Rapid Resetting of the Aortic Baroreceptors in the Rabbit and Its Implications for Short-Term and Longer Term Reflex Control

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SUMMARY. We studied the effects of sustained changes in resting mean arterial pressures (MAP) on arterial baroreceptor properties in anesthetized rabbits and on the baroreceptor-heart rate reflex in conscious animals. The rabbits had balloons implanted round their aorta and vena cava, for producing transient changes in MAP about the resting MAP. Aortic baroreceptor function curves were obtained at different resting MAP by relating balloon-induced changes in MAP to either (1) integrated aortic nerve activity or (2) unit baroreceptor activity. Any sustained change in resting MAP reset the unit function curves in the same direction within 15 minutes by altering their threshold without affecting gain. The effect was reversible and independent of starting pressure. It was the same whether resting MAP was altered by vasoactive drugs (nitroprusside, phenylephrine) or was changed by withdrawing or infusing blood in sympathetically blocked rabbits. We studied baroreflex function in conscious rabbits by deriving MAP-heart period (HP) curves at different resting MAP. Nitroprusside lowered baroreflex threshold for evoking bradycardia, whereas phenylephrine increased threshold. From our analysis, the resting MAP-mediated changes in receptor threshold accounted for the reflex threshold changes. Altered baroreceptor properties did not account for changes in baroreflex HP range produced by both drugs, and in reflex gain; these were probably due to afferent interactions in the CNS. Because of rapid arterial baroreceptor resetting, transient changes (of about 30 seconds or less) in MAP of moderate magnitude evoked normal reflex heart rate responses at each resting MAP. After changes in resting MAP sustained for 15 minutes or longer, reflex changes in resting heart rate were considerably smaller than in the absence of resetting. Therefore the arterial baroreceptors provide the baroreflex with a "floating" rather than a fixed set point, determined by the prevailing MAP. (Circ Res 50: 428-439, 1982)

McCUBBIN et al. (1956) were the first to show that the arterial baroreceptors become "reset" in dogs with chronic experimental hypertension. This resulted in a shift in the function curve relating baroreceptor activity to blood pressure in the direction of the elevated mean arterial pressure (MAP). Since then, the phenomenon has been confirmed in numerous studies in several species (Kezdi, 1962; Aars, 1968; Angell-James, 1973; Brown et al., 1976; Sleight et al., 1977) but there has been disagreement about the rate of development of baroreceptor resetting. In many of the studies, resetting appeared to lag several days behind the rise in blood pressure (McCubbin et al., 1956; Kezdi, 1962; Sleight et al., 1977), whereas, in others, resetting occurred after several hours (Krieger, 1970; Munch et al., 1980) or even more rapidly (Salgado and Krieger, 1978; Coleridge et al., 1980, 1981).

In preliminary studies, we recently observed that vasodilator drugs produced rapid resetting of the baroreceptor-heart rate reflex of the conscious rabbit, so that the threshold for eliciting bradycardia shifted in the direction of the lower blood pressure (Korner and Oliver, 1980). Possible mechanisms for altering baroreflex properties include (1) changes in the arterial baroreceptor properties, (2) interactions in the central nervous system (CNS) involving the input from the arterial baroreceptors and from other afferents (Korner 1979), and (3) direct effects of the drugs on the CNS. The present investigation was undertaken to determine to what extent the reflex resetting was accounted for by resetting of the arterial baroreceptors themselves.

Accordingly, we examined changes in the properties of the aortic baroreceptors in anesthetized rabbits during sustained falls in MAP elicited by different doses of sodium nitroprusside. It became apparent that the properties of the baroreceptors (studied in whole nerve and unit preparations) became reset within minutes after altering MAP. Therefore the study was extended to examine aortic baroreceptor resetting produced by the pressor drug phenylephrine and by "passive" MAP changes resulting from blood volume manipulations in sympathetically blocked rabbits. In addition, we extended the earlier observations on the baroreceptor-heart rate reflex in conscious rabbits by studying the effects of different doses of nitroprusside and phenylephrine on the baroreflex curves and on the changes in resting heart
rate, to evaluate the significance of the rapid arterial baroreceptor resetting on the overall changes in reflex properties.

Methods

The experiments were performed in crossbred rabbits weighing between 2.0 and 3.0 kg. We implanted two Silastic perivascular balloons around the thoracic aorta and inferior vena cava at two preliminary operations, at least 1 week apart (Korner et al., 1972). Two weeks of recovery were allowed after the last operation.

The investigation consisted of (1) baroreceptor studies under anesthesia and (2) baroreceptor-heart rate reflex studies in conscious rabbits. In each type of experiment, sustained changes in resting MAP were produced in a number of ways, and we studied the effects of these alterations on function curves characterizing the properties of the baroreceptors or of the baroreflex. The function curves were derived by observing the evoked responses during transient changes in blood pressure about the prevailing resting MAP produced by inflating the perivascular balloons.

