Impaired Cardiopulmonary Baroreflex Control of Renal Nerves in Renal Hypertension

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SUMMARY. We recently reported that arterial baroreflex control of renal nerve traffic is impaired in renal hypertensive rabbits. The purpose of this study was to determine if vagal cardiopulmonary baroreflex control of renal nerve traffic is also impaired. Experiments were performed in 10 hypertensive (mean arterial pressure ± SE in conscious state, 110 ± 3 mm Hg) and 10 normotensive (79 ± 1 mm Hg) chloralose-anesthetized rabbits. Responses to graded blood volume expansion (+5, +10, +15 ml/kg) with dextran in saline were recorded with all baroreflexes intact, after sinoaortic baroreceptor denervation, and after vagotomy. With arterial and cardiopulmonary baroreflexes intact, volume expansion resulted in decreases in renal nerve traffic of −12 ± 2%/mm Hg increase in left atrial pressure in normotensive rabbits, but of only −5 ± 2%/mm Hg in hypertensive rabbits (P < 0.05). This difference is particularly striking in view of the larger maximum increases in arterial (25 ± 7 vs. 12 ± 3 mm Hg) and left atrial pressure (9 ± 1 vs. 6 ± 1 mm Hg) during volume expansion in hypertensive vs. normotensive rabbits. After sinoaortic baroreceptor denervation, the responses of normotensive rabbits were preserved (−11 ± 3%/mm Hg), while those of hypertensive rabbits were impaired further (−2 ± 1%/mm Hg). Vagotomy abolished responses of renal nerves to volume expansion in both groups. These data demonstrate striking impairment of vagal cardiopulmonary baroreflex control of renal nerve traffic in renal hypertension. Even though arterial baroreflexes have been shown to be abnormal in renal hypertension, they still may partially compensate for markedly impaired cardiopulmonary baroreflex control of the renal nerves. (Circ Res 57: 741–747, 1985)
goal of our study was to determine if the vagal cardiopulmonary baroreflex control of renal nerve activity is impaired in rabbits with renal hypertension. A second goal was to determine if the relative roles of arterial and cardiopulmonary baroreflexes in the control of renal nerve activity during volume changes is altered in renal hypertension.

Methods

Production of Renal Hypertension

Fourteen New Zealand white male rabbits were rendered hypertensive by unilateral renal wrapping (cellophane) with contralateral nephrectomy under general anesthesia. Two additional rabbits were rendered hypertensive by bilateral renal wrapping. The results from the two models were pooled because they were similar. Anesthesia was induced with sodium thiopental (25 mg/kg, intravenously) followed by nitrous oxide administered with oxygen.

Preparation for Acute Experiment

The acute experiments were performed 6–8 weeks after renal wrapping. Rabbits were anesthetized with intravenous (ear vein) sodium thiopental (25 mg/kg) followed by α-chloralose (50 mg/kg, intravenously). Supplemental doses of chloralose were administered hourly. After tracheal intubation, the animals were ventilated artificially with a mixture of oxygen and room air. Decamethonium bromide (2 mg/kg) or pancuronium bromide (0.5 mg) was administered as needed to block muscle activity during ventilation. Body temperature was maintained between 37°C and 39°C by external warming. Changes in cardiac filling pressure were assessed by placing a catheter in the aorta via the left femoral artery for measurement of arterial pressure. Mean arterial pressure was computed as the diastolic pressure plus one-third of the pulse pressure, or was obtained by electronic averaging of the pulsatile signal. Changes in cardiac filling pressure were assessed by positioning a catheter in the left atrium following a left thoracotomy. We felt that it was important to record changes in pressure on the left side of the heart, since it was most likely that this side would be most affected by the hypertension. Moreover, the prevailing view is that increases in pressure on the left side of the heart are associated with increases in sympathetic nerve traffic to the kidneys (Thoren, 1979). Another catheter was inserted into inferior vena cava via the left femoral vein for infusion of volume and for withdrawal of blood. Arterial blood gases and pH were measured periodically and corrected when necessary by adjusting the respiratory frequency. PaO2 of the arterial blood was always above 200 mm Hg, and PaCO2 and pH were maintained between 25 and 35 mm and between 7.35 and 7.5, respectively. Body temperature was maintained between 37°C and 39°C by external warming.

Denervation of Reflex Pathways

The aortic nerves were identified as they course near the vagus and join the superior larygeal nerves. Fine silk ties were carefully looped around these nerves for subsequent section. The carotid sinus nerves were prepared for interruption by carefully passing silk ties around all the structures that course between the internal and external carotid arteries. Carotid baroreceptors were denervated by ligating and sectioning these structures. Interruption of aortic and carotid sinus nerves resulted in sinoaortic baroreceptor denervation. The failure of large arterial pressure increases resulting from volume expansion to inhibit renal (see Results) nerve traffic after sinoaortic and vagal denervation was taken as evidence of complete arterial baroreceptor denervation. The vagi were prepared for subsequent denervation by carefully positioning a silk tie around each cervical vagus.

