Baroreflex depression persists in the early phase after hypertension reversal

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Farah, V. M. A., E. D. Moreira, M. C. Irigoyen, and E. M. Krieger. Baroreflex depression persists in the early phase after hypertension reversal. Am J Physiol Regulatory Integrative Comp Physiol 280: R1620–R1626, 2001.—The baroreflex control of heart rate (HR) was evaluated in conscious chronic renal hypertensive rats (RHR; 1K-1C, 2 mo) under control conditions and after reversal of hypertension by unclipping the renal artery or sodium nitroprusside infusion. Unclipping and nitroprusside infusion were both followed by significant decreases in the mean arterial pressure (unclipping: from 199 ± 4 to 153 ± 8 mmHg; nitroprusside infusion: from 197 ± 9 to 166 ± 6 mmHg) as well as slight and significant increases, respectively, in the baroreflex bradycardic response index (unclipping: from 0.2 ± 0.04 to 0.6 ± 0.1 beats·min⁻¹·mmHg⁻¹; nitroprusside infusion: from 0.1 ± 0.04 to 0.5 ± 0.1 beats·min⁻¹·mmHg⁻¹). However, this index was still depressed compared with that for normotensive control rats (2.1 ± 0.2 beats·min⁻¹·mmHg⁻¹). The index for the baroreflex tachycardic response was also depressed under control conditions and remained unchanged after hypertension reversal. RHR possessed markedly attenuated vagal tone as demonstrated by pharmacological blockade of parasympathetic and sympathetic control of HR with methylatropine and propranolol, respectively. A reduced bradycardic response was also observed in anesthetized RHR during electrical stimulation of the vagus nerve or methacholine chloride injection, indicating impairment of efferent vagal influence over the HR. Together, these data indicate that 2 h after hypertension reversal in RHR, the previously described normalization of baroreceptor gain occurs independent of the minimal or lack of recovery of baroreflex control over HR.

Baroreceptors; baroreflexes; resetting; vagal function

IT IS WIDELY ACCEPTED THAT the baroreceptors are reset to operate at higher pressures in chronic hypertension (19). Resetting of the baroreceptors, characterized by the displacement of the pressure threshold for baroreceptor activation, is accompanied to a variable extent by a decrease in the gain of the baroreceptor pressure-afferent activity curve. Indeed, we have previously observed a decreased slope, with an attenuation of 36% of the gain of the baroreceptors, in chronic renal hypertensive rats (RHR) (22). Within a more physiologic range, in response to changes of +10 and −10 mmHg, decreases in the gain of 56 and 42%, respectively, were observed (22). When the time course of the depression was studied, a depression similar to that observed after 2 mo of hypertension was already demonstrable after only 2–6 days of hypertension (23). Therefore, part of the impairment usually observed in the baroreflexes of hypertensive individuals could be attributed to the depressed gain of peripheral baroreceptors.

The first direct demonstration that the resetting of baroreceptors in hypertension is a reversible process was obtained by electroneurographic techniques. Reversal of baroreceptor resetting was observed after rapid and sustained pressure normalization in rats with renal hypertension of 2-mo duration (27) and confirmed in rats with long-lasting hypertension (30). Direct (28) and indirect (4) evidence obtained in dogs also indicates that reversal of the resetting process occurs faster than the initial resetting. Moreover, in chronic RHR, the reversal of resetting is pronounced but incomplete (60–80%) within the first 2 h of pressure normalization, whereas the baroreceptor gain is normalized (22). Such rapid recovery of baroreceptor sensitivity may be of great physiological importance, because the baroreflex will act to maintain the blood pressure at a normal level during reversal of hypertension (antihypertensive treatment). However, the relationship between the reversal of resetting and recovery of peripheral baroreceptor sensitivity and the recovery of integrated baroreflex control of heart rate (HR) have yet to be established. It has been reported that the carotid baroreceptor stimulus-response characteristics were normal in dogs when studied 3–7 mo after repair of aortic coarctation (14). It has also been reported that the sensitivity of the baroreceptor reflex control of HR had returned to normal levels when assessed 1–25 days after reversal of renal hypertension in rats (16) or after 6 wk in rabbits (9). Although there was no change in baroreflex sensitivity during the first 24 h after reversal of renal hypertension in rats (2K-1C), the sensitivity of the reflex had significantly increased 3 wk later and did not differ from that of normotensive controls (6).

