The Renal Sympathetic Baroreflex in the Rabbit
Arterial and Cardiac Baroreceptor Influences, Resetting, and Effect of Anesthesia

Patricia K. Dorward, Walter Riedel, Sandra L. Burke, Judith Gipps, and Paul I. Komer
From the Baker Medical Research Institute, Melbourne, Australia

SUMMARY. Curves relating renal sympathetic nerve activity and mean arterial pressure were derived in conscious rabbits during ramp changes in mean arterial pressure, elicited by perivascular balloon inflation. The renal sympathetic nerve activity-mean arterial pressure relationship consisted of a high-gain sigmoidal region about resting, where renal sympathetic nerve activity rose or fell in response to moderate falls and rises of mean arterial pressure. With larger pressure rises, renal sympathetic nerve activity first fell to a lower plateau and then reversed at even higher mean arterial pressure. When mean arterial pressure was lowered below resting, renal sympathetic nerve activity rose to an upper plateau and then reversed abruptly toward resting at low mean arterial pressure. Both arterial and cardiac baroreceptors exerted substantial inhibitory influences on renal sympathetic nerve activity at all pressure levels. These effects appeared additive over the central high gain region of the curve, but beyond this region there were non-additive interactions. The latter were affected considerably by alfathesin anesthesia. In other experiments, we studied the effects of sustained alterations in resting mean arterial pressure induced by infusing nitroprusside and phenylephrine, which produced rapid resetting of the renal baroreflex. The latter could be accounted for, in part, by resetting of the threshold of the arterial baroreceptors and in part by contributions from other afferents, probably the cardiac receptors. During resetting associated with nitroprusside-induced falls in resting blood pressure, high-gain reflex adjustments in renal sympathetic nerve activity to moderate changes in mean arterial pressure were preserved, but during resetting associated with phenylephrine-induced rises in resting mean arterial pressure, the resting renal sympathetic nerve activity lay on the lower curve plateau, resulting in reduction in the apparent gain of the reflex renal sympathetic nerve activity response to moderate changes in mean arterial pressure. (Circ Res 57: 618-633, 1985)

THERE has been much recent interest in the role of cardiopulmonary baroreceptor reflexes and their interrelationship with reflexes arising from the arterial baroreceptors (Oberg and White, 1970a, 1070b; Pelleitter et al., 1971; Komer et al., 1973; Mancia et al., 1973, 1975, 1976; Mark et al., 1973; Koike et al., 1975; Chen, 1978; Chen et al., 1978, 1979; Iriki et al., 1979; Guo et al., 1982; Thames et al., 1982; Abboud, 1982; Abboud and Thames, 1983; Ludbrook and Graham, 1984). These studies have shown that the magnitude of reflex effects on heart rate and sympathetic constrictor tone evoked from each of the above inputs is affected by the level of activity of the other receptor group.

However, there still is uncertainty about the role of the cardiopulmonary baroreceptors in the integrative autonomic adjustments in intact animals. Opinions differ as to whether they contribute to the reflex responses during relatively small intravascular pressure changes near resting levels, or whether they mainly affect the responses at very high blood pressures (Mancia et al., 1973, 1975, 1976, Guo et al., 1982). One factor that may have contributed to the uncertainty is that most studies have investigated only the role of afferents traveling in the vagus. The role of the sympathetic afferents has not been considered, although we now know that the cardiac receptors which give rise to these afferents become activated by moderate pressure changes and can mediate powerful reflex effects (Brown 1979; Thorén, 1979; Malliani, 1982). In addition, the vagal afferents eliminated by cervical vagotomy or cold block include not only those arising from baroreceptors in the heart and pulmonary vessels, but also those coming from a variety of receptors from the gastrointestinal tract and lung, some of which can influence autonomic activity [e.g., lung inflation receptors (Daly and Robinson, 1968)]. In circulatory disturbances, the role of these gastrointestinal and pulmonary afferents is of less interest than that of afferents arising from the heart and pulmonary vessels. Last, most previous analysis on the role of the cardiopulmonary afferents has been performed under anesthesia. Anesthetics often produce selective depression of central synapses, so that the autonomic responses to particular stimuli are distorted, compared with those of conscious animals (Komer et al., 1968; White and McRitchie, 1973; Zimpfer et al., 1974).

Our first objective in these experiments was to
characterize the renal sympathetic baroreflex and to examine the role of the cardiac and arterial baroreceptors in the reflex regulation of renal sympathetic nerve activity (RSNA) in conscious rabbits. We recorded RSNA during balloon-induced rises and falls of intravascular pressure, and derived mean arterial pressure (MAP)-RSNA function curves. We then compared the baroreflex responses before and after selective denervation of the cardiac and arterial baroreceptors. We used procaine instilled through a pericardial catheter to block reversibly cardiac afferents and efferents (Arndt et al., 1981; Dorward et al., 1983; Ludbrook and Graham, 1984) in rabbits with functioning arterial baroreceptors and again after sinoaortic denervation. Since most previous work has been performed in anesthetized animals, we investigated the extent to which this altered the various components of the renal sympathetic baroreflex by comparing the responses before and after alfathesin anesthesia in another group of rabbits. This agent was chosen because it is less depressant on autonomic function than other agents in common use (Timms, 1976; Blake and Korner, 1981).

Our second objective was to examine whether sustained changes in resting MAP altered the properties of the renal sympathetic baroreflex. Such changes have been shown to produce rapid resetting of the arterial baroreceptors (Coleridge et al., 1981, 1984; Kunze, 1981; Dorward et al., 1982; Munch et al., 1983). We produced graded alterations in resting MAP by continuous infusions of nitroprusside and phenylephrine, and derived function curves in the usual way at each level of resting blood pressure.

Methods

Operations and Procedures

We used 20 crossbred rabbits (between 2.0 and 3.0 kg) in which three preliminary operations were performed under halothane anesthesia after induction with propanidid (Epontol, Bayer) (Dorward et al., 1982). First, we implanted a Silastic perivascular balloon around the thoracic aorta through a left thoracotomy. One week later we performed a right thoracotomy for placing a balloon around the inferior vena cava. In some rabbits we inserted a Silastic catheter into the pericardial sac at this operation (Dorward et al., 1983) and stitched pacing electrodes to the left atrium at the left thoracotomy operation. The pacing electrodes were two lengths of Teflon-coated stainless steel wire, each folded in half, with the wire at the bend exposed and twisted to form a loop which was secured to the atrium with several stitches. The wire leads were protected by Silastic tubing, and the pericardium was stitched over the electrodes; the sutures were covered with a small piece of nylon fabric to promote fibrosis and to ensure against subsequent leakage of procaine from the pericardial sac.

At least 2 weeks later, we implanted the renal sympathetic nerve electrode. This consisted of two lengths of either multistrand platinum iridium wire (Medwire, Inc.) or single-strand stainless steel Teflon-coated wire (Gore, Inc.). The exposed ends were wound into short spirals, and the electrode was stitched to the renal artery to prevent movement between nerve and electrode (Fig. 1). The intact nerve was slipped into the bare wire spirals, taking great care to maintain its blood supply, and the entire preparation was embedded in a silicone gel (Silgel 604, Wacker Chemie, Munich) (Korner et al., 1980).