Baroreceptor Studies under Anesthesia

The central ear artery and vein were cannulated under 0.5% local lidocaine anesthesia. The rabbits were then anesthetized either with halothane or with intravenous (iv) alfathesin (0.350-0.700 mg/kg per min total steroid) for the surgical procedures. After surgery was completed, anesthesia was maintained with alfathesin (0.175 mg/kg per min, iv) (Blake and Korner, 1981) and the rabbits were paralyzed with succinyl choline (50 mg bolus + 0.78 mg/min iv infusion). They were ventilated artificially with 35% O2 at a respiratory minute volume of 0.8-1.0 liter/min. This maintained arterial Pco₂ between 25 and 30 mm Hg (measured by Radiometer model ABL 1 blood analyzer), close to arterial PCO₂, which occurs mainly in systole with each arterial pressure waveforms: discharge patterns during these pressure pulses could then be compared (e.g., Fig. 4). On the other hand, the relationship between MAP and unit activity expressed as spikes/sec. Expressing discharge as spikes/beat provides the most direct quantitative information about unit firing, which occurs mainly in systole with each arterial pressure pulse. With the ramp method, it took 1.5-2 minutes to scan the baroreceptor responses from threshold to about 120-140 mm Hg (Fig. 1) and frequent repeat measurements were thus possible. For each unit we determined the relationship between (1) MAP and unit activity expressed as spikes/beat and (2) MAP and the discharge expressed as spikes/sec. Expressing discharge as spikes/beat provides the most direct quantitative information about unit firing, which occurs mainly in systole with each arterial pressure pulse. With the ramp method, it was always possible to find pressure pulses during control and treatment periods with identical MAP, closely similar pulse pressures and heart period, and virtually superimposable systolic pressure waveforms: discharge patterns during these pressure pulses could then be compared (e.g., Fig. 4). On the other hand, the relationship of MAP during the ramps to discharge expressed as spikes/sec is important from the viewpoint of evoking reflex activity through the CNS.

To derive the MAP-spikes/beat relationship, we inflated the venous balloon until MAP came below threshold and held the pressure at this subthreshold level for 10-15 seconds (Fig. 1A). MAP was then allowed to rise evenly at 1-2 mm Hg/sec until the venous balloon was deflated. The aortic balloon then was inflated to produce the same rate of rise of MAP until the pressure was about 20-30 mm Hg above resting. When the threshold was reached, the unit fired one action potential/beat and continued to do so as MAP slowly increased until its firing rate became two spikes/beat. Each increment in spikes/beat occurred over a range of MAP, often separated by a short segment of the ramp with a mixed firing pattern. The baroreceptor function curves were obtained by plotting the mid-point of successive MAP ranges against the number of spikes/beat (Fig. 1C, left). Baroreceptor curves obtained from duplicate ramps agreed closely (Fig. 1C, right). They were displaced a few mm Hg to the left of "adapted" function curves obtained from graded pressure steps, each maintained for 30 seconds (Fig. 1C, right). Thus the rate-sensitive compo-
nent of the baroreceptor responses to the slow pressure ramps was only small.

Balloon inflation altered pulse pressure and the waveforms of the arterial pressure pulse, as well as heart rate (Fig. 1B), in a manner that was closely reproducible in individual rabbits. The average reduction in MAP from the control resting value produced by the venous balloon was 37 mm Hg and was associated with a consistent rise in heart rate by this level of alfathesin anesthesia (Blake and Korner, 1981).

The relationship between MAP and unit activity expressed as spikes/sec was calculated as (1000 x spikes/beat)/average heart period at mid-range MAP.

**Reflex Studies in Conscious Rabbits**

Sigmoid curves relating MAP to the heart period (HP, pulse interval) were derived by observing the HP responses evoked by 6-8 graded rises from resting MAP and the same number of falls, with each change in pressure maintained for 30 seconds (Korner et al., 1972, 1979). The relationship between MAP and HP has the advantage over the MAP-HP curves, rabbits received the following successive doses of nitroprusside, each for 1 hour: i.e., 5% dextrose control, 2.5, 5, and 10 μg/kg per min. Baroreflex studies were also performed after parasympathetic blockade with methscopolamine (see below). This experiment was done either 1 week before or 1 week after the study. For the receptor studies, a shorter protocol was used, consisting of a control period (15 minutes), mostly a single rate of nitroprusside infusion (5 μg/kg per min) given over 30-135 minutes in different experiments followed, where possible, by a recovery period (15-60 min).

Phenylephrine hydrochloride was given in the baroreflex experiments in doses of 0 (5% dextrose control), 2.5, and 5 μg/kg per min iv, each for 1 hour. For the unit baroreceptor studies, the shorter protocol was used, the rabbits being infused with either 5 or 7.5 μg/kg per min for 30–60 minutes during the treatment period.

To produce sympathetic blockade the rabbits received either phenoxybenzamine (6 mg/kg, iv) over a period of 40 minutes, or guanethidine sulfate (10 mg/kg, iv) over 1 hour, followed by phentolamine mesylate (2 mg/kg bolus + 0.025 μg/min iv, each for 1 hour).

**FIGURE 1.** A: Records showing MAP (mm Hg) with calibration scale and pulsatile arterial pressure, offset to a lower level for greater clarity. The venous balloon was first inflated to bring MAP below threshold; subsequently a slow pressure ramp was produced by first releasing the venous balloon and then inflating the aortic balloon. B: (a-d) Short segments of the pressure ramps have been recorded on an expanded time scale from different points indicated by arrows; they show unit activity (upper trace) and waveform of arterial pressure (mm Hg). Heart rates were 260 beats/min in traces a–c and 220 beats/min in d. C: Left—Relation of unit activity (spikes/beat) to MAP (mm Hg) obtained during the ramp shown in A and B (b–d) Right—Unitary activity from the same baroreceptor (closed circles) has been related to the mid-range MAP (mm Hg) as explained in text. The other solid symbols on the right denote responses to duplicate pressure ramps which are compared with a "steady state" response with each pressure step maintained for 30 seconds (open circles, interrupted lines).