Recording and Quantification of Nerve Activity

The left renal sympathetic nerves were exposed using a flank incision and retroperitoneal approach. A branch of the nerves was sectioned and, after removal of the sheath from the cut central end, immersed in mineral oil and placed on bipolar Ag/AgCl electrodes for recording of action potentials. The technique for quantification of nerve traffic has been described in detail previously (Felder and Thames, 1981). In brief, the recorded spikes were amplified with a Grass P511 preamplifier, and the amplified nerve activity was visualized on a Tektronix oscilloscope. The output also was led to a nerve traffic analyzer that measured the frequency of spikes that exceeded a selected voltage (just above the noise). Each spike that crossed the threshold generated a voltage step that was independent of spike and amplitude. These normalized voltage steps were integrated to determine the number of spikes counted over a period of time. This counting technique is different from integration of the raw voltage signal commonly referred to as integration. The counter is digital in design, and counts linearly at instantaneous frequencies up to 10 kHz. The absolute value of the recorded traffic is dependent on the number of active fibers on the recording electrodes and on the level of the window discriminator and, thus, may have limited meaning. This was particularly true in our study, since our nerve recordings were obtained from bundles of fibers of varying size obtained from the renal nerves. Thus, all responses of renal nerve traffic are normalized for their basal values.

Protocol

Experiments were performed in 16 hypertensive and in 16 normotensive rabbits. Responses to graded blood volume expansion with 6% dextran in normal saline (154 mEq/liter) were recorded in 10 hypertensive and 10 normotensive rabbits with all baroreflexes intact, after sinoaortic denervation, and after vagotomy (group I). In the remaining six hypertensive and six normotensive rabbits (group II), volume expansions were done with all baroreflexes intact and after vagotomy (sinoaortic baroreflexes intact). Dextran was administered in 5 ml/kg increments for a total expansion of 15 ml/kg at a rate of approximately 2.5 ml/min. Left atrial pressure, arterial pressure, and renal sympathetic nerve traffic were recorded during volume expansion with each state of innervation.

Data Analysis

Values for control were averaged over 30–60 seconds prior to volume expansion. During volume expansion, average values were obtained for successive periods of approximately 10–15 seconds at the end of each volume increment. The relationship between increases in left atrial pressure and decreases in renal nerve traffic and the effects of the state of innervation on this relationship were assessed by analysis of variance. Differences between hypertensive and normotensive rabbits also were assessed by analysis of variance. Probability levels less than 0.05 were considered statistically significant.
were considered significant. Results are presented in the text and figures as mean ± SE.

**Results**

**Group I**

Experiments were done in 10 rabbits with hypertension 6–8 weeks after renal wrapping and in 10 age-matched controls. The basal mean arterial pressures recorded in conscious rabbits (central ear artery) were significantly higher in hypertensive (110 ± 3 mm Hg) than in normotensive rabbits (79 ± 1 mm Hg). At the beginning of the protocol following anesthesia and thoracotomy, the respective pressures for these groups were 92 ± 10 and 76 ± 6 mm Hg (P < 0.05). Basal left atrial pressures were not significantly different (3.4 ± 0.7 and 4.0 ± 0.9 mm Hg, respectively). At the conclusion of the experiments, the heart was removed and the left ventricle was weighed. The left ventricle-to-body weight ratio was significantly higher in hypertensive (1.4 ± 0.2 g/kg) than in normotensive (1.1 ± 0.03 g/kg) rabbits, although the difference was modest. The mean body weight of the normotensive group was 3.2 ± 0.2 kg and of the hypertensive group was 3.0 ± 0.2 kg. These weights were not significantly different.