On day 7, after electrode implantation, we performed sinoaortic denervation (SAD) under halothane-propanidid anesthesia in the rabbits used for the afferent analysis (Chalmers et al., 1967a, 1967b, 1967c; Blombery and Korner, 1979). Recovery was rapid from this operation, with the animals eating and drinking within hours of its completion. At the time of the experiment, 24 hours after SAD, the animals appeared to be in good condition and were grooming themselves normally. Average weight loss over the 24 hours was 0.05 kg (range 0.02-0.08 kg). After SAD, balloon-induced changes in MAP of 20-30 mm Hg always elicited heart rate changes of <5 beats/min (Blombery and Korner, 1979) (see Results for RSNA changes). Both resting MAP and RSNA were more labile than in normal rabbits, with the former variable showing the characteristic fluctuations that we have previously observed in SAD rabbits studied about 7 and 14 days after denervation (Chalmers et al., 1967a; Blombery and Korner, 1979; Korner, Badoc, and Head, unpublished data). In normal rabbits with intact arterial baroreceptors, we did observe significant changes in some of the renal baroreflex curve parameters 24 hours after surgery, but they were relatively small (see Results). Ludbrook and Graham (1985) found that, in SAD rabbits, the MAP fell during exercise, instead of rising as in normal rabbits. The falls

FIGURE 1. Diagram showing electrode placed around the renal nerve, as explained in text.
were similar 1 hour, 1 day, and 7 days after denervation, despite some time-related changes in resting MAP (Ludbrook et al., 1985). We have therefore assumed that the RSNA responses to balloon inflation 24 hours after SAD represent responses that are characteristic of this preparation, and that they would not differ greatly over a similar time span.

Minor operative procedures were performed on the day of each experiment under local 0.5% lidocaine anesthesia. These involved cannulating the central ear artery and vein, and retrieving the tubing from the perivascular balloons and the leads from the renal nerve and pacing electrodes. Animals then rested in their boxes for at least 45–60 minutes before the start of control measurements (for protocols, see Results).

Pulsatile arterial pressure, MAP, heart rate, and integrated RSNA were recorded continuously during the experiment on a Grass model 7 polygraph; in some experiments we also measured right atrial pressure (RAP). The balloon-induced blood pressure changes and associated RSNA activity, together with the resting values over 60 seconds preceding inflation, also were recorded on magnetic analog tape (Hewlett-Packard, model 3968A FM tape recorder).

For pacing the heart, the pacing electrodes were connected to a Grass SD9 stimulator for stimulation at a pulsewidth of 1 msec and 7–10 V. In each rabbit, the heart was paced at a constant rate, which varied from 300–350 beats/min between rabbits, i.e., in the upper range of heart rate.

Renal Nerve Electrode
RSNA was recorded by a low noise differential amplifier, using a bandwidth of 50 Hz to 1 kHz. It was calibrated by passing a 10-µV, 1-kHz signal through the recording circuit at the beginning of each experiment. Amplified potentials were rectified and integrated over 1-second periods above an adjustable voltage level which excluded baseline noise. We set the integrator to give zero reading during the short silent periods seen between bursts of RSNA by viewing both raw and rectified signals on a storage oscilloscope. A rapid rise in arterial pressure produced by brief balloon occlusion of the aorta, or rapid release of the caval balloon after previous occlusion, both greatly extended the duration of the silent periods. However, in conscious rabbits, even these rapid MAP rises did not completely reduce RSNA to zero in all the accompanying 1-second integration cycles, although they did so under anesthesia. We used the minimum 1-second integrated RSNA value recorded during these rapid MAP changes as an estimate of noise level in each rabbit. This averaged 1.6 ± 0.28% of the upper plateau RSNA value obtained during the standard slow venous balloon-induced fall in MAP (see below, and Figs. 2 and 3).

We administered the ganglionic blocking drug trimetaphan camphorsulfonate to some conscious rabbits (see Drugs), which completely abolished RSNA over the entire range of MAP values tested, confirming the postganglionic nature of the discharge. After trimetaphan, noise level was 2.3 ± 0.25% of the upper plateau level, i.e., closely similar to the noise level obtained by the routine method.

In all rabbits, the pattern of resting RSNA in relation to the arterial pressure pulse, and the effects of balloon inflation were similar to those observed previously when recording efferent activity from the severed nerve in anesthetized rabbits (Iriki et al., 1977; Dorward and Korner, 1978). This, together with the results with trimetaphan, suggests that in the intact nerve we were recording predominantly efferent, rather than renal afferent, activity (e.g., Recordati et al., 1978).

MAP-RSNA Curves
Aortic balloon inflation raises MAP and pulse pressure, left ventricular pressure and RAP, and, presumably, other intracardiac and pulmonary circulatory pressures (Korner et al., 1972; Ludbrook, 1984). Similarly, inflating the venous balloon lowers all the above pressures. Korner et al. (1972) found that during square-wave changes in MAP, pulse pressure and RAP were highly correlated. Similarly, in the present experiments, aortic and venous balloon inflation produced corresponding changes in RAP, although the relationship was not linear (see Results, Fig. 2, lower). We have not previously observed any differences in RAP responses between normal, SAD, and autonomically denervated rabbits. Such differences have been reported in other experiments with balloon inflation (e.g., Recordati et al., 1978).

![Figure 2. Upper: MAP-RSNA curve from a conscious rabbit with all afferents intact. Data points are consecutive 1-second average values for MAP and integrated RSNA (µV) during aortic and venous pressure ramps. The large open circle is the common resting value, and the line shows the fitted logistic curve. The arrow on the left indicates RSNA at the lowest MAP during maximum venous balloon inflation, which was taken as the hypotensive value. The arrow on the right shows RSNA at the highest MAP during maximum aortic balloon inflation, which was taken as the hypertensive value. Lower: changes in RAP associated with changes in MAP during inflation of the aortic and venous balloons. The fine lines show results from individual rabbits; the circles give the average relationship obtained from five rabbits.](http://circres.ahajournals.org/content/57/4/620/F2.large.jpg)
cally blocked rabbits subjected to graded Valsalva-like maneuvers (Blombery and Korner, 1982). We have used the MAP changes as an index of the intravascular pressure changes accompanying balloon inflation. When studying the effects of different treatments on the MAP-RSNA relationship, we have always examined the parameter changes in the middle and both ends of the MAP range, which will encompass a wide spectrum of cardiac pressure changes. We obtained MAP-RSNA curves by slowly inflating each balloon, to produce ramp changes in MAP at the rate of 1–2 mm Hg/sec (Dorward et al., 1982). After deflation, MAP and RSNA returned to control levels in under a minute. Each response curve was derived from a pair of aortic and caval balloon inflations, 2 minutes apart. Pulsatile arterial pressure and integrated RSNA were digitized from the data previously recorded on magnetic tape, together with the resting values obtained over the preceding 30 seconds. We also recorded pressure and RSNA calibrations.

When the arterial baroreceptors were intact, both average MAP and integrated RSNA (μV/sec) were determined over 2-second intervals. MAP-RSNA data points were displayed graphically to specify the end of the resting period and to edit occasional outlying points during the pressure ramps (Fig. 2, upper). These sometimes occurred in association with small pressure reversals, or in conjunction with movements of the rabbit. We averaged the resting MAP and RSNA values for 30 seconds before each balloon inflation and expressed the data points during the pressure ramp as changes from these values. For each pair of aortic and venous balloon inflations, we averaged the individual resting value before each inflation and adjusted the data for each ramp to the average resting value by adding the difference between the actual and common resting values to each point of the ramp.

In rabbits with functioning arterial baroreceptors, we fitted a sigmoidal logistic function over the MAP range 55–110 mm Hg: RSNA decreased from a maximum value at the upper plateau to a minimum value at the lower plateau (Fig. 3, upper). We used a general nonlinear regression program to fit this part of the curve (Marquardt, 1963). The equation used was as follows:

\[ \text{RSNA} = P_1 + P_2/(1 + \exp[P_4(MAP - P_3)]) \]

where \( P_1 = \) lower plateau; \( P_2 = \) RSNA range between upper and lower plateaus; \( P_3 = \) MAP at half RSNA range; \( P_4 = \) a coefficient to calculate the average gain, \( G \), of the curve, which is given by \( G = - P_2 \times P_4/4.56 \), and equals the slope between the two inflection points of the curve. The upper plateau equaled \( P_1 + \) RSNA range. In addition, we defined two parameters at the extremes of the curve: (1) the hypotensive RSNA value at the lowest MAP attained with maximal caval balloon inflation, and (2) the hypertensive RSNA value at the highest MAP during maximum aortic balloon inflations (Figs. 2 and 3, upper).