Drugs and Blood Volume Manipulations

Sustained changes in resting MAP were induced either by iv infusions of sodium nitroprusside or phenylephrine in both the receptor and baroreflex studies. In some receptor experiments, resting MAP was altered by withdrawing or infusing blood in rabbits with sympathetic blockade. In the experiments to determine changes in the integrated aortic nerve activity function curves and the baroreflex MAP-HP curves, rabbits received the following successive doses of nitroprusside, each for 1 hour: i.e., 5% dextrose control, 2.5, 5, and 10 μg/kg per min. Baroreflex studies were also performed after parasympathetic blockade with methscopolamine (see below). This experiment was done either 1 week before or 1 week after the study. For the receptor studies, a shorter protocol was used, consisting of a control period (15 minutes), mostly a single rate of nitroprusside infusion (5 μg/kg per min) given over 30-135 minutes in different experiments followed, where possible, by a recovery period (15–60 min).

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mg/kg per min, iv, infusion). We confirmed the effectiveness of both regimes, using the tests described by West et al. (1975). After sympathetic blockade, the rabbits were given 30 ml heparinized blood from a donor rabbit + 30 ml of 10% low molecular weight dextran to minimize the fall in blood pressure. MAP then was lowered or raised by removal or infusion of blood through a right jugular vein catheter (“passive” blood volume manipulations). Each level of resting MAP was maintained for 30 minutes by appropriate small blood volume adjustments.

For parasympathetic blockade, methscopolamine was given in a dose of 1 µg/kg per min, iv, for at least 40 minutes before the start of the control measurements. This produced a constant high level of muscarinic receptor block as demonstrated by graded electrical stimulation of the vagus under anesthesia. During methscopolamine, the reflex heart rate changes were abolished by propranolol or guanethidine, suggesting that they were mediated through the cardiac sympathetic nerves. In the present experiments, the maximal baroreflex-mediated tachycardia was slightly less after methscopolamine (317 beats/min; see lower HP plateau of 189 msec in control curve, Fig. 9) than before the drug (333 beats/min; lower HP plateau 180 msec; P < 0.05).

We have assumed that this means that, in normal rabbits, baroreflex-mediated tachycardia is associated not only with an increase in sympathetic activity, but also with reduction in vagal negative chronotrophic activity right up to maximum tachycardia. It has been shown that under special conditions of electrical stimulation the vagus can exert a small positive chronotrophic effect, mediated through muscarinic receptors on the SA node, in addition to the well known large negative chronotrophic effects (Lano et al., 1973; Levy and Martin, 1979). Neither the significance of these effects, nor whether they are evoked reflexly, is known. We therefore prefer the simpler hypothesis outlined above, for the difference in maximum tachycardia response before and after methscopolamine. Last, our finding that maximum heart rates are higher before than during muscarinic block is not in accordance with the recent suggestion that vagally released acetyl choline inhibits norepinephrine release from cardiac sympathetic terminals through muscarinic presynaptic receptors (Rand et al., 1975), at least not under the present conditions of reflex stimulation.

Statistical Analysis

Most of the unit baroreceptor curves exhibited some degree of curvilinearity. Displacement of the curves during sustained changes in blood pressure produced by the various treatments were parallel. We found that under these circumstances it was adequate to use linear covariance regression analysis, rather than curvilinear regression, and we compared the slopes and adjusted means between control, treatment, and recovery periods (Snedecor and Cochran, 1967). The difference in adjusted means at corresponding points of the control and “reset” function curves has been termed the curve shift. The latter provides a satisfactory estimate of the changes in threshold of the unit and was more reproducible.

The estimated shifts in function curves relating MAP to spikes/beat were compared with shifts calculated from curves relating MAP to spikes/sec by means of a paired t-test. We assessed the significance of the differences between control and treatment periods by resting variables and slopes of the function curves both by the paired t-test within each treatment group and by analysis of the data obtained from the four experimental groups (Table 1). Critical values for a modified t-statistic were obtained by the Bonferroni procedure (Wallenstein et al., 1980) and from the Studentized range (Snedecor and Cochran, 1967).

In the reflex experiments, the effects of different doses of each vasoactive drug on the resting variables and the parameters of the baroreflex MAP-HP curves were examined by analysis of variance after partitioning the between-treatment sums of squares into individual degrees of freedom. Average baroreflex curves were obtained by reconstructing the sigmoid curve from the mean parameter values (Blake and Komer, 1981).