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Therefore, the present experiment was undertaken to study the following characteristics in RHR (1K-1C, 2-mo duration): 1) the extent of the impairment of baroreflex-mediated bradycardia and tachycardia during a control period; 2) the influence of a 2-h period of hypertension reversal (unclipping or sodium nitroprusside infusion) on the depressed baroreflexes; and 3) the intrinsic heart rate (IHR), vagal and sympathetic tone, and also the bradycardic responses to both electrical stimulation of the vagus nerve and methacholine chloride injection exhibited by RHR during a control period.

MATERIALS AND METHODS

Chronic (2-mo duration) one-kidney, one-clip, male, hypertensive rats, weighing from 250 to 290 g, were used in this study. One day before the experiment, while the rats were under ether anesthesia, arterial and venous catheters were implanted through the femoral artery and vein for measurement of the arterial pressure (AP) and drug administration, respectively. A jugular cannula was also implanted for sodium nitroprusside infusion. The catheters were exteriorized through the back of the neck.

Blood pressure was recorded continuously in conscious, freely moving rats with a strain gauge transducer (Statham P23Db, Hato Rey, Puerto Rico) connected to a Hewlett Packard recorder (7754). HR was measured by counting the AP pulses in a 1-s interval.

To evaluate the baroreflex control of HR, increasing doses of phenylephrine (0.25 to 16 μg/ml) and sodium nitroprusside (2.5 to 40 μg/ml) were administered to conscious unrestrained rats via bolus injections (0.1 ml). These injections produced abrupt changes in AP (at least 4 pressure increases or decreases of 10–40 mmHg). Maximum changes in HR, which corresponded to maximum changes in mean AP (MAP), were used to calculate an index for each type of baroreflex-mediated response (bradycardic and tachycardic). The mean index for each rat was calculated as the mean value of all points (ΔHR/ΔMAP) for the bradycardic responses; another index was calculated for the tachycardic responses (1, 7). The results obtained in hypertensive rats during the control period were compared with those obtained 2 h after the reversal of hypertension.

Reversal of hypertension was achieved by removing the clip from the renal artery (under ether anesthesia) in one group of rats (n = 8) and by sodium nitroprusside infusion (20 μg/ml, individually adjusted) in another group of rats (n = 7).

The vagal and sympathetic tone was studied in a different group of conscious hypertensive rats. These rats underwent methylatropine (3 mg/kg; Sigma Chemical) and propranolol (4 mg/kg; Sigma Chemical) injections 1 day after cannula implantation. On the first day of the study, the resting HR was recorded under quiet conditions with the rat kept in its own cage; the methylatropine was injected immediately after recording the resting HR. Because the HR response to methylatropine was maximal and stable after 10–15 min (29), this time was selected as the standard time for HR measurement. The propranolol was injected 15 min after the methylatropine, and the response was measured 10–15 min later. The IHR was evaluated after simultaneous blockade with propranolol and methylatropine. We have previously observed (26) that these drugs still promote blockade 30 min after injection. Therefore, on the second day of the study, propranolol was administrated first to reverse the sequence of drug administration. The effect of the methylatropine was evaluated as the difference between the maximum HR after methylatropine injection and the control HR. The effect of the propranolol was evaluated as the difference between the control HR and the minimum HR after propranolol injection. The vagal tone was evaluated by determining the difference between the IHR and the HR after propranolol injection. The sympathetic tone was evaluated by determining the difference between the IHR and the HR after methylatropine injection.