In curves obtained after SAD, we used another averaging procedure, since RSNA points were more scattered at a given MAP than when the arterial baroreceptors were intact and the fit of a logistic function was unsatisfactory. The data were divided into 5 mm Hg MAP bins above and below resting MAP in each rabbit, and the average RSNA was determined for each bin. As before, resting MAP and RSNA were averaged for 30 seconds before each pressure ramp and the data for aortic and venous balloon inflation were adjusted to a common resting value.

![Graphical representation of MAP-RSNA curves](Image)

**Figure 3.** Upper: average curve in conscious rabbits with all afferents intact relating MAP (mm Hg) to RSNA (normalized units), showing the various parameters discussed in the text. Apart from the values shown, the hypotensive reversal response was the upper plateau minus the hypotensive value; the hypertensive reversal response was the hypertensive value minus the lower plateau. The dashed line is the noise level recorded during ganglionic blockade. Lower: average MAP-RSNA curves obtained in seven conscious rabbits with afferents intact at the animals' spontaneous heart rate and during left atrial pacing at constant heart rate.

Upper and lower plateaus were determined by inspection of the curves and the average gain by linear regression between inflection points. Hypertensive and hypotensive RSNA values were determined as in rabbits with intact arterial baroreceptors.

There was considerable variation between rabbits in the amplitude of the upper RSNA plateau values recorded on day 6 (range 3–35 μV/sec). This approximately 10-fold difference was considerably greater than the 1.3-fold difference observed in the upper heart rate plateau values (315–410 beats/min). Hence, the difference in RSNA plateau between animals was probably due in part to nonbiological factors, e.g., the position of the electrode in relation to the nerve. In addition, we also found evidence of time-related signal attenuation within rabbits (see Results). We therefore normalized the MAP-RSNA curve in each experiment in each rabbit, by expressing RSNA in terms of the upper plateau level of the rabbit's control curve which was taken to equal 100 normalized units (NU).
Baroreceptor-Heart Rate and Nasopharyngeal Reflexes

MAP-heart rate curves were derived in some experiments from the same blood pressure ramps used to obtain MAP-RSNA curves, using the same iterative logistic program. The parameters defined included the upper and lower heart rate plateaus, the heart rate response range between plateaus, the average gain, and BP50 (Korner et al., 1972). We also looked for hypertensive and hypotensive heart rate responses, corresponding to analogous parameters of the renal sympathetic baroreflex.

The nasopharyngeal reflex was evoked while the rabbit rested quietly in its box. After resting MAP, RSNA, and heart rate were recorded, a puff of cigarette smoke was blown close to its nose through a fine plastic catheter over a period of 1-2 seconds, which is a strong stimulus for this reflex; recording continued for another 40-60 seconds (White and McRitchie, 1973; McRitchie and White, 1974). The integrator was set at 1 second and the nasopharyngeal response was taken as the average RSNA change from resting over the 6 seconds of maximum activity.

Blockade of Cardiac Nerves with Procaine

We instilled 5% procaine intrapericardially to block both efferent and afferent cardiac nerves, using an initial dose of 0.4 ml, followed by booster injections of 0.1-0.2 ml at 7-minute intervals (Dorward et al., 1983). We used brief aortic balloon inflation to test the blockade of cardiac efferents by checking that the reflex reduction in heart rate was abolished. In addition, after SAD procaine blocked the reflex reduction in RSNA with large elevations of MAP, in agreement with previous findings (Dorward et al., 1983; Ludbrook and Graham, 1984). Arndt et al. (1981) and Samodelov et al. (1982) have recorded both efferent and afferent activity from cardiac vagus and sympathetic nerves and showed that the same concentrations of procaine blocked both kinds of activity.

Nitroprusside and Phenytoinrine

Sodium nitroprusside was administered by intravenous infusion in doses of 0 (5% dextrose), 2.5, 5, and 10 µg/kg per min, each lasting 0.5 hour. The order of administration of the different doses was in accordance with a Latin squares experimental design, to eliminate bias (Snedecor and Cochran, 1980). Reflex measurements began 15 minutes after the start of each dose, when resting MAP, RSNA, and heart rate were recorded. After 7-10 minutes, we observed no differences in MAP-RSNA curves similar in doses of 0, 1, 2, and 4 µg/kg per min.

Trimetaphan Camphorsulfonate

This ganglionic blocking agent was administered at a rate of 0.5-1.0 µg/kg/min iv, in conjunction with 0.5-1.0 µg/kg per min nopepinephrine to maintain blood pressure close to the previous resting value.

Alfathesin Anesthesia

The rabbits were anesthetized with Alfathesin (Glaxo, Australia) (0.24 mg/kg per min) and were paralyzed with succinyl choline (initial dose, 50 mg, followed by 6 mg after 7-10 minutes) and artificially ventilated with oxygen-enriched air at a respiratory minute volume of 0.8-1.0 liter/min. This maintained arterial PCO2 at 29.7 ± 0.8 mm Hg and P02 at 98.9 ± 5.2 mm Hg, i.e., in the range of normal rabbits. We used a combination of anesthesia, paralysis, and artificial ventilation to simulate conditions used in most previous studies on arterial-cardiopulmonary interrelationships.

Statistical Analysis

Significant differences in curve parameters during treatment and recovery periods were assessed by two- or three-way analysis of variance (ANOVA) (Snedecor and Cochran, 1980). Linear regression was used to determine gain and BP50 of the MAP-RSNA curves after SAD. In some comparisons between mean parameter values, we used the f-statistic modified according to the Bonferroni procedure, to assess significance (Wallenstein et al., 1980).

Results

We performed one series of experiments in which the MAP-RSNA and MAP-heart rate relationships and the nasopharyngeal RSNA response were determined on days 1, 6, and 8 after electrode implantation. All other experiments were performed on day 6 to day 8 after the electrode was implanted.

MAP-RSNA Relationship in Normal Rabbits

In conscious rabbits studied on days 6-8 after electrode implantation, a small rise in MAP during aortic balloon inflation was sufficient to lower RSNA from the resting value to the lower plateau (Figs. 2 and 3, upper). The latter ranged from 6-12 NU (i.e. 6-12 percent of the upper plateau of the control curve) in different groups, which was significantly above the noise level of about 1-2 NU (P for significance of difference <0.025). The significant elevation above noise level of the conscious rabbit's lower RSNA plateau was characterized by the slow ramp rises in MAP used in our experiments. As seen in Figure 2, the lower plateau in a given animal was maintained over about 10 seconds of gradual balloon inflation. The differences in individual RSNA values making up the lower plateau were due to differences in the duration of the silent periods occurring within each 1-second integration cycle (see Methods: Renal Nerve Electrode). The lower plateau was maintained over the range of MAP between 85 and 105 mm Hg and then increased to the hypertensive value (Fig. 3). With falls in MAP due to venous balloon inflation, RSNA increased to the upper plateau, which was well maintained between MAP of about 65 and 50 mm Hg and was followed by an abrupt fall to the hypertensive RSNA value (Fig. 3). RAP had already fallen to its minimum value by the time the upper RSNA plateau had been reached (Fig. 2). It remained close to the minimum with further reduction in MAP, and then returned toward resting in conjunction with the hypertensive reversal response (Fig. 2). We observed no differences in MAP-RSNA curves in seven rabbits obtained during spontaneous reflex heart rate changes, and during pacing at constant heart rate (Fig. 3, lower). The MAP-RSNA relationship of normal rabbits thus included (1) a sigmoid component between
upper and lower plateaus with a central high-gain portion, (2) the hypotensive reversal response observed during large falls in blood pressure, and (3) a smaller hypertensive reversal response evoked by large rises in pressure.