Results

Baroreceptor Studies

Integrated Aortic Nerve Activity

The relationship between MAP and integrated whole aortic nerve activity was determined in six anesthetized rabbits, infused successively with 0, 2.5, 5, and 10 µg/kg per min of sodium nitroprusside. With increasing doses of the drug there were increasing falls in resting MAP below initial control (see Fig. 2, inset). Baroreceptor function curves were constructed during the second half of each hour’s infusion period. Nitroprusside produced approximately parallel dose-related displacement of the function curves in the direction of the lower resting MAP (P < 0.005) (Fig. 2). The difference in the curve shifts (see Methods) averaged 10, 16, and 23 mm Hg, i.e., significantly less than the corresponding reductions in resting MAP from control (16, 26, and 36 mm Hg). During recovery, resting MAP rose by 27 mm Hg, to a value slightly below initial control (Fig. 2). This time the baroreceptor curve was shifted in the direction of the pressure rise by an average of 15 mm Hg. Infusion of nitroprusside thus produced rapid and reversible shifts in the whole aortic nerve baroreceptor function curve.
Baroreceptor Units

Effects of Nitroprusside and Phenylephrine. Following control observations the effects of nitroprusside (5 μg/kg/min i.v.) were studied in 13 units from 13 rabbits. Those of phenylephrine (5 or 7.5 μg/kg/min and in some experiments both doses) were examined in 9 units from seven rabbits. In most experiments, repeated curves were obtained every 15 minutes. With this dose of nitroprusside, resting MAP reduction averaged 29 mm Hg, with a small reduction in pulse pressure (3.3 ± 1.6 mm Hg), and the change in heart rate was small and variable (Table 1). With phenylephrine, there was a consistent fall in resting heart rate of about 50 beats/min and a rise in MAP averaging 23 mm Hg (Table 1); pulse pressure decreased by 4.7 ± 1.2 mm Hg.

With both nitroprusside and phenylephrine, the baroreceptor unit function curves shifted in the direction of the change in MAP (Fig. 3). Thus, during the falls in resting MAP induced with nitroprusside, a unit fired more spikes/beat than under control conditions at identical pressures during the ramp stimuli (Fig. 4, upper) and the converse occurred during rises in resting MAP induced with phenylephrine. When the vasoactive drug was stopped and MAP recovered, the curves shifted toward initial control (Fig. 3). The magnitude of the shift was approximately similar to the changes in threshold observed in the units (Table 1).

The "resetting" of the unit function curve occurred within 15 minutes of the start of nitroprusside infusion, with no further shift observed in the function curves at 15-minute intervals up to 60 minutes in the six units studied (Table 2). In two other units, "resetting" produced by nitroprusside did not alter during 135 minutes of observation. With phenylephrine, the shift observed was largest at 15 minutes. It then decreased slightly and remained stable for the last 30 minutes of observation (Table 2).

In 9/13 units, the slope of the ramp responses was parallel during administration of nitroprusside, and, similarly, in 9/9 units, there was no change in slope with phenylephrine (Fig. 3) as assessed by analysis of covariance (Snedecor and Cochran, 1967). Even in units where the changes were significant, slopes increased only slightly, i.e., by not more than 5-10% of control.

The vasoactive drugs produced relatively small change in configuration of the resting arterial pressure pulse, but this did not account for the shifts in the function curves. The main determinant of the shifts

<table>
<thead>
<tr>
<th>Treatment group dose and no.‡</th>
<th>Resting MAP (mm Hg)</th>
<th>Resting heart rate (beats/min)</th>
<th>Baroreceptor threshold (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside (5 μg/kg per min) [13]</td>
<td>101.5 ± 29.3* 2.68</td>
<td>301 +1.2 3.6</td>
<td>52.45 ±10.3* 2.0</td>
</tr>
<tr>
<td>Phenylephrine (5 or 7.5 μg/kg per min) [9]</td>
<td>101.6 +22.8 3.53</td>
<td>274 −50.4* 6.3</td>
<td>66.9 +8.9* 1.4</td>
</tr>
<tr>
<td>Bleeding [9]</td>
<td>84.9 −27.0* 2.93</td>
<td>294 −13.4 6.9</td>
<td>47.9 −10.0* 2.0</td>
</tr>
<tr>
<td>Infusion [3]</td>
<td>76.7 +11.0† 2.08</td>
<td>273 −6.7 8.4</td>
<td>46.7 +5.1* 0.7</td>
</tr>
</tbody>
</table>

**SED** = standard error of difference (control-treatment), (ΔT).

* P < 0.01; † P < 0.05.

‡ Number of units in brackets.

§ n = 9 (see Methods; units with irregular firing below threshold excluded).

¶ n = 6 (as above).
appeared to be the alteration in resting MAP. This was suggested by the distinctive differences in unitary firing pattern between control and treatment periods obtained with matched arterial pulses with virtually superimposable systolic phase (Fig. 4).

The shifts in the function curves differed relatively little whether unitary firing was expressed as impulses/beat or impulses/sec (Fig. 5, Table 3). In the nitroprusside experiments, where changes from control in resting heart rate were small and variable, there was no significant difference between the estimates (Table 3). With phenylephrine, where there was a large uniform change in heart rate (Table 3) the shift was about 30% higher ($P < 0.001$) when expressed as spikes/sec than when expressed as spikes/beat.

Effects of “Passive” Blood Pressure Changes. In seven rabbits, pretreated with either phenoxybenzamine or guanethidine + phentolamine, MAP was either lowered or raised from control by withdrawal or infusion of blood. The control resting MAP in these animals was somewhat lower than in unblocked rabbits and their baroreceptor units had slightly lower control thresholds (Table 1).

