Baroreceptor Reflex Control of Heart Rate During Development of Coarctation Hypertension

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To study whether resetting of the baroreceptors is accompanied by normal reflex activity to the heart, we analyzed time-course changes of pressure, heart rate, baroreceptor reflex sensitivity, and plasma renin activity during the development of coarctation hypertension. Baseline heart rate was measured daily, and plasma renin activity and reflex changes in heart rate (bolus injections of either phenylephrine or nitroprusside, 0.2–25.6 μg/kg i.v.) were recorded at different times in coarcted and sham-coarcted rats. Hypertension was stable (−39% from baseline mean arterial pressure of 112±3 mm Hg), whereas heart rate (333±4 beats per minute) showed a biphasic behavior: bradycardia at 6 hours (264 ±7 beats per minute) and tachycardia at 5 days (418±14 beats per minute). On day 10 of hypertension, heart rate was normal. Plasma renin activity was markedly increased only after 6 hours (4.9 times). Reflex bradycardia exhibited a progressive impairment: The slopes of the regression lines between changes in heart rate and changes in mean arterial pressure were not significantly reduced at 6 and 48 hours when the resetting was in development (changes of 17% and 28% from a control of −1.89±0.20 beats per minute/mm Hg) but were significantly depressed after the resetting had been completed (−51% and −56% at 5 and 10 days, respectively). Reflex tachycardia was significantly reduced in all periods studied (75%, 78%, 52%, and 61% at 6 hours and 2, 5, and 10 days, respectively; −3.92±0.42 beats per minute/mm Hg in sham rats). We conclude that reflex bradycardia but not reflex tachycardia is preserved at early coarctation, when the resetting of the baroreceptors is developing. At established hypertension, when the complete resetting is present, the marked impairment of both reflects an abnormality in the central mediation of the reflex, possibly triggered by angiotensin II. (Hypertension 1992;19[suppl II]:11-159–II-163)
Methods

Male Wistar rats aged approximately 3 months and weighing 200–260 g were used. For continuous recording of HR of conscious, unrestrained rats, two flexible stainless steel electrodes, isolated in all extension except in the extremities, were implanted with rats under ether anesthesia in the axilar region (lead I of the electrocardiogram) and tunneled subcutaneously to the back of the neck. The reference electrode was implanted in the dorsal muscle of the neck. The distal extremities of the three electrodes were fixed to a three-pin miniaturized socket, and the assembly was fastened on the skull surface with fast polymerizing metacrylate. After surgery, the rats were given 60,000 IU penicillin (Pentabiotico Veterinário, Fontoura-Wyeth, SP, Brazil) and returned to their individual cages (35x35x60 cm) in the recording room, receiving food and water ad libitum.

Hypertension of the superior part of the systemic circulation was produced by subdiaphragmatic aortic coarctation (coarcted hypertensive rats, CHRs) according to a technique previously described in detail.1-2-4 Sham-coarcted rats (SRs) served as controls. Time-course changes of HR of freely moving CHRs and SRs were measured daily from electrocardiographic records (model 3400 recorder, Gould Instruments, Cleveland, Ohio) with rats at rest.

Sequential changes of both arterial pressure and baroreceptor reflex sensitivity were determined at the control period and 6 hours and 2, 5, and 10 days after surgery in other groups of SR and CHRs chronically instrumented for electrocardiogram and submitted to carotid and jugular cannulation (PE-50 polyethylene tubing, Clay Adams, Parsippany, N.J.), performed with rats under ether anesthesia immediately after HR recordings. Simultaneous arterial pressure and HR measurements (now by means of arterial pressure pulses) were recorded 2-3 hours later when the rats had recovered from ether anesthesia. Reflex changes in HR were produced by repeated bolus injections (0.1 ml) of graded doses of phenylephrine (0.2, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 µg/kg) and sodium nitroprusside (0.4, 0.8, 1.6, 3.2, 6.4, 12.8, and 25.6 µg/kg) into a jugular vein, and control and peak mean arterial pressure (MAP) and HR changes for each response were measured. Instantaneous HR was determined by the number of pulses of arterial pressure in 1 second. Phenylephrine and nitroprusside injections were made at random, and subsequent injections were not made until the recorded parameters had returned to preinjection levels. The intravenous injection of vehicle (saline) alone did not change the recorded parameters.

