descending thoracic aorta in a conscious dog. The initiation of aortic stretch (left panel) is indicated by the increase in aortic diameter. Notice the similar increase in both proximal and distal pressures, indicating the lack of direct mechanical obstruction to blood flow by aortic distension. After 5 minutes (middle panel), the pressor and heart rate responses were still maintained. \( \alpha \)-Adrenergic blockade (phentolamine 1 mg/kg) (right panel) virtually abolishes the pressor response to aortic stretch, while an increase in heart rate is still present.
At the plateau of the response, the average increase in mean arterial pressure was 31 ± 3% from 100 ± 3 mm Hg and in heart rate 20 ± 3% from 91 ± 3 beats/min (n = 20, P < 0.01). The increase in aortic diameter at the site of the distension, measured in 10 dogs by ultrasound, was 9.6 ± 0.4% from 16 ± 1 mm. In the other 10 dogs, a similar stretch was obtained by distending the rubber cylinder with the volume of saline that at surgery had been found to increase aortic diameter by about 10%; the extent of the distension was verified at autopsy (see Methods).

**Pharmacological Blockades**

α-Adrenergic receptor blockade with phentolamine (1 mg/kg, iv) reduced mean arterial pressure to 89 ± 3 mm Hg and increased heart rate to 135 ± 12 beats/min, while the diameter of the segment of the aorta surrounding the cannula was not modified. Under these conditions, the pressor response to aortic stretch was virtually abolished (Fig. 2), while the heart rate response was preserved (Table 1).

The increase in heart rate was reduced either by β-adrenergic blockade with propranolol (1 mg/kg, iv) or by muscarinic blockade with atropine (0.2 mg/kg, iv) and abolished by their combination (Table 1). The pressor response was essentially unmodified.

After combined α- and β-adrenergic and muscarinic receptor blockade, both the pressor and heart rate responses were abolished (Table 1).

**Effects of Vagotomy and Carotid Sinus Denervation**

The specific goal of this study was to assess the effects of aortic stretch in conscious animals with an intact cardiovascular innervation. However, in order to identify the afferent limb of the reflex, six animals, after control aortic stretches, were subjected to a classic cardiovascular "denervation," i.e., the section of both carotid sinus nerves and vagi.

As can be appreciated in Figure 3, the pressor reflex was not only maintained, but was even more apparent. In fact, the increase in mean arterial pressure observed after denervation (49 ± 8% from 112 ± 17 mm Hg) was greater (P < 0.05) than that observed in the same dogs before denervation (29 ± 5% from 100 ± 4 mm Hg). However, the heart rate response, which was present before denervation (23 ± 3% from 87 ± 4 beats/min), was no longer detectable from the higher baseline level (162 ± 9 beats/min) present after denervation.

**Sham-operated Dogs**

The reproducibility of the reflex response over time was tested in four dogs that had exhibited a control pressor response of 37 ± 2% from 84 ± 2 mm Hg and heart rate response of 26 ± 3% from 94 ± 5 beats/min with an aortic distension of 8 ± 1% from 16 ± 1 mm. Subsequently, these animals were subjected to a "sham" denervation (see Methods). Twenty-four to 48 hours after completion of this procedure, both the pressor (39 ± 5%) and heart rate response (20 ± 2%), as well as the baseline values (90 ± 4 mm Hg and 101 ± 4 beats/min, respectively) were similar to those observed before the "sham" denervation.

**Table 1 Effects of Various Blockades on the Reflex Response to Aortic Stretch in Conscious Dogs**

<table>
<thead>
<tr>
<th>Blockade</th>
<th>MAP Baseline (mm Hg)</th>
<th>HR Baseline (beats/min)</th>
<th>MAP Blockade (mm Hg)</th>
<th>HR Blockade (beats/min)</th>
<th>MAP Muscarinic blockade (mm Hg)</th>
<th>HR Muscarinic blockade (beats/min)</th>
<th>MAP α- and β-blockade (mm Hg)</th>
<th>HR α- and β-blockade (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline control</td>
<td>100±3 31±3</td>
<td>91±3 32±3</td>
<td>89±3* 21±5</td>
<td>81±4 10±1</td>
<td>109±5 30±7†</td>
<td>161±13** 6±2†</td>
<td>102±5 3±1†</td>
<td>137±9** 2±1†</td>
</tr>
<tr>
<td>% change</td>
<td>31±3† 20±3†</td>
<td>3±2† 21±5†</td>
<td>29±7† 10±1†</td>
<td>6±2† 27±3†</td>
<td>-1±1†</td>
<td>3±1†</td>
<td>2±1†</td>
<td></td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure (in mm Hg at control), HR = heart rate (in beats/min at control). Baseline values during blockades different from baseline control values (†P < 0.05; ††P < 0.01). † † † † † † † † different from control, P < 0.01; † † † † † † † different from control, P < 0.05; † † † † † † † † † † † † † † † different from control response, P < 0.01.
Reduction of Baroreflex Sensitivity with Aortic Stretch