In the unit shown in Fig. 6, lowering MAP by withdrawal of blood produced a parallel shift in the baroreceptor curve by 15 minutes, with the unit firing more spikes/beat at a given ramp MAP than before (Fig. 4, lower). Restoration of resting MAP by reinfusion of blood restored the curve close to initial control position, whereas further infusion shifted the curve in the direction of the higher resting MAP; the shift was once again reversed by withdrawal of blood (Fig. 6). In none of the units were the control and treatment slopes of the function curves significantly different from control.

| Table 2 |

| Time-Related Effects on MAP and Baroreceptor Curve Shift in Units Studied Serially for 60 Minutes |

| Nitroprusside† |  
|---|---|---|---|---|---|---|
| MAP (mm Hg) | 6 | 95 | $-28.8$ | $-26.5$ | $-25.5$ | $-26.5$ | 1.78 |
| Curve shift (mm Hg) | 6 | | $-12.7$ | $-12.6$ | $-12.6$ | $-11.8$ | 0.99 |
| Phenylephrine†† |  
|---|---|---|---|---|---|---|
| MAP (mm Hg) | 5 | 100.8 | $+13.4$ | $+14.2$ | $+14.2$ | $+13.6$ | 0.70 |
| Curve shift (mm Hg) | 5 | | $+10.1^*$ | $+6.5$ | $+6.4$ | $+7.5$ | 0.98 |

† Nitroprusside infusion 5 μg/kg per min.
†† Phenylephrine infusion 5 or 7.5 μg/kg per min.
* Difference [15 min – (average of 30 + 45 + 60 min)] = 3.3 ± 1.13 (SEM); $P < 0.02$.
§ SEM = standard error of mean of single time from analysis of variance.

n = number.
different either during infusion or withdrawal of
blood, as assessed by analysis of covariance. With
only minimal changes in resting heart rate in these
animals, there was no significant difference in es-
F estimated curve shifts whether unit activity was expressed
as spikes/beat or spikes/sec (e.g., Fig. 5).

Curve Shifts in the Various Maneuvers. Figure 7
shows the results obtained in all units studied, plotted
to evaluate the effect of the initial resting MAP on the
magnitude of the curve shift with different maneu-
vers. Each line is a two-point graph, plotting initial
and final resting MAP against the curve shift. The
slope of the line thus indicates the magnitude of the
shift/unit Δ resting MAP. The lefthand side shows the
data obtained from different maneuvers produc-
ing sustained decreases in resting MAP, i.e., during
nitroprusside infusion after recovery from phenyl-
ephrine infusion and during removal of blood in
sympathetically blocked rabbits. The relationship be-
tween starting resting MAP and shift/unit change of
resting MAP was not significantly different from zero
with the regression coefficient relating the above var-
iables 0.0015 ± 0.0015 shift units/mm Hg starting
MAP, for all the downward changes in resting MAP in
Figure 7. The three maneuvers that produced sus-
tained rises in resting MAP are shown on the right-
hand side of Figure 7 when resting MAP increased
after stopping the nitroprusside infusion, during
phenylephrine infusion, and during infusion of blood.
Again, there was no significant relationship between
initial pressure and the slopes of the plotted lines,
with the regression coefficient 0.002 ± 0.0014 again
not significantly different from zero.

Since the initial resting MAP level did not influence
the shift of the function curve during the various
treatments, it has been ignored in Figure 8 where the
rises and falls in MAP taken from the control value
preceding a given maneuver have been plotted against
the baroreceptor curve shifts during the maneuver.
The upper panels show data obtained during admin-
istration of vasoactive drugs. The middle panels show
data from blood volume manipulations in sympathe-
ically blocked rabbits. In each group, the regression
lines relating change in MAP to baroreceptor curve
shift were linear and passed through the origin. There
was little difference in the slopes of the four regres-
sion lines as is evident in the lower panels in Fig 8
where the results obtained during administration of
vasoactive drugs and during blood volume manipu-
lation changes have been superimposed. On average,

<table>
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<th>TABLE 3</th>
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<tr>
<td>Baroreceptor Curve Shift when Unitary Activity was Expressed as</td>
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<tr>
<td>Spikes/Beat and as Spikes/Sec</td>
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<td>n</td>
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<tr>
<td>Nitroprusside (5 μg/kg per min)</td>
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<tr>
<td>Phenylephrine (5 or 7.5 μg/kg per min)</td>
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</table>

ΔMAP, ΔHR = change from control resting mean arterial pressure and heart rate, ± SEM. SED = standard error of difference in estimated shifts.

* P < 0.001 between the two estimates of shifts.
Dorward et al. / Rapid Baroreceptor Resetting and Its Consequences

DECREASING MAP

INCREASING MAP

FIGURE 7. Each line represents a 2-point plot relating the initial and final level of resting MAP (mm Hg) to the magnitude of the shift in a baroreceptor function curve during a given treatment. (Left) Results during maneuvers where resting MAP decreased from preceding level, i.e., nitroprusside infusions (NP) (top); recovery from phenylephrine (PE) (middle); bleeding sympathetically blocked rabbits (lower). (Right) Results during maneuvers where resting MAP increased from preceding level, i.e., recovery from nitroprusside (top); phenylephrine infusion (middle); infusion of blood in sympathetically blocked rabbits (lower). The different dashed symbols in the lower panels show responses in rabbits sympathetically blocked with either phenoxybenzamine, or guanethidine + phentolamine.

for both rises and falls in resting MAP of 10 mm Hg, the baroreceptor function curve shift was about 4 mm Hg.