In 13 normotensive control rats (NCR) and 11 RHR anesthetized with chloralose (60 mg/kg iv), the decrease in HR produced by electrical stimulation (5 V, 2 ms, and 2–32 Hz for 7 s) of the distal end of the sectioned right vagus nerve was measured. The interval between stimulations was determined by the time required for the HR to return to the prestimulation level. After vagal stimulation, the chronotropic (HR) responsiveness to stimulation of muscarinic receptors was tested by intravenous injections of increasing doses (4, 8, and 16 ng/kg) of methacholine chloride. Body temperature was maintained at 37°C by external heating.

One day after the end of the experiments, blood was sampled for determination of the plasma renin activity (PRA). Approximately 1 ml of free-flowing blood was collected from conscious unrestrained rats into tubes containing disodium EDTA (1 mg/ml blood). The blood was iced and spun at 4°C. The plasma was then separated and frozen at −20°C until incubation and assay for PRA. The PRA was measured by radioimmunoassay, as described in detail elsewhere (20).

All data are expressed as means ± SE. Statistical analysis was performed by two-way analysis of variance followed by the multiple comparison Bonferroni test or the unpaired Student’s t-test, when appropriate. Differences were considered to be significant for P values <0.05.

RESULTS

Baroreflex index after unclipping. Basal MAP and HR were higher in RHR (n = 8) than in NCR (n = 17), with mean values of 199 ± 4 vs. 111 ± 1 mmHg and 422 ± 16 vs. 366 ± 6 beats/min, respectively. Two hours after the renal artery unclipping was performed, the MAP significantly decreased in RHR to 153 ± 8 mmHg, without alteration of the HR (421 ± 12 beats/min).

During the control period, the baroreflex index for bradycardic responses was drastically reduced in the RHR, representing only 9% of that for the NCR (0.2 ± 0.04 vs. 2.1 ± 0.2 beats·min⁻¹·mmHg⁻¹). Two hours after unclipping, the index significantly increased to 0.6 ± 0.1 beats·min⁻¹·mmHg⁻¹; however, this value still represented only 27% of the NCR value (Fig. 1).

The baroreflex index for tachycardic responses during the control period was also depressed in the RHR, corresponding to only 25% of the NCR value (0.9 ± 0.2 vs. 3.6 ± 0.2 beats·min⁻¹·mmHg⁻¹). Two hours after unclipping, the index remained unchanged at 1.0 ± 0.2 beats·min⁻¹·mmHg⁻¹ (Fig. 1).

Baroreflex index after sodium nitroprusside infusion. Basal MAP and HR were higher in RHR (n = 7) than in NCR (n = 17), with mean values of 197 ± 9 vs. 111 ± 1 mmHg and 405 ± 14 vs. 366 ± 6 beats/min, respectively. During the 2-h period of the sodium nitroprusside infusion, the MAP of the RHR decreased signifi-
significant to 166 ± 6 mmHg, without alteration of the HR (440 ± 21 beats/min).

During the control period, the baroreflex index for bradycardic responses was drastically reduced in RHR, representing only 6% of that for the NCR (0.1 ± 0.04 vs. 2.1 ± 0.2 beats·min⁻¹·mmHg⁻¹). During the infusion, the index significantly increased to 0.5 ± 0.1 beats·min⁻¹·mmHg⁻¹, but this value still represented only 24% of the corresponding NCR value (Fig. 1).

During the control period, the baroreflex index for tachycardic responses was also depressed in RHR compared with NCR, representing only 29% of the NCR value (1.03 ± 0.2 vs. 3.6 ± 0.2 beats·min⁻¹·mmHg⁻¹). During the nitroprusside infusion, the index remained unchanged at 0.94 ± 0.3 beats·min⁻¹·mmHg⁻¹ (Fig. 1).