The relationship between MAP and heart rate was also sigmoid (Fig. 4C). During aortic balloon inflation, heart rate fell to a lower (bradycardia) plateau until MAP exceeded about 110 mm Hg, when there was diminution of bradycardia, analogous to the hypertensive RSNA reversal response. However, during pressure reduction produced by venous balloon inflation, the upper tachycardia plateau was well maintained, and there was no heart rate change corresponding to the hypotensive RSNA reversal response.

**Time-Related Effects**

There were no significant differences in curve parameters between duplicates obtained during the control, treatment, and recovery periods. Reproducibility was good; for example, the standard error between duplicates of the upper RSNA plateau averaged 6% of the mean value (100 NU). The preparation also remained stable over a 3-hour period, as assessed by comparing the control curves with the recovery curves obtained about 2 hours after procaine (Fig. 5; Table 1). We observed complete recovery in RSNA range, upper and lower plateau levels, gain, and in the hypertensive reversal response. However, BF50 and the sigmoid component of the recovery curve were shifted to a lower MAP range, about 5 mm Hg below control, in parallel with the change in resting MAP (see Resetting). In addition, there was some attenuation of the hypotensive reversal response during the recovery period, which averaged 70% of the control value ($P < 0.05$).

We examined longer term time-related effects in another series of five normal rabbits, in which measurements were obtained on days 1, 6, and 8 after implanting the electrode. There was progressive attenuation of the absolute magnitude of the signal, which affected all components of the curve (Figs. 4A and 6). The relative sizes of the upper RSNA plateau over the three experimental days averaged 2.3:1:0.6, and corresponding values for the lower plateau and RSNA range were similar (Fig. 6). The absolute rate of signal attenuation expressed in terms of the day 6 upper plateau averaged 1 NU/hr over the entire period of these experiments.

We also determined the magnitude of the nasopharyngeal RSNA reflex in these animals over the same period (Fig. 6). With this reflex, the rise in RSNA was maximal about 4–8 seconds after smoke stimulation and returned to resting after 30–60 seconds; it was not associated with signs of distress or discomfort. The same smoke stimulus has previously been shown to produce complete cessation of renal blood flow (White et al., 1973; McRitchie and White, 1974). On each day, the nasopharyngeal RSNA response was about double the upper RSNA plateau (Fig. 6). The relative magnitude of the nasopharyngeal RSNA responses on days 1, 6, and 8 were, respectively, 1.95:1:0.52, which was closely similar to that observed with the upper plateau of the renal baroreflex.

After each MAP-RSNA curve was normalized in terms of its upper plateau (= 100 NU see Methods), the differences between the normalized curves obtained on the three experimental days were rela-
Figure 5. Upper: average MAP-RSNA curves obtained from seven conscious rabbits during the initial control period (time 1) and after recovery (time 2) from intrapericardial procaine, approximately 2.5 hours later, obtained on day 6 after electrode implantation when the arterial baroreceptors were intact. Lower: control and recovery curves in the same rabbits in experiment on day 8, after arterial baroreceptor denervation.

Figure 6. Average nasopharyngeal RSNA responses and the upper and lower plateau values obtained in five conscious rabbits on days 1, 6, and 8 after electrode implantation. Results are expressed as a percentage of the upper plateau on day 6. The bar on the day 6 value of each variable is ± 1 SEM based on the within-animal variance as determined by ANOVA.

assumed that it was due to physical rather than biological factors in view of (1) the restoration of the neural signal in two rabbits with no recordable RSNA on day 6, by removal of excess fluid around the electrode gel-complex after exposing the electrode under anesthesia; (2) the small differences in properties of the normalized MAP-RSNA curves, which paralleled the absence of differences in MAP-heart rate curves (Fig. 4, B and C); (3) the similarity of postoperative changes in normalized resting RSNA and resting heart rate (Fig. 4, B and C). Our findings show that the signal attenuation can be neglected in experiments lasting 2–3 hours, but that it must be allowed for in longer experiments.

Role of Arterial and Cardiac Baroreceptors

We performed two experiments in seven rabbits on days 6 and 8 after electrode implantation. On day 6, the arterial baroreceptors were intact, and we examined the effects of blocking the cardiac nerves with procaine. On day 8, we again studied the effects of blockade of the cardiac nerves in the same rabbits, one day after SAD. We have assumed that the average rate of electrode signal attenuation between days 6 and 8 was similar in these rabbits to that observed in the parallel series in Figures 4 and 6.
Procaine lowered resting heart rate from 268 beats/min (control) to 252 beats/min (SED 7 beats/min; \( P = 0.05 \)). However, pacing made no difference to the MAP-RSNA relationship during control and treatment periods so that we have pooled the results obtained at the rabbits’ spontaneous heart rate and during pacing for assessing the effect of treatment.

After blocking the cardiac nerves, RSNA was significantly above control at resting RSNA and during balloon-induced falls in MAP (Fig. 7, curves ac and a; Table 1). The greatest difference between curves ac and a was at the hypotensive RSNA value (69 NU), followed by the difference at the upper plateaus (28 NU) and the difference at resting RSNA (9.1 NU); \( P < 0.001 \) for all differences). By contrast, during rises in blood pressure above resting, the differences between the curves were small and not statistically significant (Fig. 7). After procaine, there were no significant changes in gain and BP_{50} (Table 1).

Guo et al. (1982) have observed large rises in MAP and in vascular resistance immediately after cutting the vagi, with considerable attenuation of these responses by about 10–15 minutes after vagotomy. We obtained four MAP-RSNA curves between 3 and 45 minutes after giving procaine. There were no significant changes over this period either in resting MAP or in resting RSNA. However, in the first curve, the elevation of the upper plateau was less marked than in the other three (Fig. 8). This suggests that the action of procaine was gradual at onset, with maximum blockade of cardiac nerves attained at about 5–10 minutes after starting the drug.

Thus, in the presence of the arterial baroreceptors, the cardiac baroreceptors had an inhibitory effect on RSNA during venous balloon inflation. This inhibition increased progressively with increasing falls in MAP and became maximal at the hypotensive reversal response (Fig. 7, cf. differences between curves ac and a).

**Sinoaortic Denervation**

Normalization of the curves was performed, as usual, on the upper plateau of the control curve after SAD, when the cardiac receptors were still functioning (Fig. 7, curve c). When the absolute value of the plateau was expressed in \( \mu \text{V/sec} \), it averaged 52 ± 3.7% of the day 6 value in the same rabbits, which was similar to the signal attenuation between days 6 and 8 in the parallel group of sham-operated rabbits (Figs. 4 and 6). If we assume a similar rate of signal attenuation in both groups of rabbits, then the absolute level of upper plateau after SAD would correspond approximately to the upper plateau in the intact rabbit after maximum unloading of the arterial baroreceptors when all afferents were intact, i.e., 100 NU in each experiment can be considered approximately equivalent.