Using the method of Smyth et al. (1969), the slope of the regression line obtained by plotting the pulse interval against systolic arterial pressure during the pressure rise produced by the iv injection of phenylephrine (50 μg/kg) was used as an expression of baroreflex sensitivity. As shown in Figure 4, the control slope, obtained in the absence of aortic stretch, was relatively steep and averaged 18 ± 2 msec/mm Hg in the group of seven animals studied. In contrast, the slope obtained at the plateau of the pressor rise induced by aortic stretch was significantly (P < 0.01) less steep. The average reduction in baroreflex sensitivity in the group of animals was 57 ± 7% (P < 0.01). It is important to mention that the starting hemodynamic parameters were not identical in the two experimental conditions. In the absence of aortic stretch, systolic arterial pressure was lower (146 ± 8 and 174 ± 8 mm Hg, respectively, P < 0.02) and heart period was longer (535 ± 90 and 631 ± 87 msec, respectively, P < 0.01).

Stimulus Response Characteristics

Figure 5 summarizes the results obtained in eight dogs with progressively increasing aortic distensions. The curve relating the increase in aortic diameter to the corresponding pressor response indicated a distension of about 2% as the threshold of the reflex. The stimulus-response curve also shows that, beyond an increase in aortic diameter of 10%, there is no further augmentation of the pressor response.

Discussion

This study demonstrates that a pressor sympathetic reflex with positive feedback characteristics is operative in the conscious, fully innervated dog. Stretching a short segment of the descending thoracic aorta induced a proportional rise in systemic arterial pressure, as well as an increase in heart rate, and simultaneously depressed baroreflex sensitivity.

Reflex Nature of the Stimulus

The reflex nature of the response to aortic distension was proved by its disappearance after appropriate pharmacological blockades. Pretreatment with phentolamine, which blocks α-adrenergic receptor-mediated responses, in spite of the concomitant tachycardia, abolished the increase in systemic arterial pressure.

The increase in heart rate was reduced by either β-adrenergic receptor or muscarinic receptor blockade given singly and was abolished by their combination. However, these data can only suggest that efferent vagal withdrawal and β-adrenergic activation contributed synergistically (Schwartz et al., 1973) to the reflex tachycardia.

Indeed, it is difficult to ascertain the relative contribution of sympathetic and parasympathetic efferent mechanisms, in view not only of the complexity of their interactions (Levy, 1971) but also of the modified baseline conditions consequent to the administration of the various blocking agents. However, the maintenance of a small (6%), albeit significant, tachycardia response after muscarinic receptor blockade, but not after denervation, cannot
be attributed simply to the increased baseline heart rate, which was elevated similarly in the two conditions. Other factors are likely to play a role, such as the augmentation of the chronotropic response to a given adrenergic stimulus after muscarinic blockade (Vatner et al., 1979). In addition, carotid sinus nerve section and vagotomy, by abolishing a major afferent input to the brain stem, are likely to alter the "central excitatory state" (Sherrington, 1906). On the other hand, the time factor involved in the preparation of the denervated animals does not seem to play an important role, for the reflex tachycardia was preserved in the "sham-operated" experiments. In conclusion, it appears that this reflex has a more powerful effect on arterial pressure than on heart rate.

As to the afferent limb of the reflex, the observation that the pressor reflex was not only present after bilateral carotid sinus and vagal nerve section, but was even increased in magnitude, confirms that the afferent pathway of the reflex is in the sympathetic nerves (Lioy et al., 1974) and that the scarce vagal sensory innervation of the descending thoracic aorta (Donald and Edis, 1971) did not contribute importantly to mediation of the excitatory reflex response. These findings obviously do not imply that the distension of more distal tracts of the aorta should elicit a similar pressor reflex.