Sympathetic and vagal tone in RHR and NCR. The basal HR, IHR, and HR responses to drug blockades are shown in Figs. 2 and 3. The MAP and basal HR were higher in RHR (n = 7) than in NCR (n = 10), with values of 204 ± 6 vs. 113 ± 2 mmHg and 366 ± 7 vs. 344 ± 5 beats/min, respectively.

The change in HR in response to methylatropine (atropine effect) was significantly smaller in RHR (29 ± 12 beats/min) than in NCR (88 ± 7 beats/min). After propranolol injection, the change in HR (propranolol effect) was significantly greater in RHR (−39 ± 7 beats/min) than in NCR (−19 ± 4 beats/min) (Fig. 2).

The sympathetic tone (the difference between the HR after methylatropine injection and the IHR) was similar in RHR and in NCR (58 ± 9 vs. 56 ± 8 beats/min, respectively). However, the vagal tone was significantly reduced in RHR compared with NCR (10 ± 6 vs. 51 ± 5 beats/min, respectively) (Fig. 3).

The IHR obtained after methylatropine and propranolol blockade was significantly lower (by 39 beats/min) in RHR than in NCR (337 ± 6 vs. 376 ± 5 beats/min, respectively).

Vagal nerve stimulation in RHR and NCR. During the control period, MAP and HR were higher in RHR (n = 13) than in NCR (n = 11), with mean values of
194 ± 4 vs. 112 ± 2 mmHg and 377 ± 6 vs. 349 ± 8 beats/min, respectively.

As shown in Fig. 4, the RHR group had smaller bradycardic responses to electrical stimulation than the NCR group at frequencies of 2 (10 ± 2 vs. 11 ± 2 beats/min), 4 (36 ± 7 vs. 48 ± 12 beats/min), 8 (67 ± 13 vs. 122 ± 18 beats/min), 16 (141 ± 22 vs. 221 ± 25 beats/min), and 32 Hz (259 ± 25 vs. 284 ± 26 beats/min). However, these differences were only statistically significant at frequencies of 8 and 16 Hz.

Bradycardic responses to methacholine chloride. As shown in Fig. 5, the bradycardic responses to 1.25 (12 ± 4 vs. 37 ± 10 beats/min), 2.5 (43 ± 15 vs. 80 ± 30 beats/min), and 5 ng/rat (137 ± 32 vs. 187 ± 31 beats/min) of methacholine chloride were reduced in the RHR group (n = 10) compared with the NCR group (n = 8). However, a statistically significant difference between groups was only found for the 1.25-ng/rat dose.

PRA. The PRA measured in an RHR group (n = 7) was similar to that of an NCR group (n = 6), at values of 1.6 ± 0.4 vs. 2.6 ± 0.7 ng ANG I/ml, respectively.
DISCUSSION

There were several major findings in the present study. First, the baroreflex control of HR was markedly attenuated in RHR. Second, the decrease in MAP but not HR that occurred in RHR 2 h after partial reversal of hypertension (via unclipping or sodium nitroprusside infusion) was accompanied by minor recovery of baroreceptor reflex-mediated bradycardia (from 9 to 27% of NCR values); however, no recovery of baroreceptor reflex-mediated tachycardia was observed. The time course of depressed baroreflex function that has been described previously in the same model of hypertension in rats ranges from 1 to 60 days (24). Moreover, we have already observed (22), in the same model of hypertension (RHR), an ~40% depression in the gain of the baroreceptor function curve. Therefore, the attenuation in the baroreflex control of HR observed during the control period in the present study could be explained, at least partially, by hyposensitivity of the afferent nerves.