The pattern of RSNA responses after SAD (but with cardiac receptors intact) was profoundly altered (Fig. 7, curve c). Resting RSNA now was on the upper plateau and showed no further increase with falls in MAP to about 40–50 mm Hg. There still was a significant hypotensive reversal response of 19.1 ± 6.8 NU (\( P < 0.05 \)) which was about one-third of that observed before SAD (Table 1). With aortic balloon inflation, elevation of MAP above resting produced no alteration in RSNA until MAP of about 90 mm Hg. However, with greater pressure rises, RSNA decreased gradually to a somewhat ill-defined lower plateau of about 50–60 NU, before rising to the hypertensive value at MAP > about 120 mm Hg. The resulting reversal response was about three
### TABLE 1
Parameters and Resting Values* in Seven Conscious Rabbits before and after Sinoaoitic Denervation

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>P</th>
<th>R</th>
<th>SED</th>
<th>C</th>
<th>P</th>
<th>R</th>
<th>SED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotensive value (NU)</td>
<td>43.8 ± 8.4</td>
<td>109.7 ± 9.4</td>
<td>65.4 ± 8.4</td>
<td>± 8.4</td>
<td>80.9 ± 139.7</td>
<td>104.2 ± 23.5</td>
<td>92.7 ± 19.1</td>
<td>± 19.1</td>
</tr>
<tr>
<td>Upper plateau (NU)</td>
<td>101.0 ± 10.0</td>
<td>128.0 ± 10.0</td>
<td>104.1 ± 8.6</td>
<td>± 8.6</td>
<td>100.0 ± 151.6</td>
<td>104.2 ± 23.5</td>
<td>104.2 ± 23.5</td>
<td>± 23.5</td>
</tr>
<tr>
<td>Resting RSNA (NU)</td>
<td>32.8 ± 6.4</td>
<td>41.9 ± 6.4</td>
<td>36.4 ± 6.4</td>
<td>± 2.2</td>
<td>98.0 ± 122.6</td>
<td>89.3 ± 8.7</td>
<td>89.3 ± 8.7</td>
<td>± 8.7</td>
</tr>
<tr>
<td>Lower plateau (NU)</td>
<td>11.1 ± 1.2</td>
<td>12.8 ± 1.2</td>
<td>12.1 ± 1.6</td>
<td>± 1.6</td>
<td>53.5 ± 103.4</td>
<td>57.0 ± 10.6</td>
<td>57.0 ± 10.6</td>
<td>± 10.6</td>
</tr>
<tr>
<td>Hypertensive value (NU)</td>
<td>25.6 ± 6.0</td>
<td>31.8 ± 6.0</td>
<td>27.2 ± 6.0</td>
<td>± 6.0</td>
<td>97.3 ± 211.0</td>
<td>126.1 ± 25.6</td>
<td>126.1 ± 25.6</td>
<td>± 25.6</td>
</tr>
<tr>
<td>RSNA range (NU)</td>
<td>90.0 ± 115.2</td>
<td>92.5 ± 5.6</td>
<td>± 5.6</td>
<td>± 5.6</td>
<td>46.5 ± 48.0</td>
<td>47.2 ± 23.0</td>
<td>47.2 ± 23.0</td>
<td>± 23.0</td>
</tr>
<tr>
<td>Average gain (NU/mm Hg)</td>
<td>-5.7 ± 6.2</td>
<td>-5.1 ± 6.2</td>
<td>-5.1 ± 6.0</td>
<td>± 0.6</td>
<td>-1.7 ± 1.5</td>
<td>-1.1 ± 0.4</td>
<td>-1.1 ± 0.4</td>
<td>± 0.4</td>
</tr>
<tr>
<td>BP₅₀ (mm Hg)</td>
<td>76.0 ± 77.0</td>
<td>72.0 ± 7.0</td>
<td>72.6 ± 1.5</td>
<td>± 1.5</td>
<td>101.7 ± 77.1</td>
<td>88.4 ± 6.3</td>
<td>88.4 ± 6.3</td>
<td>± 6.3</td>
</tr>
<tr>
<td>Resting MAP (mm Hg)</td>
<td>86.0 ± 81.3</td>
<td>76.2 ± 1.3</td>
<td>76.7 ± 1.3</td>
<td>± 1.3</td>
<td>78.0 ± 70.7</td>
<td>76.6 ± 1.6</td>
<td>76.6 ± 1.6</td>
<td>± 1.6</td>
</tr>
<tr>
<td>Hypotensive reversal (NU)</td>
<td>57.3 ± 18.9</td>
<td>38.7 ± 18.9</td>
<td>± 8.6</td>
<td>± 8.6</td>
<td>19.1 ± 11.9</td>
<td>11.3 ± 11.6</td>
<td>11.3 ± 11.6</td>
<td>± 11.6</td>
</tr>
<tr>
<td>Hypertensive reversal (NU)</td>
<td>14.5 ± 19.0</td>
<td>15.6 ± 15.6</td>
<td>± 5.9</td>
<td>± 5.9</td>
<td>43.8 ± 107.6</td>
<td>69.1 ± 21.1</td>
<td>69.1 ± 21.1</td>
<td>± 21.1</td>
</tr>
</tbody>
</table>

* During control (C), intrapericardial procaine (cardiac nerve block) (P), and recovery (R) periods. Results in each rabbit based on quadruplicate determination; RSNA values normalized on each experimental day as explained in text.

† P for difference from control < 0.05; SED = standard error of difference within rabbits based on ANOVA.

#### Discussion

The gain of the RSNA response over the pressure-sensitive part of the curve was about one-fifth of that in normal rabbits and the BP₅₀ (102 mm Hg) was significantly increased (Table 1). In this preparation, the pressure-related inhibition of RSNA occurred over a higher range of blood pressures than in normal rabbits. After procaine, resting heart rate fell from the control value of 289 beats/min to 230 beats/min (SED 8 beats/min; P < 0.001). Pacing again did not alter the MAP-RSNA relationship, and we have pooled the data at the rabbits' spontaneous and paced heart rates for assessing the effects of procaine.

After cardiac nerve block, resting RSNA was close to the middle of the pressure-sensitive RSNA range. The latter was about half that of rabbits with functioning arterial baroreceptors. With venous balloon inflation, a small rise in RSNA to an upper plateau was evoked by falls in MAP. However, the hypertensive reversal response of 11.9 ± 12.6 NU was no longer statistically significant. After procaine, RSNA was significantly higher in curve o than in curve c during falls in MAP, with differences greatest at low blood pressures and least at MAP 80–90 mm Hg (Fig. 7). Thus, the cardiac baroreceptors had an inhibitory effect on RSNA, which was similar in the presence or absence of the arterial baroreceptors (Fig. 7, see differences between curves ac and a, and between curves c and o).

With rises in MAP produced by aortic balloon inflation, RSNA declined to an ill-defined plateau (Fig. 7, curve o). The most striking feature of curve o was the magnitude of the hypertensive value (211 NU), which was about double the upper plateau (Fig. 7, lower). Hence, the reversal response was twice the value observed in these rabbits when the...
cardiac receptors alone were functioning (Fig. 7; Table 1). During rises in MAP > 90 mm Hg the difference between curves o and c again increased progressively. This suggests a marked inhibitory effect from the cardiac receptors during elevation in blood pressure over an MAP range encompassed by the lower plateau and hypertensive value in normal rabbits.

Alfathesin Anesthesia

This was studied in five rabbits in which control measurements were obtained without anesthesia. The rabbits then received alfathesin plus succinyl choline and artificial ventilation, but were not subjected to surgery. During anesthesia, the resting MAP fell by 7.9 ± 2.9 mm Hg (P < 0.025); resting RSNA increased significantly from a value of 17.6 NU before anesthesia to 28.1 NU during anesthesia (SED 1.2; P < 0.001).

The MAP-RSNA relationship was shifted during anesthesia in the direction of lower resting MAP (see Resetting) but there were no significant changes in upper plateau, RSNA range, or gain (Fig. 9). During aortic balloon inflation, the lower plateau fell to noise level, from 6.7 NU before anesthesia to 0.8 NU during anesthesia (SED 1.0; P < 0.01). The most striking change was the marked attenuation of the hypotensive reversal response, which equaled 50.5 NU before anesthesia and was only 8.5 NU during anesthesia (P < 0.001).

The effects of alfathesin anesthesia on the baroreceptor-heart rate reflex were much greater than on the renal baroreflex (Fig. 9). The upper plateau was depressed by about 30 beats/min, while the lower plateau was raised by 97 beats/min (P < 0.001) from the value observed before anesthesia (Fig. 9). Gain and heart rate response range were both reduced to about one-third the value before anesthesia, and resting heart rate was significantly increased.