The physiological properties of aortic sympathetic myelinated and unmyelinated sensory nerve fibers have been characterized in earlier reports (Uchida, 1975; Malliani and Pagani, 1976). Sympathetic mechanoreceptors were distributed throughout the thoracic aorta and had a tonic impulse activity at arterial pressures within the physiological range. Increases in aortic pressure obtained either mechanically or with pressor drugs enhanced their impulse activity which occurred in phase with systolic pulses; moreover, the firing rate was higher during the ascending portion of the pressor stimulus than during its plateau, i.e., the sympathetic aortic mechanoreceptors displayed both static and dynamic sensitivity. In postmortem studies, their firing rates were gradually increased when the aortic walls were subjected to progressive distensions (Malliani and Pagani, 1976).

Since, during aortic distension, it is not possible to measure precisely the pressure acting on aortic walls (Malliani et al., 1979), in the present experiments we measured aortic diameter as an index of the stimulus initiating the reflex.

Adequacy of the Stimulus

The threshold for the reflex was found to be represented by a stretch increasing aortic diameter by 2%. A saturation of the pressor reflexes was observed when aortic diameter was increased beyond 10%. In the conscious animal, similar increases in aortic diameter accompany arterial pressure rises falling within the physiological range. For instance, in the conscious adult sheep, an increase in mean aortic pressure of 44 mm Hg induced with angiotensin, iv, was accompanied by 6.4% increase in aortic diameter (Pagani et al., 1979b). Thus, it is not surprising that we did not observe pain reactions to the aortic distensions used in this study.

As to the entity of the stimulus, some further considerations seem appropriate. First, the distension was applied to a limited portion of the thoracic aorta, corresponding to about two intercostal spaces. Second, we used a steady stimulus, while sympathetic aortic afferents are more sensitive to pulsatile stretch (Malliani and Pagani, 1976). Therefore, the activation of the mechanoreceptors of the thoracic aorta was likely to be far from maximal.

It is possible that the pressure used to distend the cylinder might reduce transiently the blood flow in aortic vasa vasorum (Heistad et al., 1978). However, this event should not represent an important factor, as aortic mechanoreceptors are insensitive to ischemic anoxia (Malliani and Pagani, 1976).

As to the possibility that aortic distension might cause a transient spinal ischemia as a consequence of a temporary occlusion of the intercostal arteries, this seems to be ruled out by the autopsy finding that the ostia of the intercostal arteries originating from the tract of the aorta surrounding the cannula were permanently occluded.

Reduction of Baroreflex Sensitivity

Baroreflex sensitivity was significantly depressed during aortic stretch, as compared to the normal resting control state.

According to the method of Smyth et al. (1969), baroreflex sensitivity was expressed as the slope of the relationship between systolic arterial pressure and pulse interval, assuming a linear function, during the pressor rise produced by the iv injection of phenylephrine, a powerful α-adrenergic agonist. It is important to point out that this technique implies a simple relationship between systolic arterial pressure and baroreceptor control of heart rate, which is likely to be an over-simplification. However, this method has proved useful in assessing short term changes in the functional properties of the baroreflex during several behavioral situations, such as sleep (Smyth et al., 1969), exercise (Vatner and Pagani, 1976), heart failure (Eckberg et al., 1971; Higgins et al., 1972), or volume loading (Vatner et al., 1975) both in conscious animals and in human beings. The present study provides evidence for a peripheral mechanism which inhibits baroceptive regulation of heart rate through a spino-bulbar pathway. Some additional considerations are, however, necessary.

First, it must be pointed out that the possible modifications of baroreflex function due to some abnormality induced by the implanted aortic cannula were likely to be trivial, as the slopes observed in this study (18 msec/mm Hg) were similar to the slopes found using a similar method in conscious
Role of a Pressor Sympathetic Reflex in Conscious Dogs

The reflex mechanism described in this study is capable of increasing arterial blood pressure and heart rate in response to a stimulus that mimics the stretch produced on aortic walls by an increase in aortic pressure—hence, the positive sign for this feedback mechanism, as opposed to the negative feedback characteristics of the baroreflexes (Franz, 1974).

As to the possible role of these excitatory reflexes, the maintenance of sustained increases in arterial blood pressure and heart rate necessary to physiologic states such as emotion or exercise may depend partly on their activation. Moreover, some of the changes in the range of operation, gain, and stability of negative feedback baroreflexes may be due to their central and peripheral interactions with positive feedback mechanisms.

In conclusion, the hypothesis of an interplay of cardiovascular reflexes of opposite signs may open a new approach for analyzing the "quantity" (Pickering, 1978) of arterial blood pressure, both in physiology and in pathophysiology.

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