In the present study, the reversal of hypertension was accompanied by minimal recovery of bradycardic responses and no change in tachycardic responses to changes in MAP. In contrast, our previous results (22) obtained 2 h after unclipping in RHR showed complete normalization of the gain of baroreceptor function accompanied by a still incomplete reversal of pressure threshold resetting. Comparison of our present and previous results (22) shows that the blood pressure was reduced (~40 mmHg) to the same extent in both studies after reversal of hypertension, although the baseline MAP values were different (190 mmHg in the present study vs. 170 mmHg in the previous study). Therefore, neither the similar decrease in blood pressure nor the incomplete resetting observed 2 h after unclipping (22) appears to be related to the maintenance of depressed baroreflex responses (23). Rather, these findings suggest that other factors, such as the absolute AP level or different sites of the reflex arc (afferent branch or central areas), may be contributing to this impairment.

The autonomic nervous system is composed of the sympathetic and parasympathetic circuits. These circuits are assumed to maintain the regulation of HR on the basis of their mutual functional antagonism. In the present study, we found marked attenuation of the vagal tone and the atropine effect in RHR, with an increased propranolol effect. In addition, we found that the RHR group had significantly lower bradycardic responses to electrical stimulation of the efferent vagus nerve (8 and 16 Hz) and to methacholine chloride administration (4 ng/rat). Thus the discrepancy between the previously reported degree of baroreceptor hyposensitivity (22) and the much larger depression of baroreflex control of HR observed here may be explained by additional alterations in the peripheral components of the vagal and sympathetic nerves and/or in the central integration of the reflex.

Although we did not evaluate bradycardic responses to electrical and pharmacological vagal stimulation after reversal of hypertension (2 h), the depressed baroreflex index observed at this time could be due to maintenance of parasympathetic impairment. Depressed parasympathetic tone has been demonstrated in patients with borderline hypertension, associated with elevated sympathetic tone (17), as well as in patients with established hypertension (18). Spectral analysis of HR variability in essential hypertension is also associated with enhanced sympathetic and reduced vagal tone (13). In addition, a decrease in vagal tone has been described (2) in other RHR (2K-1K and 1K-1C), and strong attenuation of methacholine chloride-induced bradycardia (10) was observed in rats 6 h after sinoaortic denervation. The HR responses to methacholine chloride or to vagal electrical stimulation were always lower in RHR than in control rats. However, we observed statistical significance only in the HR range <50 beats/min in response to methacholine chloride, whereas in response to vagal stimulation, the HR depression was observed only in the range of 150–200 beats/min. Therefore, the alterations we found in the autonomic control of HR may represent an important contributor to the depressed baroreflex index in RHR.

Another possible explanation for the partial recovery of bradycardia and the lack of recovery of tachycardia 2 h after reversal of hypertension is the actions of “antihypertensive neutral renomedullary lipid” (ANRL). This lipid is released from granulated interstitial cells of the renal medulla after renal artery unclipping. In experimental renal hypertension, ANRL is released from the earlier hypotensive kidney when it is suddenly reperfused at high AP after unclipping (25). The postclipping fall in MAP involves a suppression of tonic sympathetic activity that could be explained by the actions of these depressor agents; these agents also excite inhibitory actions directly on cardiovascular effector cells and/or the release of adrenergic transmitter (12). However, we found no difference in baroreflex responses when the reversal of hypertension was produced by unclipping or by sodium nitroprusside infusion. Thus our findings provide no support for the hypothesis that depressor agents released from the reperfused kidney are responsible for changes in the baroreflex index.

Another methodological aspect of this study that could have influenced our results is the use of ether anesthesia during surgical reversal. Two hours after reversal of hypertension by unclipping, the ether anesthesia could have been affecting the recovery of the baroreceptor reflex-mediated bradycardia and tachycardia. Although we cannot exclude the effect of the ether anesthesia at this time, the similar results obtained with nitroprusside infusion in conscious rats reduce the likelihood of this possibility. Moreover, the brief nature of the unclipping procedure (no more than 10 min), combined with our previous results showing complete normalization of the baroreceptor gain 2 h after unclipping under anesthesia (22), seems to indicate that the present results were not attributable to ether anesthesia.

