Reversibility of Baroreceptor Hyposensitivity During Reversal of Hypertension

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The extent and characteristics of reversal of baroreceptor resetting after pressure normalization were studied in rats with renal hypertension of 2 months' duration. During the control period, the displacement of the entire baroreceptor function curve was accompanied by a decrease slope, indicating that the gain sensitivity was depressed by 36% in the renal hypertensive rats. In response to changes of +10 and −10 mm Hg in the control pressure, the gain sensitivity was attenuated by 56% and 42%, respectively. Two minutes after unclipping and bleeding when necessary, mean arterial pressure decreased from 171±11 to 134±11 mm Hg and remained at approximately the same level for the 2-hour period of observation. The extent of reversal of the mean pressure threshold for activation of the baroreceptors was approximately constant (−60%) in the time range of 2–120 minutes. The extent of reversal was slightly higher when the changes in systolic pressure threshold divided by the total change in control diastolic pressure were calculated (maximal of 83%). During the first 20 minutes, the displacements of the curves were parallel with no change in the depressed gain sensitivity. Complete normalization of gain sensitivity was observed after 90–120 minutes. The data indicate that, within the first 2 hours of pressure normalization of chronic renal hypertensive rats, 1) reversal of the resetting of pressure threshold is pronounced (60–80%) but still incomplete and 2) gain sensitivity returns completely to normal. (Hypertension 1990;15:791–796)

The time needed for the baroreceptors to reset to hypertension or hypotension is relatively short. Rapid or acute resetting of approximately 40% appears within the first minutes and remains stable for hours, whereas complete resetting (100% when the change in pressure threshold for activation of the baroreceptors matches the total change in pressure) takes approximately 2 days to develop during hypertension or hypotension in rats. This lability of the baroreceptors makes the baroreceptor reflex a very effective mechanism for regulating blood pressure within a narrow range independently of the pressure level permanently exhibited by the individual. The effectiveness of the baroreceptor reflex mechanism, however, would be very limited if the resetting process was not reversible, that is, if a normotensive level of operation did not accompany the return to normal pressure.

The first direct evidence (by electroneurographic techniques) that the resetting of baroreceptors in hypertension is a reversible process was demonstrated after rapid and sustained pressure normalization in rats with renal hypertension of 2 months' duration. Complete reversal of the baroreceptor resetting (the decrease in pressure threshold matched the total decrease of pressure) was observed within the first 6 hours after pressure normalization. Three days after unclipping, the rats with normalized blood pressure responded to sinoaortic denervation with the same pressure increase as the normotensive rats, indicating that the entire baroreceptor reflex mechanism was again adapted to control pressure at normotensive levels. In spontaneously hypertensive rats (SHR) treated with antihypertensive therapy for 2 or more weeks, reversibility of baroreceptor resetting was correlated mostly with regression of hypertrophy of the tunica media of the aorta rather than with normalization of blood pressure. The degree of aortic hypertrophy (44% increased thickness), however, had no influence on the degree of reversibility because reversibility was the same in rats with sustained renal hypertension of 2 and 6 months' duration. Direct and indirect evidence obtained in dogs also indicates that reversal of the resetting process occurs faster than the initial resetting. Sensitivity of the baroreceptor reflex control of heart rate returned toward normal when assessed either 1–25 days after reversal of renal hypertension in rats or after 6 weeks in rabbits. The carotid baroreceptor stimulus-response characteristics were normal when

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studied 3–7 months after repair of coarctation of aorta in dogs.\(^1\)

The present experiments were undertaken to study the following during the reversal of renal hypertension in rats: 1) how quickly the reversal of the resetting (shifts in pressure thresholds) starts and its sequence during the first minutes after pressure normalization, and 2) whether the reversal of resetting (pressure threshold) is accompanied by changes in the gain sensitivity of the baroreceptors (pressure-discharge relation).

