The Role of Arterial Baroreceptors in the Regulation of Arterial Pressure in Conscious Dogs

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SUMMARY To elucidate the role of arterial baroreceptors in the acute regulation of arterial pressure in the conscious animal, arterial pressure was lowered and raised in intact, conscious dogs, and in dogs after bilateral section of both carotid sinus and aortic nerves (total arterial baroreceptor denervation, TABD). Pressure was altered by intravenous bolus injections and continuous infusions of nitroglycerin and methoxamine and also by hemorrhage. TABD resulted in a change in peak mean arterial pressure 2-4 times as great as that seen in intact dogs following injection of nitroglycerin or methoxamine. However, when the time taken for the arterial pressure disturbance to return to control levels, as well as the absolute change in arterial pressure, was considered (the pressure-time product), responses of dogs with TABD were far greater for nitroglycerin (7-9 times that seen in intact dogs) and methoxamine (11-15 times). Arterial pressure responses of dogs with selective section of the carotid sinus nerves were intermediate but closer to those of intact dogs than to dogs with TABD. With infusion of drugs or following hemorrhage, responses of mean arterial pressure were 3- to 5-fold greater in dogs with TABD than in intact dogs, indicating that the static open loop gain of the arterial baroreceptor system ranged from 2 to 4.

THE ROLE of the major arterial baroreceptors in the regulation of arterial pressure has been a subject of considerable investigation.1-14 Most studies delineating the function of these receptors have been performed in a variety of animal species and preparations, the majority of which have been anesthetized. However, since general anesthesia is now known to affect many aspects of circulatory control,13 including the function of the baroreceptors,16, 17 there is increasing interest in the role of these receptors in the conscious state. Accordingly, more recent studies have been performed in conscious dogs with denervated baroreceptors.13-17 A recent study by Cowley et al.1 demonstrated that the arterial baroreceptor reflexes were not of importance in long-term regulation of arterial pressure.

The goal of the present investigation was to examine the role of the carotid sinus and aortic nerves in regulation of arterial pressure in response to acute hypotension and hypertension induced by alterations in peripheral vascular resistance, accomplished by injecting nitroglycerin and methoxamine intravenously. These drugs have little direct effect on the heart or central nervous system, but primarily affect the vascular bed to lower and raise arterial pressure.10 In addition, the acute response to hypotension induced by rapid hemorrhage was examined. The role of the arterial baroreceptors was assessed by comparing the responses of arterial pressure and heart rate before and after recovery from bilateral denervation of both the aortic and carotid sinus nerves, i.e., total arterial baroreceptor denervation (TABD), and after recovery from denervation of only the carotid sinus nerves, leaving the aortic nerves intact.

Methods

A midline cervical incision was made and the carotid sinus nerves were sectioned bilaterally in seven dogs under pentobarbital Na anesthesia, 30 mg/kg. In 25 dogs both the carotid sinus and aortic nerves were sectioned bilaterally (TABD). Adequacy of carotid sinus nerve section was confirmed in all dogs at operation and in five dogs 1-2 weeks later by observing no change in arterial pressure or heart rate to bilateral carotid artery occlusion. The aortic nerves were sectioned according to the technique described by Edis and Shepherd.3 The completeness of TABD was confirmed at operation and also in the conscious dogs on the day of study by observing the reflex heart rate responses to an intravenous bolus of nitroglycerin (nitroglycerin USP, Lilly), 48 µg/kg. Absence of heart rate changes following nitroglycerin and methoxamine was accepted as confirmation of TABD. Any dog showing a reflex heart rate response of more than 6 beats/min in a direction opposite to that of arterial pressure was excluded from the study. This resulted in excluding 13 of 25 dogs in which TABD was attempted.