Another methodological aspect of this study is the control of HR on the basis of their mutual functional antagonism. In the present study, we found marked attenuation of the vagal tone and the atropine effect in RHR, with an increased propranolol effect. In addition, we found that the RHR group had significantly lower bradycardic responses to electrical stimulation of the efferent vagus nerve (8 and 16 Hz) and to methacholine chloride administration (4 ng/rat). Thus the discrepancy between the previously reported degree of baroreceptor hyposensitivity (22) and the much larger depression of baroreflex control of HR observed here may be explained by additional alterations in the peripheral components of the vagal and sympathetic nerves and/or in the central integration of the reflex.

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Central alteration of the baroreflex control of HR is another possible mechanism by which to explain our results. It is possible that excess activity of the renin-angiotensin system (RAS) was partly responsible for maintaining the depressed baroreflex responses observed in our severely hypertensive RHR (blood pressure over 190 mmHg). In previous observations of rats with high renin hypertension and chronic RAS overactivity (15), we found similar degrees of attenuation for the bradycardic and tachycardic responses (75 and 73%, respectively). Furthermore, the reflex sympathetic activity in these rats was impaired by 78 and 89% when the baroreceptors were loaded or unloaded, respectively (15). However, the RHR in the present study, as described before elsewhere (11), did not exhibit increased levels of circulating plasma renin. Therefore, in this model of hypertension (RHR), the continued impairment of baroreflex control of HR even after reversal of hypertension could not be explained by an overly active systemic RAS.

Another explanation for the relative lack of recovery of baroreflex control of HR found 2 h after reversal of hypertension relates to the potential for cardiac hypertrophy to alter cardiopulmonary reflexes. Indeed, in humans with borderline hypertension, the cardiopulmonary reflexes are increased, whereas in rats with cardiac hypertrophy induced by myocardial infarction or isoproterenol treatment, the cardiopulmonary reflexes are impaired (21, 31). Moreover, changes in the chronotropic and inotropic properties of the heart have been demonstrated in rats with volume overload-induced cardiac hypertrophy (3), which could be contributing to changes in reflex control. The attenuated baroreflex index observed in exercise-trained rabbits has been attributed to changes in cardiac afferent activity, probably due to increasing stretch on the heart by increased blood volume associated with the resulting cardiac hypertrophy (5). Although not directly assessed, the hypertensive rats used in the present experiment probably exhibited marked cardiac hypertrophy. This notion is based on unpublished data from our laboratory documenting a 62% increase in left ventricular weight in rats with a level and duration of hypertension similar to those observed in the present study. If a comparable level of cardiac hypertrophy was present in this study, the blunting effect produced by the cardiopulmonary receptors on the baroreflexes would still be acting 2 h after reversal of hypertension.

In summary, the present data demonstrate that the baroreflex control of HR remains depressed 2 h after the reversal of hypertension. This depressed baroreflex control persists despite the normalization of the depressed gain of the baroreceptors, as demonstrated in our previous study (22). It seems that other factors, such as peripheral efferent (vagus nerve) and cardiopulmonary reflexes, that remained altered could be responsible for the only minor degree of baroreflex recovery observed 2 h after hypertension reversal. Therefore, within the first hours of pressure recovery from hypertension, a time course dissociation exists between the normalization of the gain sensitivity of the baroreceptors and the recovery of the other components of the neurogenic reflex pathways.

**Perspectives**

The depressed baroreflex control of HR that remains after a 2-h period of recovery from hypertension is likely to have implications regarding cardiovascular regulation. It may contribute to changes in HR variability as well as to the reduced activity of parasympathetic system-mediated reflex responses observed in hypertensive individuals (13, 17, 18). Moreover, reduction of vagal activity is usually associated with changes in the density and sensitivity of muscarinic receptors. The different adrenergic-cholinergic interactions in cardiac tissue, not only during hypertension but also during reversal of hypertension, may be related to the process of cardiac hypertrophy and remodeling.

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