For temporal screening of the activity of the renin-angiotensin system, other groups of rats were coarcted or sham-coarcted and had a carotid artery cannula implanted 6 hours before the arterial pressure determination and blood collection. Free-flowing blood (~1 ml) was collected in disodium EDTA (1 mg/ml blood), iced and spun at 4°C, and the plasma was frozen at −20°C until incubation and was assayed as described in detail elsewhere.10 PRA was measured by radioimmunoassay.

Results are expressed as mean±SEM. For each rat, the relation between changes in HR and MAP was estimated using linear regression analysis. The regression coefficient (slope) was taken as an index of baroreceptor reflex sensitivity. Significant differences between groups were evaluated by one-way analysis of variance and Dunnett's test (p<0.05).

Results

Heart Rate Changes

The acute and stable hypertension developed by CHRs (a maintained increase of approximately 39% from a baseline value of 112±3 mm Hg; Figure 1) caused a biphasic behavior in baseline HR: an intense transient bradycardia at 6 hours (264±7 versus 333±4 beats per minute in the control period) followed by a longer tachycardic period that started after day 3, peaked on day 5 (418±14 beats per minute), but normalized on day 10 of CH (333±16 beats per minute).
Baroreceptor Reflex Control in Hypertension

Michelini et al

Figure 2. Line plots show reflex changes in heart rate (HR) during increases or decreases in mean arterial pressure from control values (C) in sham-coarcted (SR, n=18) and coarcted (CHR) rats after 6 hours (6h; n=13) and 2 days (2d; n=9) (left panel) and after 5 days (5d; n=8) and 10 days (10d; n=8) of hypertension (right panel). Linear regression equations are HR (SR)=8.64-1.89x and -5.18-3.92x; HR (CHR-6h)= -6.65-1.57x and -9.25-0.97x; HR (CHR-2d)= -2.87-1.37x and 12.72-0.87x; HR (CHR-5d)= -4.94-0.93x and 19.31-1.88x; HR (CHR-10d)=3.52-0.84x and 2.32-1.54x, respectively, for phenylephrine-induced increases and nitroprusside-induced decreases in mean arterial pressure. Linear regressions for SR—6h, SR—2d, SR—5d, and SR—10d were similar and are represented by a single line, which is repeated in both panels.

Activity of the Renin-Angiotensin System

Subdiaphragmatic aortic constriction that caused similar increases in arterial pressure (156±7, 149±4, 144±8, and 151±10 mm Hg at 6 hours and 2, 5, and 10 days, respectively; 114±3 mmHg in SRs) determined a marked increase of PRA at 6 hours (n=13): 7.74±1.72 versus the control value of 1.57±0.33 ng angiotensin I/ml/hr in SRs (n=10). After 2 and 5 days, PRA values were still increased, but the differences were not statistically significant: 2.52±0.75 (n=3) and 4.02±1.45 ng angiotensin I/ml/hr (n=7), respectively. After 10 days, PRA was normal (0.92±0.34 ng angiotensin I/ml/hr, n=11).

Discussion

In this study, two important observations were made. The first concerns the time course for the intense tachycardia that follows the complete resetting of baroreceptors: It starts on day 3 of hypertension, peaks on day 5, but returns to baseline HR after 10 days. Second, during the development of hyper-
tension, the impairment of both baroreceptor-mediated bradycardia and baroreceptor-mediated tachycardia is not simultaneous but occurs at distinct times: Reflex tachycardia was precociously and consistently impaired within the first hours of CH, whereas reflex bradycardia showed a progressive depression attaining significance only after the resetting of arterial baroreceptors had been completed.