Arterial pressure was sampled through the catheter previously implanted in the aorta and measured with a calibrated Statham P23Db strain gauge manometer. A cardiograph, triggered by the signal from the arterial pressure pulse, provided instantaneous and continuous records of heart rate. Data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph at a paper speed of 1 mm/sec. Statistical analysis was performed on the data according to standard techniques.18

Eighteen dogs were studied in the intact conscious state and 12 dogs 2-4 weeks following TABD. Five of these 12
dogs were studied both before and following denervation. All studies were carried out with the unsedated, trained dogs lying quietly in a darkened laboratory in order to avoid the wide fluctuations in arterial pressure that occur in denervated dogs if they are disturbed or excited.1-4

Nitroglycerin and methoxamine were administered intravenously in bolus doses of 2, 4, 12, 24, and 48 μg/kg in a volume of 1 ml through an indwelling catheter. In addition, five intact dogs were infused with nitroglycerin (4, 8, 16, and 32 μg/kg per min) and methoxamine (8, 16, and 32 μg/kg per min), allowing 120 seconds for stabilization at each dose level. In addition to peak changes in mean arterial pressure and heart rate produced by bolus doses of the drugs, the total magnitude of the deviation in mean arterial pressure from control was measured (Fig. 1) by integrating it over the time taken for pressure to return to the control level by planimetry; this product is referred to as the "pressure-time product" and is expressed in mm Hg sec. On separate days hemorrhage at a rate of 1 ml/sec was induced until 25 ml/kg of blood were removed. To assess gain of arterial baroreceptors, the formula described by Milhorn15 was used, i.e., open loop gain = [(AC) open/(AC) closed] - 1, where AC designates the steady state disturbance in arterial pressure induced by either nitroglycerin or methoxamine infusion or by hemorrhage, when the arterial baroreceptor reflex loop was open (TABD) or closed (intact).

Results

The control arterial pressures both in the dogs with carotid sinus nerve section alone (107 ± 5 mm Hg) and in those with TABD (111 ± 5 mm Hg) were significantly higher (P < 0.05) than in the intact group (92 ± 3 mm Hg). Heart rates of the intact dogs (83 ± 3 beats/min) and the dogs with carotid sinus nerve section (84 ± 6 beats/min) were similar and were significantly lower than those in the TABD group (115 ± 7 beats/min) (P < 0.01).

EFFECTS OF AORTIC AND CAROTID SINUS NERVE SECTION (TABD)

Nitroglycerin

In intact dogs nitroglycerin reduced mean arterial pressure and increased heart rate transiently. After recovery from TABD the same doses of nitroglycerin elicited no change in heart rate but 2- to 3-fold greater reductions in mean arterial pressure. In addition, the recovery time for arterial pressure was significantly longer (Fig. 1). The pressure-time products for all but the lowest dose of nitroglycerin were 7 to 9 times greater than normal (Table 1).

When nitroglycerin was administered by infusion to conscious, intact dogs, mean arterial pressure did not fall significantly at the lowest dose. At the larger doses approxi-
approximately 3- to 5-fold greater reductions in mean arterial pressure occurred in the dogs with TABD as compared to the conscious intact dogs, corresponding to an open loop gain of 2.5-3.8 (Table 2).

**Methoxamine** (Table 3)

In intact, conscious dogs the two lowest doses failed to alter arterial pressure significantly. In contrast, in dogs with TABD all doses elevated arterial pressure significantly. At the three highest doses, methoxamine induced a 2- to 4-fold greater increase in mean arterial pressure in conscious dogs with TABD. The increases in the pressure-time product were 11- and 15-fold greater than in the control intact conscious dogs for the doses of 12 and 24 μg/kg, respectively.

When methoxamine was administered by infusion, a 3- to 5-fold greater increase in arterial pressure occurred in the dogs with TABD (Table 2), corresponding to an open loop gain of 2.2-3.5.

### Table 2 Effects of Nitroglycerin, Methoxamine, and Hemorrhage on Mean Arterial Pressure

<table>
<thead>
<tr>
<th>Nitroglycerin infusion</th>
<th>4 (μg/kg per min)</th>
<th>8</th>
<th>16</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact (n = 6)</td>
<td>Δ mean arterial pressure (mm Hg)</td>
<td>-4 ± 1</td>
<td>-7 ± 2</td>
<td>-15 ± 4</td>
</tr>
<tr>
<td>TABD (n = 6)</td>
<td>-19 ± 2*</td>
<td>-29 ± 3*</td>
<td>-39 ± 4*</td>
<td>-45 ± 3*</td>
</tr>
<tr>
<td>Gain</td>
<td>3.8</td>
<td>3.1</td>
<td>3.3</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Methoxamine infusion