**Methods**

Chronic (2 months) one-kidney, one clip, male renal hypertensive rats (RHR) weighing 200–250 g were used. The procedure for recording whole nerve activity of the aortic baroreceptors in rats anesthetized by pentobarbital (40 mg/kg i.v.) was similar to that used in previous studies.\(^2\)\(^,\)\(^10\)\(^,\)\(^28\)

To assure the stability of the neural recording, including the time during the maneuver to remove the clip, a flexible, thin 0.5 cm gold electrode (0.05 mm diameter) connected to a 10 cm platinum wire (0.05 mm diameter) covered by a vinyl tube (0.50×0.20 mm) was placed around the nerve and carefully insulated with silicone rubber (Wacker SIL GEL 604, Wacker Co., Munich, FRG). The pressure threshold at which the aortic baroreceptors initiated firing and the pressure-nerve activity relation from low to high pressure levels were measured during rapid (10–15 seconds) changes of pressure produced by withdrawal and infusion of blood into the femoral artery. Arterial pressure (carotid artery) and aortic baroreceptor activity were continuously monitored on an oscilloscope (5115 Tektronix Storage Oscilloscope, Tektronix, London, England) and recorded on a tape recorder (model 3960, Hewlett-Packard Co., Atlanta, Georgia) for analysis. The data presented are the average of 2–3 consistent measurements made during each experimental situation. To quantify the whole nerve activity, the nerve traffic was amplified, full waveformed, and integrated with a time constant of 3.9 msec. The integrator output provides the averaged nerve activity relation on a beat-to-beat basis by computer (model Itantec PC-XT, Itantec, Sao Paulo, Brazil) with a 10 bits analog-to-digital converter (model CAD 1016, Lynx, Sao Paulo, Brazil) and a 120 Hz sample rate.

To calculate the extent of reversals of resetting, the ratio of mean arterial pressure threshold decreases to mean arterial pressure decreases (\(\Delta MAPth/\Delta MAP\times100\%\), where MAPth is mean arterial pressure threshold and MAP is mean arterial pressure) was used as suggested by Munch et al\(^+\) with an in vitro preparation of the aortic arch of rats. Additionally, the ratio of systolic pressure threshold changes over total control diastolic pressure changes (\(\Delta SPTH/\Delta CDP\times100\)), where SPTH is systolic pressure threshold and CDP is control diastolic pressure) was used. The latter criterion was chosen because we observed in previous studies that an exact coincidence exists between the systolic pressure threshold that initiates baroreceptor firing and the control diastolic pressure of conscious rats. Also, whenever pressure is constantly changed to hypertensive or hypotensive levels, complete resetting occurs when baroreceptors again begin to fire when the systolic pressure threshold is similar to the new control diastolic pressure.\(^3\)

Direct arterial pressure was measured in freely moving rats by means of a plastic cannula inserted into the abdominal aorta through the femoral artery under ether anesthesia 1 day before the acute experiment. The cannula emerged through the back of the rat and was connected to a strain-gauge transducer (Statham P23-D, Gould-Statham, Oxnard, California) from which the signals were fed into a multichannel recorder (model 7754A, Hewlett-Packard Co.). The level of anesthesia was adjusted to maintain the arterial pressure at the same values existing in the conscious rats before recording the first baroreceptor function curve during the control period. Thereafter, the clip was removed from the renal artery and the rats bled if necessary to maintain the mean arterial pressure at approximately 130 mm Hg (pressure was continuously monitored) for the entire 120-minute period of observation. Baroreceptor function curves similar to those of the control period were repeated 2, 5, 10, 20, 30, 60, 90, and 120 minutes after pressure normalization.

Results are presented as the mean±SEM. Differences in pressure thresholds for activation of the baroreceptors were calculated by using one-sample profile analysis and the displacements of the slope of the baroreceptor function curves were calculated by using regression analysis.\(^18\) The differences were considered significant at \(p\) values of less than 0.05.