Reflex Experiments

Sodium Nitroprusside

Six conscious rabbits were infused with nitroprusside at successively higher dose rates, and changes in resting MAP, heart rate, and in baroreceptor-heart rate reflex parameters were determined during the second half of each 1-hour infusion period (see Methods). Each dose produced approximately similar decrements of MAP from the preceding level, which were all statistically significant and which were, successively, 8.5 ± 1.9 (see), 4.9 ± 1.8 and 6.3 ± 1.8 mm Hg (Fig. 9, top right). By contrast, the only statistically significant rise in heart rate occurred with the lowest dose (47 ± 6.3 beats/min, P < 0.001). The two higher doses produced rises averaging 6.2 and 7.8 beats/min which did not occur in all animals and were not statistically significant when partitioning the "between-doses" sums of squares in the analysis of variance.

In these rabbits, nitroprusside produced dose-related approximately parallel shifts of the sigmoid baroreceptor-heart rate reflex function curves in the direction of the lower MAP (Fig. 9, top left), with only small differences in average gains of the curves in relation to control. BP50 and threshold pressure for eliciting bradycardia diminished progressively, falling by about 7 mm Hg/10 mm Hg Δ resting MAP (Fig. 9). The HP range (difference between plateaus) fell progressively from a control value of 227 to 194 msec at an infusion rate of 2.5 μg/kg per min (P < 0.05) to an average value of 165 msec at the two highest doses (P < 0.01). At the low dose of nitroprusside, reduction in this parameter was almost entirely due to reduction in the upper HP plateau, but at the highest two doses, it occurred at the expense of both plateaus. At the lowest dose of nitroprusside the maximal baroreflex-mediated tachycardia was thus the same as under control conditions (333 beats/min) but at the highest two doses, it was slightly impaired (317 beats/min).

The successive resting HP values have been plotted in large closed symbols on the sigmoid baroreflex curve (Fig. 9, top left). The tachycardia at all infusion rates was significantly smaller than predicted from the preceding baroreflex curve in the absence of resetting. Transforming the HP values into heart rate, the latter should have risen by 68 beats/min from

Figure 8. (Upper) Relationship derived from different units between change in resting MAP (mm Hg) and curve shift from control (mm Hg) during nitroprusside (left) and phenylephrine (right) infusions. (Middle) Results obtained in sympathetically blocked rabbits showing relationship between change in resting MAP (mm Hg) and (1) curve shift from control during withdrawal of blood (left), (2) curve shift from control during infusion of blood (right: open squares), (3) curve shift during infusion of blood from preceding value level following hemorrhage (right, open circles); a single regression lines has been fitted to all points. (Lower) Superimposed data and regression lines from vasoactive drug experiments and blood volume manipulations.
FIGURE 9. (Left) Average baroreflex function curves obtained from six conscious rabbits showing relationship between mean arterial pressure (mm Hg) and heart period (msec) with normal autonomic function (upper) and during vagal block with methscopolamine (lower). After control curve, nitroprusside was infused at 2.5, 5, and 10 µg/kg per min, each for 30 minutes before the start of measurements. The large symbols on each curve denote the resting MAP and HP values. (Right) Resting MAP (mm Hg) and heart rate (beats/min) during control and nitroprusside periods at the different doses in normal (top) and methscopolamine-treated rabbits (lower) Bars are ± 1 SEM obtained from analysis of variance.

control at the lowest dose of nitroprusside for the observed fall in MAP instead of by 47 beats/min, the value actually observed. At the highest infusion rates, the small additional rises in heart rate (which were not significant) were about 40-60 beats/min below the expected value which approximated the maximum baroreflex-mediated tachycardia (Fig. 9, lower left).

The same rabbits were studied on another experimental day during muscarinic blockade with methscopolamine (Fig. 9, lower). Successive decrements of MAP produced by each increase in nitroprusside infusion rates averaged 12.4, 4.5, and 5.3 mm Hg (P < 0.01 for each difference). By contrast, the heart rate changes were variable and none of the increments (12.2, 0, and -4.5 beats/min) were statistically significant. The baroreflex curves were again reset in an approximately parallel fashion with significant elevation in lower plateaus at the highest two doses. The maximal tachycardia was thus 317 beats/min under control conditions and 304 beats/min with the highest dose of nitroprusside. From the baroreflex curves in Figure 9 (lower left), a rise in heart rate should have occurred for each decrement in MAP in the absence of resetting.

Phenylephrine

Phenylephrine was infused in six conscious rabbits at rates of 2.5 and 5.0 µg/kg per min and produced dose-related rises in MAP and falls in heart rate (Fig. 10, left). There was a shift in the baroreflex curves in the direction of the higher MAP (Fig. 10, right). Average gain decreased by approximately 30% (P < 0.05). HP range increased from 252 msec (control) to an average of 364 msec at 2.5 µg/kg per min and 5 µg/kg. At both doses the upper HP plateau increased in relation to control, and at the higher doses there was also a rise in lower plateau. At the lowest dose, the plot of resting HP on the baroreflex curve shows that the degree of cardiac slowing was below that expected in the absence of resetting. At the higher dose, the large rise in upper plateau component in relation to control makes it difficult to estimate the "expected" bradycardia (see Discussion). With a dose of 7.5 µg/kg per min, there were frequent cardiac irregularities, in contrast to the response under anesthesia.