<table>
<thead>
<tr>
<th>Dose (μg/kg per min)</th>
<th>8</th>
<th>16</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact (n = 6)</td>
<td>Δ mean arterial pressure (mm Hg)</td>
<td>4 ± 1</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>TABD (n = 6)</td>
<td>18 ± 5*</td>
<td>41 ± 7*</td>
<td>64 ± 9*</td>
</tr>
<tr>
<td>Gain</td>
<td>3.5</td>
<td>4.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Hemorrhage

<table>
<thead>
<tr>
<th>Blood loss (ml/kg)</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact (n = 12)</td>
<td>Δ mean arterial pressure (mm Hg)</td>
<td>-5 ± 1</td>
<td>-8 ± 2</td>
<td>-10 ± 2</td>
<td>-13 ± 4</td>
</tr>
<tr>
<td>TABD (n = 12)</td>
<td>-12 ± 2*</td>
<td>-26 ± 4*</td>
<td>-37 ± 4*</td>
<td>-48 ± 4*</td>
<td>-60 ± 5*</td>
</tr>
<tr>
<td>Gain</td>
<td>1.4</td>
<td>2.3</td>
<td>2.7</td>
<td>2.7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

CSN = carotid sinus nerve; TABD = total arterial baroreceptor denervation; n = number of dogs.

* Significantly different from intact (P < 0.01).

† TABD significantly different from carotid sinus nerve section (P < 0.01).

‡ Significantly different from intact (P < 0.05).
In intact, conscious dogs, hemorrhage reduced mean arterial pressure significantly only after 10 ml/kg of blood loss. With comparable blood loss hemorrhage induced approximately a 3- to 4-fold greater reduction in mean arterial pressure in conscious dogs with TABD, corresponding to an open loop gain of 2.0-2.7.

SECTION OF CAROTID SINUS NERVES

Nitroglycerin

The responses of mean arterial pressure, the pressure-time product, and heart rate to any given dose of nitroglycerin were intermediate between those observed in intact normal dogs and those with TABD, but in general were closer to those observed in the intact group (Table 1).

Methoxamine

The changes in mean arterial pressure and in the pressure-time product were intermediate between those occurring in intact conscious dogs and those with TABD (Table 3). As was the case for nitroglycerin, the response to methoxamine in dogs with carotid sinus nerve denervation resembled the response seen in normal dogs more than that seen in dogs with TABD. In contrast to the intermediate heart rate response produced by nitroglycerin, denervation of the carotid sinus nerves alone did not alter the extent of slowing of heart rate with any given dose of methoxamine, as compared to the intact dogs, although the pressor response to any given dose was augmented.

Discussion

The role of the arterial baroreceptors in the immediate, short-term regulation of arterial pressure has been investigated predominantly in anesthetized animals. In the present study, nitroglycerin and methoxamine were injected to determine the extent to which arterial baroreceptors buffer an acute change in arterial pressure in conscious dogs with arterial baroreceptors intact and sectioned. When only the magnitude of the pressure change was compared at doses of the drugs which induced significant changes in the intact, conscious dogs, responses 3- to 5-fold greater were observed in the dogs with TABD. These figures, however, do not provide an appreciation of the magnitude of the overall disturbance in arterial pressure induced by an abrupt change in peripheral vascular resistance.

To assess the overall disturbance produced by these hypertensive or hypotensive stimuli it is helpful to include not only the magnitude of the change, but also the time taken for return to control levels, i.e., the dynamic characteristics of the reflex controller. When the total disturbances in pressure, i.e., pressure-time products, were examined, a much more profound disturbance of arterial pressure regulation was observed following TABD, the disturbance now being approximately 6-8 times as great for nitroglycerin and 10-14 times as great for methoxamine as that observed in intact, conscious dogs. This type of analysis, which indicates not only the magnitude of the change, but also the time taken for return to control levels, i.e., the dynamic characteristics of the reflex controller. When the total disturbances in pressure, i.e., pressure-time products, were examined, a much more profound disturbance of arterial pressure regulation was observed following TABD, the disturbance now being approximately 6-8 times as great for nitroglycerin and 10-14 times as great for methoxamine as that observed in intact, conscious dogs. This type of analysis, which indicates the total disturbance induced by a fixed stimulus, i.e., an exact quantity of drug which alters peripheral vasomotor tone, has not been described previously, but underscores the importance of the arterial baroreceptor reflexes in the acute regulation of arterial pressure. Cowley et al.1 also noted a 4-fold increase in the time required to return arterial pressure to control in denervated dogs in response to postural changes.