Volume expansion resulted in increases in arterial pressure and left atrial pressure and decreases in renal nerve activity, in both normotensive and renal hypertensive rabbits. The mean data for the relationship between left atrial pressure and decreases in renal nerve activity observed under control conditions and after sinoaortic denervation are illustrated in Figures 1 and 2 for normotensive and hypertensive rabbits. Note that with arterial and cardiopulmonary baroreflexes intact (Fig. 1), the inhibition of renal nerve traffic during volume expansion was significantly smaller in hypertensive than in normotensive rabbits. This impairment occurred in spite of the significantly larger increase in arterial pressure (Fig. 1) in the hypertensive rabbits. Sinoaortic denervation did not increase arterial pressure significantly in normotensive or hypertensive rabbits, but increased renal nerve traffic in normo-
tensive (45 ± 14 to 88 ± 23 impulses (imp)/sec) but not hypertensive rabbits (55 ± 7 to 61 ± 7 imp/sec). After sinoaortic baroreceptor denervation, the responses of normotensive rabbits were preserved, but those of the hypertensive rabbits became further impaired (Fig. 2), although the residual responses still were significant. After sinoaortic and vagal denervation, responses to volume expansion were abolished. Figure 3 illustrates a typical response of a normotensive rabbit to volume changes following sinoaortic denervation. The figure illustrates the independent influence of vagal cardiopulmonary baroreflexes on renal nerve traffic. Figure 4 illustrates a particularly striking example of an impaired response to volume expansion in a hypertensive animal following sinoaortic denervation.

The relationship between increases in left atrial pressure and decreases in renal nerve activity was determined for each experiment using a least-squares linear regression model. With arterial and cardiopulmonary baroreflexes intact, the mean slope of this relationship (reflex gain) was −12 ± 2%/mm Hg rise in left atrial pressure in the normotensive group, but −5 ± 2%/mm Hg (p < 0.05) in the hypertensive rabbits. After sinoaortic denervation, the responses of the normotensive rabbits were preserved (−11 ± 3%/mm Hg), but those of the hypertensives were further (P < 0.05) impaired (−2 ± 1%/mm Hg). The responses of the hypertensive group after sinoaortic denervation, even though reduced, were significant.

**Group II**

After anesthesia and surgery, the mean arterial pressures of the hypertensive rabbits averaged 87 ± 19 mm Hg.
7 mm Hg and were significantly higher than those of the normotensive rabbits (67 ± 6 mm Hg). The left atrial pressures were not significantly different (6 ± 1.5 vs. 5 ± 1.3 mm Hg, respectively).

The mean slopes of the least-squares linear regression relationships between changes in renal nerve activity and left atrial pressure (reflex gain) obtained from volume expansions were −9 ± 0.7%/mm Hg in the normotensive rabbits and −4.0 ± 0.8%/mm Hg in the hypertensive rabbits (P < 0.05). These volume expansions were accompanied by respective increases in arterial pressure of 11 ± 4 and 15 ± 4 mm Hg.

Selective vagotomy did not alter arterial pressure significantly in hypertensive or normotensive rabbits, but increased renal nerve activity in normotensive (23 ± 8 to 41 ± 7 imp/sec) but not hypertensive rabbits (68 ± 24 to 76 ± 38 imp/sec). After vagotomy, only the arterial baroreflexes remained to buffer the hemodynamic responses to volume expansion. Thus, the reflex gains are expressed in terms of inhibition of renal nerve activity per mm Hg rise in arterial pressure which were 1.1 ± 1.8 (NS) and 3.0 ± 0.4 for hypertensive and normotensive rabbits. After vagotomy, the maximum inhibition of renal nerve traffic was −29 ± 5% for the normotensive rabbits following a 7 ± 2 mm Hg rise in arterial pressure, whereas the hypertensive rabbits had no change in traffic (−3 ± 13%) for a rise in arterial pressure of 8 ± 2 mm Hg.

**Discussion**

The first major finding of this study is that the vagal cardiopulmonary baroreflex control of renal nerve traffic is strikingly impaired in renal hypertensive rabbits. This is most clearly illustrated in Figure 2 which summarizes the mean responses after sinoaortic baroreceptor denervation. Under these circumstances, the independent influence of the vagal cardiopulmonary baroreflex can be assessed. These findings are similar to those reported by Ferrari et al., (1984) who found impaired cardiopulmonary baroreflex control of renal nerve traffic in prehypertensive Dahl salt-sensitive rats fed a low-salt diet. As in our study, the mechanism for the impairment was not established. Our findings and those of Ferrari et al. (1984) differ from those of Kezdi (1976) obtained from renal hypertensive dogs which suggested preserved sensitivity of cardiac baroreflex control of skeletal muscle vascular resistance. They also differ from those of Ricksten and colleagues (1979) obtained from anesthetized spontaneously hypertensive rats in which there was a very modest reduction in cardiopulmonary baroreflex sensitivity in the control of the renal nerves. Moreover, they observed comparable inhibition of renal nerve traffic for comparable volume changes. This was due to the greater increases in filling pressure in the hypertensive rats. In our experiments, comparable changes in volume gave rise to less inhibition of renal nerve traffic in hypertensive than in normotensive rabbits, even though increases in filling pressure were larger in the hypertensive group. Our findings also differ from those of Mark and Kerber (1982) who observed augmented cardiopulmonary baroreflex control of forearm resistance vessels during venous pooling in humans with borderline hypertension. The most obvious difference between their study and ours is that they unloaded cardiopulmonary receptors with lower body negative pressure, whereas we stimulated these receptors with volume loading. Other obvious differences include the type of hypertension and the species studied.