Discussion

Arterial Baroreceptor Resetting

We demonstrated rapid resetting of the aortic arch baroreceptor threshold whenever there was a sustained change in blood pressure, with a parallel shift in the baroreceptor unit function curves. These changes occurred in all units studied and in the population responses of the integrated aortic nerve discharge. The analysis established that the major
determinant of the resetting was the change in resting MAP. A quantitative measure of the change in threshold and firing pattern was provided by the shift in the MAP-spikes/beat unit function curves and averaged 4 mm Hg/10 mm Hg Δ resting MAP. The shift was similar for both rises and falls in resting MAP and was independent of the starting pressure over a wide range of values of resting MAP (50–130 mm Hg). Nitroprusside and phenylephrine did not exert any effects on receptor discharge other than those due to the changes in resting MAP that they elicited.

We estimated the gain of the baroreceptors from the slopes in the unit function curves. The various changes in resting MAP produced almost no changes in receptor gain. The findings thus differ from baroreceptor resetting in chronic hypertension in which the threshold also increased with the rise in resting MAP, but where there was a considerable reduction in receptor gain (Angell-James, 1973; Brown et al., 1976). Resetting of threshold and gain of the receptors may thus involve different components of the pressure-transduction process (Brown, 1980).

Our study has confirmed many of the recent findings of Coleridge et al. (1981) in aortic baroreceptor units of the dog, who demonstrated arterial baroreceptor resetting within 20 minutes of elevating blood pressure. Their units, like ours, were active at normal resting pressures. Coleridge et al. characterized their units by measuring conduction velocity. This was not done in our study but probably the units studied were virtually all "large fiber" baroreceptors. Our experiments have extended the studies of Coleridge et al. (1981) by demonstrating that rapid resetting did not involve sympathetic feedback to the receptor and by studying the reflex consequences of the resetting.

One important difference in emphasis between the receptor component of our study and that of Coleridge et al. (1981) is the wide range of starting pressures and of changes in resting blood pressure that we used to study baroreceptor properties. We concluded that the change in receptor threshold was linearly related to ΔMAP and that the different starting pressures between animals played little role. Coleridge et al. studied the effects of acute resetting by producing a 25 mm Hg change in resting MAP from a single pressure. They were more concerned with examining the role of hysteresis on receptor firing during rises and falls in pressure from a constant resting level. Our findings are entirely consistent with their suggestion that viscoelastic relaxation on "creep" of the connective tissue in the arterial wall may be responsible for rapid arterial baroreceptor resetting.

The only other unitary analysis of rapid resetting is that of Munch et al. (1980) who published a preliminary report where the threshold of baroreceptor units of rats became reset within 90 minutes after a rise in transmural pressure in the perfused aortic arch preparation. The estimate of Sleight et al. (1977) that baroreceptor resetting lagged several days behind the rise in MAP during development of renovascular hypertension was based on data from only one dog. Other estimates of the time course of baroreceptor resetting, varying from 15 minutes to weeks, have examined integrated mass discharges which did not indicate whether individual units were involved in the resetting process (McCubbin et al., 1956; Kezdi, 1962; Aars, 1968; Krieger, 1970; Sleight et al., 1977; Salgado and Krieger, 1978).

**Baroreflex Resetting and Its Consequences**

Falls in resting MAP during infusions of nitroprusside in conscious rabbits lowered the baroreflex threshold for bradycardia (through both vagal and sympathetic efferents), whereas phenylephrine-induced rises in resting MAP increased baroreflex threshold. With nitroprusside infusions the baroreflex gain did not alter and the changes in BP50 thus provide an estimate of the threshold changes in the reflex. BP50 altered by about 7 mm Hg/10 mm Hg Δ resting MAP. This is greater than the estimates of 4 mm Hg/10 mm Hg Δ resting MAP obtained in the MAP-spikes/beat function curves. The latter were used to highlight changes in discharge patterns during each beat, but the MAP-spikes/sec curves are relevant from the viewpoint of evoking reflex activity through the CNS.

The question arises whether factors other than rapid arterial baroreceptor resetting accounted for the above changes in baroreflex threshold in conscious rabbits. During the nitroprusside infusions in anesthetized animals, the estimated shifts in unit threshold between control and treatment periods were the same whether unit activity was expressed as spikes/beat or as spikes/sec. This was probably due to the minimal changes in resting heart rate in the anesthetized rabbit (Table 1) owing to the suppression of vagal efferent activity by the maintenance dose of alfathesin (Blake and Korner, 1981). On the other hand, during phenylephrine infusions, resting heart rate slowed even in anesthetized animals. Indeed, the slowing was more pronounced (Table 1) than that occurring during normal blood pressure ramps (Methods), suggesting that it was mediated through additional afferent mechanisms (see below). The cardiac slowing contributed to the approximately 30% greater shift in function curves when unit activity was expressed as spikes/sec than when it was expressed as spikes/beat. In the conscious rabbit, the changes in resting heart rate were considerably greater than under anesthesia with a given dose of each vasoactive drug, which would augment the shifts in the baroreceptor spikes/sec function curves. Assuming that the changes in aortic baroreceptor properties can be regarded as representative of all arterial baroreceptors, it would seem that rapid arterial baroreceptor resetting can account completely for the changes in baroreflex threshold.