Baroreflex Resetting Associated with Changes in Resting MAP

Changes in resting MAP were induced by infusing vasoactive drugs in two experiments to alter the threshold of the arterial baroreceptors as described by Dorward et al. (1982). In eight rabbits, we studied the changes produced by nitroprusside-induced falls in MAP. In five of these animals, the effects of phenylephrine-induced rises in MAP were studied in another experiment. With each dose of drug, the new level resting MAP was reached within 7–10 minutes from the start of infusion, so that determination of renal baroreflex properties starting at 15 minutes was within the time previously shown to produce stable resetting of the baroreceptors (Dorward et al., 1982).

Nitroprusside Infusions

Nitroprusside was given in doses of 0, 2.5, 5, and 10 µg/kg per min (see Methods) and produced an almost parallel resetting of the renal baroreflex function curves (Fig. 10). The falls in BP50 were linearly related to the falls in resting MAP with the regression coefficient 0.74 ± 0.042 mm Hg/mm Hg Δ resting MAP (P < 0.001). There were no significant changes from control in upper and lower plateaus, in RSNA range, and in the hypertensive reversal response (Fig. 10; Table 2). However, the hypotensive reversal response was significantly reduced at the two highest doses of nitroprusside (P < 0.05).

The sustained dose-related falls in resting MAP, were associated with small increases in resting RSNA (P < 0.01, Table 2). The rises in resting RSNA were significantly less than would have occurred if the MAP-RSNA relationship had remained in the control location.

Phenylephrine Infusions

Phenylephrine was given in doses of 0, 1, 2, and 4 µg/kg per min (see Methods) and induced dose-related rises in resting MAP, with associated reduction of resting RSNA (P < 0.01, Table 2). Over the entire dose range, the lower RSNA plateau was depressed progressively from 11.7 NU (control) to 5.6 NU at the highest dose (SED = 2.2 NU; P < 0.01). At the highest dose, the hypertensive value was indistinguishable from the lower plateau, so that the reversal response was absent.
Only at the two lowest doses was there parallel resetting of curves (Fig. 11). With those doses, the upper plateaus and RSNA ranges were enhanced compared with control (Table 3). In addition, BP_50 increased by 0.51 ± 0.10 mm Hg/mm Hg Δ resting MAP (Fig. 11, lower), which was significantly less than corresponding changes observed with nitroprusside (P < 0.025). Furthermore, at the highest dose of phenylephrine, the MAP-RSNA relation had returned to the control location (Fig. 11).

**Discussion**

The renal nerve electrode permitted recording of neural activity over a longer period and in a greater proportion of animals than with previous implanted

---

**Table 2**

<table>
<thead>
<tr>
<th>Parameters and Resting Values Obtained with Different Doses of Nitroprusside in Eight Conscious Rabbits</th>
<th>0</th>
<th>2.5</th>
<th>5.0</th>
<th>10.0</th>
<th>SED</th>
<th>F-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Hypotensive value (NU)</td>
<td>50.0</td>
<td>43.5</td>
<td>52.8</td>
<td>64.0</td>
<td>±6.0</td>
<td>7.4*</td>
</tr>
<tr>
<td>Upper plateau (NU)</td>
<td>100.0</td>
<td>105.6</td>
<td>96.2</td>
<td>94.7</td>
<td>±6.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Resting RSNA (NU)</td>
<td>20.0</td>
<td>34.6</td>
<td>34.9</td>
<td>40.0</td>
<td>±2.6</td>
<td>52.3*</td>
</tr>
<tr>
<td>Lower plateau (NU)</td>
<td>11.3</td>
<td>14.0</td>
<td>7.7</td>
<td>9.8</td>
<td>±2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Hypertensive value (NU)</td>
<td>26.9</td>
<td>32.0</td>
<td>21.1</td>
<td>19.3</td>
<td>±5.4</td>
<td>3.9</td>
</tr>
<tr>
<td>RSNA range (NU)</td>
<td>88.7</td>
<td>91.6</td>
<td>88.5</td>
<td>84.9</td>
<td>±6.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Average gain (NU/mm Hg)</td>
<td>−7.4</td>
<td>−7.0</td>
<td>−6.3</td>
<td>−11.1</td>
<td>±1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>BP_50 (mm Hg)</td>
<td>79.7</td>
<td>74.5</td>
<td>73.2</td>
<td>72.2</td>
<td>±1.4</td>
<td>27.4*</td>
</tr>
<tr>
<td>Resting MAP (mm Hg)</td>
<td>85.5</td>
<td>78.6</td>
<td>75.7</td>
<td>73.6</td>
<td>±1.1</td>
<td>106.9*</td>
</tr>
<tr>
<td>Hypotensive reversal</td>
<td>50.0</td>
<td>62.1</td>
<td>43.4</td>
<td>29.4</td>
<td>±7.6</td>
<td>11.3*</td>
</tr>
<tr>
<td>Hypertensive reversal</td>
<td>15.6</td>
<td>17.9</td>
<td>13.4</td>
<td>9.4</td>
<td>±5.0</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Doses are infusion rates of nitroprusside (μg/kg per min). F-values given are for linear comparisons between doses (column A) and for comparisons of averages of first two and last two doses (column B).

* P < 0.05.
TABLE 3
Parameters and Resting Values Obtained with Different Doses of Phenylephrine in Five Conscious Rabbits

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose</th>
<th>F-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypotensive value (NU)</td>
<td>60.1</td>
<td>96.0</td>
</tr>
<tr>
<td>Upper plateau (NU)</td>
<td>100.0</td>
<td>132.6</td>
</tr>
<tr>
<td>Resting RSNA (NU)</td>
<td>26.0</td>
<td>18.1</td>
</tr>
<tr>
<td>Lower plateau (NU)</td>
<td>11.7</td>
<td>9.7</td>
</tr>
<tr>
<td>Hypertensive value (NU)</td>
<td>20.4</td>
<td>7.0</td>
</tr>
<tr>
<td>RSNA range (NU)</td>
<td>88.3</td>
<td>122.9</td>
</tr>
<tr>
<td>Average gain (NU/mm Hg)</td>
<td>8.4</td>
<td>-8.1</td>
</tr>
<tr>
<td>BP∞ (mm Hg)</td>
<td>73.9</td>
<td>77.8</td>
</tr>
<tr>
<td>Resting MAP (mm Hg)</td>
<td>77.5</td>
<td>85.0</td>
</tr>
<tr>
<td>Hypotensive reversal (NU)</td>
<td>39.7</td>
<td>36.7</td>
</tr>
<tr>
<td>Hypertensive reversal</td>
<td>8.8</td>
<td>-2.7</td>
</tr>
</tbody>
</table>

Doses are infusion rates of phenylephrine (μg/kg per min). F-values given are for linear comparisons between doses (column A), and for comparisons of average of middle two dose with that of first and final doses (column C).

*P < 0.05.

electrodes (Schad and Seller, 1975; Lewis and Haeusler, 1975; Ninomiya et al., 1976; Riedel et al., 1982; Iriki and Kozawa, 1983). Thus, the main experiments could be performed after full recovery from the operation for implanting the electrode. Renal nerve recording in the conscious animal is free of the inertia associated with measurement of vascular resistance and of the many local factors (e.g., the renin-angiotensin system) that can affect the latter variable. We used perivascular balloons to produce slow changes in MAP from the resting value, so that our findings concerning the renal baroreflex would be relevant to steady state conditions.