The mechanism for this impairment in the vagal cardiopulmonary baroreflex control of renal nerve activity cannot be discerned from our study, but could be due to abnormalities in the cardiopulmonary receptors, in the central nervous system, or both. We studied these rabbits at a time (6–8 weeks after renal wrap) when there was a very modest degree of cardiac hypertrophy. Thoren et al. (1979) found an increased pressure threshold for stimulation of left atrial C-fibers in spontaneously hypertensive rats compared with normotensive controls. However, the sensitivity of the left atrial receptors in these two groups was not different. The degree of cardiac hypertrophy in these hypertensive rats are far greater than that observed in the renal hypertensive rabbits we studied. Obviously, recordings from cardiac receptors in renal hypertensive rabbits are needed, but once obtained, if the findings are similar to those of Thoren et al. (1979) in rats, then they would point to a central basis for the abnormality. We reported recently (Thames et al., 1984) that arterial baroreflex control of renal traffic is impaired in renal hypertensive rabbits. This was due to an abnormality in the central nervous system. Thus, it is quite possible that a central abnormality contributed to the impaired cardiopulmonary baroreflex control we observed.
(Guo et al., 1982, 1983). In contrast, the responses of hypertensive rabbits (Fig. 5B) were impaired with arterial and cardiopulmonary reflexes intact, and were essentially abolished by selective vagotomy (group II). Abnormal responses occurred in spite of the larger rise in arterial pressure in the hypertensive rabbits, and was probably due in part to impaired arterial baroreflex control of the renal nerves in renal hypertension (Thames et al., 1984). This suggests the absence of redundancy in the control of the renal nerves by arterial and cardiopulmonary baroreflexes observed in normotensive rabbits, and indicates a pattern of summation other than occlusive summation and more like simple addition. We have reported similar abnormalities in the pattern of summation of carotid and aortic baroreflexes in the control of lumbar sympathetic nerve activity in renal hypertension (Guo et al., 1983).

We would like to emphasize that the reflex responses to volume expansion are dependent on the changes in both arterial and cardiac filling pressures and, thus, on the magnitudes of the changes in input to the central nervous system from arterial and cardiopulmonary baroreceptors. In our experiments, volume expansion induced large increases in the stimulus to cardiopulmonary receptors with more modest influences on arterial baroreceptors. It is thus not surprising that vagotomy markedly reduced (normotensive rabbits) or abolished (hypertensive rabbits) the responses of the renal nerves to volume expansion. The contribution of the arterial baroreflexes to the integrated response of the renal nerves will depend on the increase in arterial pressure induced by volume expansion and on the gain of the arterial baroreflexes. This gain is reduced in renal hypertension (Thames, Gupta, and Ballon, 1984). The latter point along with the small increase in arterial pressure probably accounts for our failure to detect significant decreases in renal nerve traffic after selective vagotomy (Group II) in the hypertensive rabbits.

In conclusion, vagal cardiopulmonary baroreflex
control of the renal nerves is impaired in renal hypertension. This finding, taken with our prior observations (Thames et al., 1984), suggests a general impairment in reflex control of the renal nerves in renal hypertension.

**Addendum**

It has been reported recently [Wiggins, R.C., Glatfelter, A., Campbell, A.M., Kunkel, R.G., Ulevitch, R.J. (1985) Acute hypotension due to platelet serotonin-induced chemoreflexes after intravenous injection of dextran sulfate in the rabbit. Circ. Res. 57: 262–277] that intravenous injection of dextran sulfate results in bradycardia and hypotension in rabbits. These reflex responses were due to dextran-induced release of serotonin from platelets which in turn stimulated vagal chemosensitive endings in the lungs which served as the afferent limb of the reflex. The reflex responses we observed were not the result of stimulation of chemosensitive pulmonary receptors for several reasons. First, we observed neither hypotension nor bradycardia during volume expansion. Second, although the initial volume expansion used dextran in saline, an equivalent volume was removed prior to sinoaortic denervation (SAD) and the shed blood was used for volume expansion after SAD. In the normotensive rabbits, comparable responses were observed before and after SAD. Finally, we used dextran sulfate with an average molecular weight of 40,000 (range 15,000–25,000) whereas Wiggins et al. (1985) used dextran sulfate with an average molecular weight of 500,000. It seems likely that the stimulation of pulmonary chemoreflexes by dextran-induced release of serotonin from platelets requires this very high molecular weight dextran sulfate.

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**References**


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