As regards the changes in HP range produced by nitroprusside and phenylephrine, we may speculate, from the results of a previous analysis of the effects of arterial hypoxia (Korner et al., 1973; Iriki et al. 1977; Korner, 1980), that the two drugs produced opposite effects on the cardiopulmonary blood vol-
ume. During balloon inflation this would produce a different profile of afferent activity to the CNS from the cardiopulmonary baroreceptors in relation to a given level of arterial baroreceptor activity. Changes in HP range probably occurred owing to CNS interactions between the various baroreceptor inputs leading to difference in the recruitment of "heart rate" motoneurons by a given change in MAP during derivation of the reflex function curves (Korner, 1979). Such CNS interactions probably also accounted for the reduction in the gain of the baroreflex during phenylephrine infusions.

A further corollary of rapid arterial baroreceptor and baroreflex resetting is the attenuation of longer term reflex effects evoked by prolonged changes in resting MAP. Thus, at no dose of nitroprusside was there a sustained sympathetically mediated rise in heart rate. The decrements of resting MAP produced by each dose were sufficient to produce additional rises in heart rate from each preceding resting level in the absence of resetting (Fig. 9). These results suggest that the arterial baroreceptor discharge pattern at each resting MAP produced by each dose was adequate to produce a larger rise in heart rate above control. At lower dosages of nitroprusside the additional steady state falls in MAP did not provide sufficient input to the CNS to elevate cardiac sympathetic efferent activity above control. In intact rabbits, the lowest dose of nitroprusside elicited a sustained rise in resting heart rate above control which was mediated through reduction in vagal efferent activity. We do not know whether vagal motoneurons have a different threshold to the input from the reset arterial baroreceptors than cardiac sympathetic motoneurons, or whether interactions involving other afferents contributed to the vagal efferent response. In any event, with increases in the dose of nitroprusside the additional steady state falls in resting MAP produced no further elevation of resting heart rate. At these doses, the signal from the reset baroreceptors were again inadequate to alter the activity of heart rate motoneurons, even though the same pressure changes could have produced additional rises in heart rate in the absence of resetting.

With phenylephrine, the lowest infusion rate also produced a smaller reduction in resting heart rate from control than expected in the absence of resetting. There was thus attenuation of the longer term reflex response, much as occurred with nitroprusside. At the higher dose, the rise in upper HP plateau above control was considerable, suggesting greater recruitment of vagal heart rate neurons during balloon inflation. As discussed earlier, there was presumably greater involvement of cardiopulmonary afferents due to a rise in central blood volume. The change in upper HP plateau was too great to allow meaningful assessment of the "expected" response of the resting heart rate.

Other Implications and Conclusions

Rapid resetting of the arterial baroreceptors by changes in resting blood pressure complicates interpretation of so-called CNS resetting of arterial baroreceptors. The latter refers to changes in baroreflex properties by the level of activity of other cardiovascular afferents as a result of interactions involving the CNS autonomic pathways (Korner, 1971, 1979, 1980; Korner et al., 1973; Heistad et al., 1974). The present data suggest that any sustained change in resting MAP will alter arterial baroreceptor threshold, whether the blood pressure change is due to peripheral circulatory factors as in the present experiments or whether it is mediated through CNS mechanisms. Hence, when there has been a sustained change in blood pressure, any alteration of threshold alone in the baroreflex curve cannot be interpreted as being due to CNS interactions. On the other hand, peripherally induced arterial baroreceptor resetting per se is unlikely to alter reflex gain or effector response range. When these parameters are acutely altered by a drug or disturbance, it is probable that the changes occur owing to various CNS interactions (Korner, 1979).

If the attenuation of the source signal due to rapid arterial baroreceptor resetting affected other sympathetic activity similarly to the cardiac sympathetic during nitroprusside infusions, it would seem impossible to maintain a sustained change in efferent sympathetic activity through the arterial baroreceptor input alone. Such a change could be maintained through CNS interactions between other afferents and the input from the arterial baroreceptors. In other conditions (e.g., sleep), the CNS itself may be the major source of a sustained change in autonomic activity. In conclusion, resetting of the arterial baroreceptor threshold occurs rapidly and reversibly whenever there is a sustained alteration in blood pressure. One consequence is that autonomic responses to transient (i.e., about 30 seconds or less) alteration in MAP about the new resting pressure remain relatively normal. A second consequence is that rapid resetting of the receptor limits the magnitude of the reflex responses evoked by changes in resting MAP over a period of about 15 min or longer. The arterial baroreceptors do not therefore provide the reflex with a fixed set point but with a variable or "floating" set point determined by the steady state level of the prevailing blood pressure.

References


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Dorward et al./Rapid Baroreceptor Resetting and Its Consequences

Arndt JO, Morgenstern J, Samodelov L (1971) The physiologically relevant information regarding systemic blood pressure encoded in the carotid sinus baroreceptor pattern. J Physiol (Lond) 268: 775-791


Korner PI (1965) The role of the arterial chemoreceptors and baroreceptors in the circulatory response to hypoxia of the rabbit. J Physiol (Lond) 180: 279–303


Rapid resetting of the aortic baroreceptors in the rabbit and its implications for short-term and longer term reflex control.

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