The abrupt rise in arterial pressure that accompanied the subdiaphragmatic aortic constriction augmented the traffic of the baroreceptor and triggered at 6 hours when the resetting was not complete an increase in vagal tone and a reflex decrease in HR. At 5 days, the occurrence of tachycardia in spite of sustained elevations in pressure suggested an increased sympathetic nerve activity. Previous works have called attention to the appearance of tachycardia in CH. Transient tachycardia and increased sympathetic activity have also been observed in other rat models of hypertension, such as sinoaortic denervation and one-kidney, one clip Goldblatt rats and also in the dog developing two-kidney, one clip hypertension. The increased sympathetic activity occurs after complete resetting of the baroreceptors, indicating the contribution of a central factor that overrides the buffering action exerted by the baroreceptor reflexes. The increased PRA within the early phase of aortic coarctation is probably accompanied by central renin-angiotensin system overactivity and could have a marked influence on the appearance of tachycardia observed in these rats. Increased PRA simultaneously with higher levels of angiotensin II in both plasma and cerebrospinal fluid have been shown in two-kidney, one clip dogs, the endogenous angiotensin II levels remaining elevated for more than 7 days after the normalization of PRA. We speculate that a similar effect could be present in the coarcted rats of the present study. Thus, the late tachycardic phase and the simultaneous impairment of the baroreceptor-mediated bradycardia could be triggered by the huge earlier PRA increase and maintained by the enhanced endogenous levels of angiotensin II. Actually, overactivity of the renin-angiotensin system has been shown to participate in the pathogenesis of CH by the transient activation in the acute phase as pressure rise and by the inappropriateness of "normal" PRA coupled with expanded extracellular fluid and plasma volumes in the established phase. In this regard, we also observed in coarcted rats increased drinking from the sixth to ninth day and increased urinary volume only on the eighth to ninth day of hypertension (unpublished observations from our laboratory), indicative of enhanced volemia during the tachycardic phase. Angiotensin II is a potentiating factor of sympathetic action at central and peripheral sites, and increased angiotensin II after coarctation may strengthen the sympathetic tone, thus collaborating with the increase in HR from 3 to 8 days and facilitating its normalization on day 10 when the activity of the renin-angiotensin system (and volemia) were again normal. Normalization of HR during persistence of hypertension was also described in rats and dogs.

A normal baroreceptor reflex bradycardia was observed during the phase of increased vagal tone, because the small HR response compensated for the reduced pressor change to phenylephrine, which is blunted during the acute phase of CH. Within the first 6 hours, no change in the baroreceptor gain was described and, in the present work, no alteration in baroreceptor reflex bradycardia was observed. At 2 days, the pressure threshold was reset and the baroreceptor gain was reduced by 32%, but the baroreceptor reflex bradycardia was within the normal range (the observed depression of 28%, although close, was not significant). This period is certainly critical for baroreceptor-mediated bradycardia, in the process of changing from unaltered to depression, which is probably conditioned by the complete resetting of the afferents. Although the magnitude of resetting (pressure threshold and gain sensitivity) did not change thereafter, the reflex bradycardia showed an additional and marked impairment at 5 and 10 days, when the sympathetic tone was increased and vagal tone almost abolished (5 days) and when the pressor response to phenylephrine was normalized in the presence of maintained hypertension (10 days). The marked changes of reflex bradycardia in established hypertension suggest, besides the complete resetting with depressed gain sensitivity of the afferents, a dissociation between the baroreceptor input and the baroreceptor reflex control of HR. Progressive impairment of baroreceptor control of circulation in hypertension has also been attributed initially to an abnormality of the afferent limb of the baroreceptor reflex and later to an abnormality in central nervous system mediation of the reflex. Angiotensin II acting centrally could contribute to the impairment of reflex bradycardia, as we have shown previously by microinjecting angiotensin II or by blocking endogenous angiotensin II in the solitarii-vagal complex of the conscious rat. After administration of angiotensin II, the reduction in the baroreceptor sensitivity to increases in pressure was of the same magnitude (~49%) as that observed at 5 and 10 days of CH. Impaired baroreceptor-mediated bradycardia was also described in other models of high renin renal hypertension, such as one-kidney, one clip and aortic ligation. The reflex tachycardia was markedly depressed at all periods of CH studied. At 6 hours and 2 days, the impairment was mainly caused by the maintenance of a normal depressor response to nitroprusside, with a reduced tachycardic response (period of increased vagal tone); at 5–10 days, the sympathetic tone increased, but the depressor responses to nitroprusside were even higher than control responses. Angiotensin II may not be involved in this effect, because intravenous or intra-cerebroventricular administration of the peptide and even its microinjection into the solitarii-vagal complex did not change the baroreceptor con-
control of HR during decreases in arterial pressure. Whether other peptides or other areas are responsible for the impaired tachycardia in hypertension requires further study. On the other hand, chronic overactivity of the renin-angiotensin system may be involved in the depression of reflex tachycardia as well as reflex bradycardia.

The present results show that during the development of CH, there was a temporal change of baroreceptor-mediated bradycardia from unchanged to a marked impairment observed during the tachycardic phase, possibly by an action of angiotensin II at the solitary-vagal complex. Baroreceptor-mediated tachycardia was uniformly depressed in short- and long-term coarctation. These effects, indicating a temporal dissociation between changes in reflex bradycardia and tachycardia, suggest central impairment of the reflex, which was differential on control of parasympathetic and sympathetic tone and fully manifested after resetting of the baroreceptors had been completed.

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References


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