**Results**

**Baroreceptor Sensitivity During the Control Period**

The pressure-discharge characteristics of the baroreceptors measured during the control period showed that not only the pressure threshold for baroreceptor activation was displaced to hypertensive levels in the RHR but also that the slope sensitivity of the receptors was depressed. The pressure threshold was 43 mm Hg higher in the RHR as compared with normotensive control rats (NCR) when expressed as systolic pressure threshold values and 40 mm Hg higher when the mean arterial pressure threshold values were used. The gain of the baroreceptor curve was depressed by 36% (0.82±0.03% vs. 1.28±0.02% discharge/mm Hg) when systolic pressure or mean arterial pressure values were calculated (data from Figure 4).

In another group of rats, the gain sensitivity of the baroreceptors was analyzed when changes in pressure were circumscribed to a more physiological range (−10 and +10 mm Hg in the control pressure). Comparison of the actual values of baroreceptor discharges in one RHR with one NCR (Figure 1,
Reversibility of Resetting in Hypertension

Figure 1. Plots showing depressed gain sensitivity of baroreceptors in renal hypertensive rats near physiological range of pressure function. Upper panel: Actual changes of baroreceptor activity during a −10 and +10 mm Hg change in pressure in one normotensive and one renal hypertensive rat. Lower panel: Percentage (%) of change of baroreceptor activity during a −10 and +10 mm Hg change in pressure in normotensive (n=11) and renal hypertensive (n=9) rats.

Reversal of Threshold Resetting

The mean arterial pressure of RHR before anesthesia was 169±11 mm Hg and was maintained at the same level (171±11 mm Hg) after slow administration of sodium pentobarbital when the control mean arterial pressure threshold for baroreceptor activation was 123±8 mm Hg (Figure 2). Two minutes after unclipping and bleeding when necessary, the mean arterial pressure decreased to 134±11 mm Hg and was maintained at approximately the same level for up to 2 hours. For a total decrease of 37 mm Hg in mean arterial pressure after 2 minutes, the mean arterial pressure threshold decreased 22 mm Hg, which represents a 59% reversal of the resetting. The extent of reversal was maximal after 60 minutes (64%, using mean values of mean arterial pressure threshold and mean arterial pressure [Figure 2] or 68±13%, using the individual values); however, this percentage was not statistically different from that measured after 2 minutes. Therefore, the extent of reversal of mean arterial pressure threshold was constant during the entire 120-minute period of observation. The extent of reversal was slightly higher when changes in systolic pressure threshold divided by total changes in control diastolic pressure were calculated (Figure 3). From 64% after 2 minutes, the extent of reversal increased to 83% after 30 minutes of pressure normalization. Calculated with individual values (89±10 vs. 70±6%), this difference was not statistically significant. The extent of reversal exhibited no further increase at 1–2 hours.

Figure 2. Plotting showing sequence of reversal of baroreceptor resetting after reversal of chronic hypertension in renal hypertensive rats (n=9). Mean±SEM of mean arterial pressure (MAP) (top) and mean pressure threshold for activation of baroreceptor (MAPth) (bottom) were used to calculate extent (% in parentheses) of reversal (ΔMAPth/ΔMAP×100).
Reversal of Gain Sensitivity

During the first 20 minutes of pressure normalization, changes in systolic pressure threshold were not accompanied by changes in gain sensitivity because the displacements of the baroreceptor curves were parallel (Figure 4, upper panel). The slopes after 2 and 10 minutes (0.82±0.01% and 0.88±0.02%/mm Hg) were slightly higher than during the control period (0.82±0.03%/mm Hg); however, the differences were not statistically significant. The gain sensitivity was already different from control after 30 minutes of pressure normalization (1.01±0.02%/mm Hg, p=0.0001); however, sensitivity similar to that of NCR (1.28±0.02%/mm Hg) was only observed after 120 minutes (1.27±0.04%/mm Hg, p=0.8431). Similar results were obtained for the mean arterial pressure values (Figure 4, lower panel) except that gain sensitivity had already normalized after 90 minutes (1.29±0.03%/mm Hg, p=0.7207).