To assess the steady state open loop gain of the arterial baroreceptor system in the conscious animal, steady state responses of mean arterial pressure to continuous infusions of nitroglycerin and methoxamine, as well as to a physiological stimulus, i.e., hemorrhage, were compared in intact dogs and dogs with TABD. Using either the infusions of nitroglycerin and methoxamine or hemorrhage to disturb...
pressure, the calculated open loop gain ranged from 2 to 4. Considering that the gain of the baroreceptor is a nonlinear function, it was surprising to note the consistency of values derived in these conscious dogs in response to both hypertension and hypotension. Although the reported values for gain vary considerably, the majority of other studies performed to assess the gain of the arterial baroreceptors have reported values between 1 and 2. Exceptions are the study by Scher and Young, in which gain varied considerably, and a preliminary report by Brown and Taylor, in which acute adjustments to sinusoidal alterations in blood volume were examined in dogs with and without arterial baroreceptor nerves. It is interesting that the latter study also was conducted in anesthetized dogs. The difference between our findings and previous studies may be explained, in part, by differing definitions of the term "gain," as well as by differences of the experimental preparations, making precise comparisons of the gain derived from other studies with those from the present investigation difficult. Moreover, in the present investigation both the carotid sinus and aortic afferents were eliminated in the conscious dog, whereas most previous studies concentrated on the carotid sinus reflex in anesthetized animals. Cowley et al. also used conscious dogs and did not report as high a value for gain as we did. However, in that investigation gain was assessed from 24-hour arterial pressure distribution curves as opposed to only acute quantifiable interventions, which were examined in the present study.

The technique of TABD used in this study, i.e., bilateral cervical section of the carotid sinus and aortic nerves leaving the vagi intact, was selected because it left both vagal and sympathetic afferents intact. On the other hand, it is recognized that it could result in incomplete denervation to the extent that some aortic baroreceptor fibers traverse the cervical vagus nerves of the dog. Accordingly, 13 dogs that did exhibit small reciprocal changes in heart rate in response to hypertensive stimuli following the denervation procedure were excluded from this study in the belief that they had incomplete section of the aortic nerves. The 12 dogs that were studied did not demonstrate reciprocal heart rate changes in response to an alteration in arterial pressure. Thus, if remaining aortic baroreceptor fibers traveling in the vagi did play a role in regulation of arterial pressure in these experiments, their functional significance was minor insofar as their ability to induce reflex heart rate responses is concerned.

A recent study conducted in anesthetized dogs has shown that the aortic, as well as the carotid, baroreceptors are relatively ineffective in buffering a reduction in systemic arterial pressure below normal levels, compared to their greater potency in buffering elevations of arterial pressure. One of the conclusions drawn from that investigation was that the aortic baroreceptors act primarily to prevent acute hypertension, whereas the carotid sinus nerves buffer both hypertensive and hypotensive stimuli. To examine the contribution to arterial pressure regulation of the aortic receptors alone, we studied a series of conscious dogs after their recovery from bilateral section of the carotid sinus nerves, with the aortic nerves left intact. In this group of dogs the perturbations of arterial pressure were significantly greater with both hypotensive and hypertensive stimuli than they were in intact dogs, but far less than were observed in dogs with TABD. From these data, it is clear that the aortic nerves alone can act as an effective mechanism to buffer both elevations and reductions in arterial pressure. Thus, the results of the present study suggest that in conscious dogs aortic baroreceptors alone are able to buffer reductions as well as increases in arterial pressure.

In conclusion, this study has demonstrated the extent to which carotid sinus and aortic arch arterial baroreceptors buffer arterial pressure in response to acute hypotension or hypertension in the conscious dog. Removing arterial baroreceptors altered the time required for arterial pressure to return to baseline as much as it altered the magnitude of the pressure response to a hyper- or hypotensive agent. The aortic arch baroreceptors appeared important in buffering hypotensive as well as hypertensive responses. Values for static open loop gain of the combined baroreceptor systems in the conscious dog ranged from 2 to 4.

References

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