Our findings suggest that in normal rabbits the arterial and cardiac baroreceptors exerted inhibitory effects on virtually every component of the renal sympathetic baroreflex. In our analysis, the role of the cardiac baroreceptors was assessed from the responses obtained over a period of 45 minutes after procaine, while that of the arterial baroreceptors was assessed from the difference in pattern before and 24 hours after SAD. Ludbrook and Graham (1984) have shown that the rabbit's cardiovascular response to exercise is altered within minutes after SAD, and that this altered response subsequently remains constant over the next 7 days. This makes it unlikely that the difference in the times of measurements will alter our conclusions about the contribution of the two sets of baroreceptors on the RSNA responses of normal rabbits. Intrapericardial procaine produced rapid effects on the reflex (Fig. 8), most of which had reversed 2 hours after stopping the drug. This method of blocking the cardiac nerves was not associated with the large, transient constrictor effects that have been reported in anesthetized rabbits after cervical vagotomy (Guo et al., 1982). Intrapericardial local anesthesia has the advantage that it eliminates not only vagal but also cardiac sympathetic afferents, and that it avoids removal of afferents from lung inflation receptors which will affect constrictor tone (Daly and Robinson, 1968).

The inhibitory effects of the arterial baroreceptors on the sigmoid component of the baroreflex, including resting RSNA, lower plateau, and gain, were greater than those of the cardiac receptors. During venous balloon-induced falls in blood pressure below resting, the inhibition of RSNA mediated through the cardiac receptors increased progressively, whereas that mediated through the arterial baroreceptors decreased. The magnitude of the inhibition mediated through the cardiac receptors was independent of the presence or absence of the arterial baroreceptors (Fig. 7). In the normal rabbit, the inhibitory action of the cardiac receptors limits the magnitude of the upper RSNA plateau during unloading of the arterial baroreceptors.

During aortic balloon-induced rises in blood pressure, cardiac receptor influences could not be demonstrated when the arterial baroreceptors were intact. However, an inhibitory effect became obvious after SAD, where it was apparent at relatively high pressure levels (Fig. 7, curves c and o). This suggests that the cardiac receptors also provide inhibitory drive to the lower plateau in normal rabbits. Their inhibitory effect and that mediated through the arterial baroreceptors is not one of simple summation, but is a nonadditive interaction affecting common sympathetic neurons, similar to the occlusion responses described by Sherrington (1906) in his analysis of spinal reflexes.

In conscious rabbits, the lower plateau always remained above noise level even when resting MAP was substantially raised with phenylephrine (Table 3), although, under these conditions, it was reduced from the level observed in the normal resting state. We have not analyzed the sources of afferent drive...
involved in the greater reduction of the lower plateau with phentolamine, but the pronounced inhibitory drive from cardiac receptors at these higher blood pressures could account for the effect (cf. Fig. 7, difference between curves c and o). Only during anesthesia was it easy to reduce the lower plateau to noise level by raising the blood pressure above resting. In the conscious animal, a small component of the renal sympathetic motoneuron pool appears resistant to inhibition by pressure rises, particularly to rises in arterial pressure. Alphathesin anesthesia eliminates the sources of excitation to this part of the pool, so that rises in blood pressure abolish RSNA.

The renal hypotensive reversal response has not, to our knowledge, been described previously in animals with intact afferents (Irisawa et al., 1973; Ninomiya et al., 1973; Iriki et al., 1977; Dorward and Korner, 1978; Iriki and Kozawa, 1983). Probably this is due to the susceptibility to anesthesia of this component of the renal baroreflex. Our findings indicate that the large hypotensive reversal response, characteristic of conscious rabbits, depends on afferents traveling in both sinoaortic and cardiac nerves, and that removal of both sets of nerves abolished the response. When the cardiac nerves alone are intact, the small residual reversal response can be explained by the progressive increase in inhibition of RSNA mediated through the cardiac receptors, which eventually produces depression of the upper plateau. When the sinoaortic nerves alone are intact, a residual hypotensive reversal response is more difficult to explain. Incomplete blockade with procaine appears unlikely, since combined SAD + procaine completely abolished this component of the reflex. A paradoxical increase in firing of the arterial baroreceptors produced by distortion of the collapsing carotid sinus has been described at about the same MAP values as observed in the reversal response (Landgren, 1952; Green, 1967). An alternative explanation of the residual reversal response after blockade of the cardiac nerves could be through interactions between arterial chemoreceptors and baroreceptors, or between arterial and pulmonary baroreceptors (Paintal, 1973), resulting in attenuation of the excitation of RSNA produced by full unloading of the arterial baroreceptors. In the intact rabbit, the hypotensive reversal response thus results from non-additive facilitatory interactions resulting from changes in activity of between two to four sets of afferents. We may speculate that the turning-off of sympathetic constrictor tone during the hypotensive reversal response can be considered a last resort mechanism to abolish reflex vasoconstriction. This will help limit the extent of the fall in cardiac output when this becomes marked, which occurs with venous balloon inflation (Korner, unpublished data).

It is not surprising that the most complex components of the baroreflex are almost completely eliminated by anesthesia. The level of alphathesin used in our experiments was adequate for surgical anesthesia and deeper than in our previous study (Blake and Korner, 1981). This explains the marked depression of the vagal and sympathetic components of the baroreceptor-heart rate reflex. Indeed, the marked depression of the sigmoid component of the baroreceptor-heart rate reflex contrasts with the relatively minor effects on this component of the renal sympathetic baroreflex, emphasizing the selective nature of the central depression of particular anesthetics.

In normal rabbits, the hypertensive RSNA reversal response was smaller than the hypotensive reversal and was associated with reduction in reflex bradycardia. Both the arterial and cardiac receptors exerted a substantial inhibitory effect on the hypertensive reversal response, with that through the arterial baroreceptors larger than that mediated through the cardiac receptors. However, the inhibition through the latter afferents was substantial (Fig. 7, curves c and o); its enhancement during phenylephrine infusions could account for the abolition of the response under these circumstances. The huge reversal response evoked after removing both arterial and cardiac baroreceptor influences was twice the normal upper plateau level. This was similar to the RSNA response evoked by nasopharyngeal stimulation, which would have reduced renal blood flow to nearly zero.

Guo et al. (1982) have described an analogous reflex response in hindlimb vascular resistance of anesthetized SAD rabbits, produced by large elevations of systemic blood pressure. However, this was not observed in animals with afferents intact. In contrast to our findings in conscious rabbits, the "hindlimb hypertensive resistance response" was associated with enhancement of bradycardia. The hypertensive reversal response represents failure of the combined effects of the arterial and cardiac baroreceptors to inhibit the excitatory effects on RSNA of large rises in blood pressure and/or ischemia (see below).

Previous investigators have demonstrated inhibitory influences arising from cardiac receptors during falls in blood pressure (Obérg and White, 1970a; Obérg and Thorén, 1971; Chen et al., 1978; Thorén, 1979; Thames et al., 1982; Abboud and Thames, 1984). Of particular relevance to the present study is the possible enhanced activity of left ventricular receptors in the empty heart (Obérg and Thorén, 1971) and the demonstration of inhibitory effects evoked from left ventricular receptors by myocardial ischemia (Thames and Abboud, 1979). Linden et al. (1981) showed that some of the effects arising from left atrial receptors can influence renal sympathetic nerve activity, independent of effects arising from the arterial baroreceptors. These receptors could contribute drive to resting RSNA through simple summation of afferent influences.
Enhanced inhibitory effects through left ventricular receptors have been evoked by increasing ventricular afterload (Mark et al., 1973; Thorén, 1979; Malliani, 1982). These probably contributed to the inhibition of the lower plateau and hypertensive response. Our experiments provide no information on whether the inhibitory influences from the cardiac receptors evoked during rises in blood pressure involved the same receptors as produce enhancement of inhibition during pressure falls.

After combined SAD + cardiac receptor blockade, RSNA was still altered by balloon inflation. Possible afferent sources include pulmonary baroreceptors (Paintal, 1973) and a range of C-fiber afferents mediating spinal and supraspinal reflexes (Malliani, 1982). Lower body ischemia could have contributed to the large hypertensive reversal response, although it was transient, and not sufficient to cause the animals apparent distress. Moreover, the findings of Guo et al. (1982) with phenylephrine suggest that it is the increase in MAP, rather than ischemia, that evoked the hypertensive reversal response, since the ischemia in their experiments was probably considerably smaller with phenylephrine than with aortic balloon inflation.