Discussion

These results clearly indicate that the reversal of resetting of the pressure threshold for baroreceptor activation from hypertension to normotension is a very rapid process. Only 2 minutes of pressure normalization in RHR with hypertension of 2 months' duration is enough time to produce a pronounced (approximately 60%) reversal in the resetting of the baroreceptors (mean arterial pressure threshold and systolic pressure threshold). Although the extent of reversal of mean arterial pressure threshold remained constant for up to 2 hours, the extent of reversal for systolic pressure threshold values was slightly higher and attained its maximum (83%) after 30 minutes. In previous studies, we found that reversal of resetting was complete (100%) in the majority of the RHR analyzed 6 hours after removal of the renal clip, independent of the duration of hypertension. Changes of the entire baroreceptor function curves indicated that the large displacements of the pressure thresholds toward normal within the first 20 minutes of pressure normalization were not accompanied by improvement in the gain sensitivity, which was depressed in the RHR. The sensitivity starts to increase only after 20 minutes but becomes similar to that of NCR, 90–120 minutes after pressure normalization. Therefore, this is the first demonstration that the gain sensitivity of the baroreceptor, which is depressed in chronic RHR, can return to normal within a 2-hour period of pressure normalization, at a time when the resetting of the pressure thresholds have not completely reverted. Thus, the reversibility of the gain sensitivity of the baroreceptor after pressure normalization starts later than the reversal of the pressure thresholds but normalizes sooner when the reversal of resetting (pressure threshold) is still incomplete.

Resetting of the baroreceptor in chronic hypertension with a variable extent of depressed sensitivity was documented in several animal species. The mechanisms of resetting, however, are still unclear. Acute resetting observed within the first minutes of hypertension, which remains stable for hours with no change in gain, has been attributed to viscoelastic relaxation of the arterial wall; to ionic, chemical, and endothelial factors; or to alteration in the intrinsic neural properties of the receptors. Rapid resetting is a partial resetting (approximately 40%), however, and will only become complete when the shifts in baroreceptor threshold match the total increase in...
pressure, which occurs after approximately 2 days for the aortic baroreceptor of rats. Because the time needed for complete resetting coincides with the time needed by the resting diastolic caliber to reach maximal dilatation during onset of hypertension, it seems that complete resetting occurs when increased diastolic pressure no longer effectively strains diastolic caliber. In this new state of equilibrium, the sustained elevated diastolic pressure no longer stimulates the receptors that are distorted only when the resting caliber is again momentarily distended by the pulse pressure. In freely moving RHR, aortic pulsation was twice that of normotensive rats despite the fact that distensibility and stiffness were similar. Thus, under physiological conditions, a decreased receptor sensitivity to strain was demonstrated similar to that described for the aorta of SHR or rats during growth, studied in vitro. A depressed gain sensitivity of the baroreceptor was observed in RHR when the baroreceptor pressure-discharge relation was compared with that of NCR in the present study. The decreased sensitivity was observed in the entire baroreceptor function curve (from threshold to saturation) and also when the analysis of the pressure-activity characteristics was circumscribed to a more physiological range of pressure changes (−10 and +10 mm Hg in the control pressure). It is remarkable that slope sensitivity returned to normal 2 hours after pressure normalization when the extent of reversal of pressure threshold was approximately 60% (ΔMAPth/ΔMAP, where MAPth is mean arterial pressure threshold) or approximately 80% (ΔSPth/ΔCDP). Nevertheless, the time required for both the baroreceptor set points and gains to return to normal after pressure normalization from hypertension is very brief. This can be of great physiological importance.
during antihypertensive treatment because it greatly diminishes the intensity and duration of the mechanisms elicited reflexly by the baroreceptor during reversal of hypertension. Even when the major driving force for reversal of baroreceptor resetting seems to be the decrease in pressure, it is possible that different antihypertensive treatments modulate the process differently. Sodium nitroprusside but not verapamil, in chronic RHR, produced a greater extent of reversal than that expected from the same decrease in pressure produced by hemorrhage. Our data demonstrated that reversibility of baroreceptor resetting and normalization of gain sensitivity occur within the first few hours with characteristics very similar to those described earlier, when baroreceptor function was assessed only days, weeks, and months after pressure normalization.15-17

References


Key Words • renal hypertension • baroreceptor reflex • hypotension • baroreceptors • baroreceptor resetting
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