**Resetting**

We have previously found that nitroprusside-induced falls and phenylephrine-induced rises in MAP alter the threshold of the arterial baroreceptors by about 0.4 mm Hg/mm Hg ∆ resting MAP. This degree of resetting remained stable from between 15 minutes and 2 hours after the attainment of the new resting MAP (Dorward et al., 1982). Resetting of the whole aortic nerve activity during similar drug infusions is somewhat larger [about 0.55 mm Hg/mm Hg ∆ MAP (Dorward, unpublished observations)]. In the present experiments, the changes in threshold of the renal sympathetic baroreflex (assessed from the changes in BP_a) with nitroprusside were significantly greater (0.74 mm Hg/mm Hg MAP), suggesting that additional factors contributed to its resetting. Additional factors also were present in relation to reflex resetting with phenylephrine in view of the highly nonlinear relationship between dose of phenylephrine and change in threshold, as well as in the changes in the upper RSNA plateau. Probably the other determinants of reflex resetting were central interactions between the arterial baroreceptors and other afferents, particularly those arising from the cardiac receptors. Cardiac receptor involvement is suggested by the reduction in the hypotensive reversal response observed with the two higher doses of nitroprusside and by the progressive reduction in lower curve plateau and in the hypertensive reversal response with phenylephrine (see above).

The findings with nitroprusside help to explain the reduction in renal baroreflex threshold observed during spontaneous falls in resting MAP (e.g., between control and recovery curves in Figure 5) and during the reduction in resting MAP which accompanied anesthesia. With both vasoactive drugs, there probably are changes in resting cardiac volumes which may alter the contribution made by the cardiac receptors to the afferent input profile to the central nervous system. For example, with high doses of phenylephrine, the acute rise in resting MAP probably increases left ventricular resting volume, enhancing wall stress and producing more pronounced alterations in cardiac receptor activity during subsequent pressure changes (cf. Mark et al., 1973). With nitroprusside, the reflex resetting was related to dose (and changes in resting MAP) over the entire range. However, with phenylephrine, changes in reflex threshold and in other curve parameters occurred at only the two lower doses; with the higher dose, the MAP-RSNA curve was restored back to control. In contrast, our previous studies of arterial baroreceptor resetting showed linear increases in receptor thresholds with all doses of phenylephrine (Dorward et al., 1982). We have not investigated the reason for the nonlinearity in reflex resetting with increasing doses in phenylephrine and increasing rises in resting MAP; a disproportionate increase in inhibitory influences arising from the cardiac receptors, due to a large increase in resting chamber volume, could account for the observed effect.

The average gain of the sigmoid component of the MAP-RSNA relationship was not altered with either nitroprusside or phenylephrine (Figs. 10 and 11). With nitroprusside, resting RSNA remained on the steep portion of the curve and increased in proportion to the fall in resting MAP. This allows the animal to respond relatively normally to transient rises and falls in blood pressure of moderate magnitude (cf. Dorward et al., 1982).

In contrast, rises in resting MAP during phenylephrine infusions, shifted resting RSNA onto the lower plateau of the curve at the two highest doses. This has important consequences for circulatory homeostasis; with resting RSNA on the lower plateau, only a fairly large fall in MAP will elicit reflex elevation in RSNA. Thus the apparent gain of the reflex over a moderate range of pressures about resting is greatly reduced, even though the gain of the sigmoid component of the function curve is relatively unaffected. This becomes apparent only from analysis of the full reflex function curve. Incorrect conclusions about gain would arise from analysis of RSNA responses evoked by smaller pressure changes about the resting value. In this type of acute elevation of resting MAP, the more pronounced sympathetic inhibition of resting RSNA helps to limit the hemodynamic load on the heart, but at the cost of diminished effectiveness of neural regulation during moderate pressure changes about resting.

During alfathesin anesthesia, the resetting of the
threshold of the sigmoid component of the reflex and the small rise in resting RSNA were very similar to the effects of nitropresside in the conscious animal. Alfathesin has peripheral vasodilator properties (Blake and Korner, 1981) which could be the main determinant of the above changes. In contrast, the effects of the drug on the lower RSNA plateau and hypotensive reversal response are clearly mediated through its effects on the central nervous system.

Conclusion

Our analysis suggests that changes in intravascular pressures associated with a circulatory disturbance produce simultaneous changes in the afferent signals arising from several groups of pressure-sensitive receptors. In the normal rabbit, the cardiac and arterial baroreceptors each contributes significant inhibitory drive to the renal sympathetic baroreflex over the entire range of blood pressure. These effects are approximately additive over the high-gain part of the sigmoid component of the function curve, but become increasingly nonlinear at the extremes of MAP. The most complex interactions, including the hypotensive reversal response and the lower plateau, are most susceptible to the effects of anesthesia, emphasizing the advantage of unanesthetized animals for the analysis of complex neural events. Changes in resting MAP produce resetting of the arterial sympathetic baroreflex, which accounts for the shifts in reflex threshold during spontaneous alterations in blood pressure. Reflex resetting is explained in part by resetting of the threshold of the arterial baroreceptors and in part by central interactions associated with alterations in afferent input, including that arising from the cardiac receptors.

We are grateful to Marjorie Nicholson who prepared the manuscript.

This study was supported by grants from the National Health and Medical Research Council and the Life Insurance Medical Research Fund of Australia and New Zealand.

Dr. Riedel's present address is: Max Planck Institute, D-6350 Bad Nauheim, Parkstrasse 1, West Germany.

Address for reprints: Professor P.I. Korner, Baker Medical Research Institute, Commercial Road, Prahran, Victoria 3181, Australia.

Received July 2, 1986; accepted for publication July 24, 1985.

References


Chalmers JP, Korner PI, White SW (1967a) The relative roles of the aortic and carotid sinus nerves in the rabbit in the control of respiration and circulation during arterial hypoxia and hyperventilation. J Physiol (Lond) 188: 435–450

Chalmers JP, Korner PI, White SW (1967b) Local and reflex factors affecting the distribution of the peripheral blood flow during arterial hypoxia in the rabbit. J Physiol (Lond) 192: 537–548


Iriti M, Dorward PK, Korner PI (1977) Baroreflex 'resetting' by arterial hypoxia in the renal and cardiac sympathetic nerves of the rabbit. Pfliegers Arch 370: 1–7


Koike H, Mark AL, Heistad DD, Schmid PG (1975) Influence of cardiopulmonary vagal afferent activity on carotid chemore-
Receptor and baroreceptor reflexes in the dog. Circ Res 37: 422-429


Mancia G, Donald DE, Shepherd JT (1973) Inhibition of adrenergic outflow to peripheral blood vessels by vagal afferents from the cardiopulmonary region in the dog. Circ Res 33: 713-721


Painal AS (1973) Vagal sensory receptors and their reflex effects. Physiol Rev 53: 159-227


Sherington CS (1906) The Integrative Action of the Nervous System. New Haven, Yale University Press


Timms RJ (1976) The use of the anesthetic steroids alphalone-alphalone in studies of the forebrain in the cat (abstr). J Physiol (Lond) 256: 71P-72P


INDEX TERMS: Anesthesia • Arterial baroreceptors • Cardiac receptors • Conscious rabbit • Implanted electrode • Nasopharyngeal reflex • Renal sympathetic baroreflex • Baroreflex resetting
The renal sympathetic baroreflex in the rabbit. Arterial and cardiac baroreceptor influences, resetting, and effect of anesthesia.
P K Dorward, W Riedel, S L Burke, J Gipps and P I Korner

Circ Res. 1985;57:618-633
doi: 10.1161/01.RES.57.4.618

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/57/4/618