Chronic AT₁ Receptor Blockade Alters Autonomic Balance and Sympathetic Responses in Hypertension

Simone M.M.S. Bezerra, Claudia M. dos Santos, Edson D. Moreira, Eduardo M. Krieger, Lisete C. Michelini

Abstract—In the coarctation hypertension model, we have shown that chronic treatment with losartan causes both normalization of impaired reflex control of heart rate and partial correction of the depressed aortic nerve activity/pressure relationship, even with the persistence of hypertension. In the present study, we analyzed the effects of angiotensin II blockade on the efferent pathways of coarcted and sham-operated groups treated chronically with vehicle or losartan (10 mg/kg per day PO). Hypertension was induced by subdiaphragmatic aortic coarctation, and the treatments lasted 9 days (4 control and 5 experimental days). On day 5, autoregressive power spectral analysis was performed on heart rate recordings made in conscious rats. Other groups were used for sympathetic splanchnic nerve activity recordings made simultaneously with pressure (anesthetized rats) at basal condition and during loading/unloading of baroreceptors. Losartan treatment induced a significant reduction in basal pressure but did not interfere with the development of hypertension (similar pressure increases of 24% and 28% over control values in losartan and vehicle groups, respectively). In vehicle-treated rats, establishment of hypertension was accompanied by a marked change in power spectral density from high- (1.19±0.06 Hz, 33±6%) to low-frequency components (0.42±0.03 Hz, 54±6%), with increased low-frequency–to–high-frequency ratio. When compared with sham-operated vehicle-treated rats, there was also increase in the gain of sympathetic activity/pressure relationship, with displacement of lower plateau toward high levels of sympathetic activity. No changes in the power spectral density and sympathetic activity/pressure relationship were observed when hypertension developed in the presence of chronic angiotensin type 1 (AT₁) receptor blockade. The data suggest that angiotensin II, activated during the establishment of coarctation hypertension, acts via AT₁ receptors to alter sympathovagal balance, facilitating the sympathetic outflow to heart and peripheral circulation during baroreceptors unloading. Data also indicate that the observed effects are not conditioned by preexisting pressure levels. (Hypertension. 2001;38[part 2]:569-575.)

Key Words: receptors, angiotensin II ■ losartan ■ blood pressure ■ heart rate ■ hypertension, experimental ■ rats

It is well known that the renin-angiotensin system (RAS) is involved in cardiovascular regulation and in the development/maintenance of hypertension.¹⁻⁵ The presence of an endogenous RAS in brain areas involved in cardiovascular regulation has been confirmed by several techniques.³⁻⁶,⁷ Stimulation of high affinity angiotensin (Ang) II receptors⁸ leads to a set of coordinated autonomic and endocrine responses yielding to blood pressure increase and hypertension.¹²⁻⁵,⁸⁻⁹

Blockade of RAS usually reverses the angiotensin-induced effects simultaneously with a significant pressure reduction. It is not well established if the various autonomic/endocrine changes observed in hypertension were caused only by the direct effect of Ang II, by the concomitant blood pressure increase, or by a combination of both. In this regard, coarctation hypertension (CH) caused by subdiaphragmatic aortic constriction is an advantageous model of hypertension.¹²⁻⁵,¹³

In CH, pressure increase is determined mainly by the elevated resistance interposed to the circulation (mechanical factor¹⁰⁻¹¹), in such a way that converting-enzyme inhibition and angiotensin type 1 (AT₁) receptor blockade cause small reductions but do not impair the development and magnitude of hypertension.¹²⁻¹³

In CH rats, we showed that increased baseline heart rate (HR) and the impaired baroreceptor reflex control of HR were Ang II–specific effects, not conditioned by the hypertensive levels, because chronic AT₁ receptor blockade normalized both, without interfering with the pressure load.¹² We showed also that Ang II, activated during CH, depressed the afferent signaling of aortic baroreceptors.¹³ However, aortic nerve gain was only partially corrected by chronic AT₁ receptor blockade,¹³ suggesting that complete normalization of baroreflex control of the heart should involve other effects.
Not knowing if the characteristic hypertension-induced changes in the sympathetic tone to the periphery and its reflex control are caused by Ang II itself and/or by the concomitant pressure elevation, the objectives of the present study were (1) to determine in CH and normotensive control rats the effects of chronic blockade of AT<sub>1</sub>-Ang II receptors on both basal sympathetic tone and sympathetic nerve activity during loading/unloading of baroreceptors and (2) to determine the autonomic balance to the heart in CH and normotensive rats treated chronically with vehicle or losartan.

**Methods**

Male Wistar rats (ICB, University of San Paulo), aged 3 to 4 months and weighing 200 to 300 g, were used. During the experimental period, the rats were housed in individual cages on a 12-hour/12-hour light/dark schedule and allowed free access to standard laboratory chow and water. All surgical procedures and protocols used were in accordance with Ethical Principles in Animal Research (Brazilian College of Animal Experimentation) and were approved by University of Sao Paulo Ethical Committee for Animal Research. Rats were treated orally for 9 days with vehicle (VEH) (distilled water, 1 mL · kg<sup>−1</sup> · d<sup>−1</sup>) or losartan (LOS) (10 mg · kg<sup>−1</sup> · d<sup>−1</sup>). After a control period (4-day treatment), half of the rats in VEH and LOS groups were submitted to CH, whereas sham-operated rats (SH), the other half, served as controls.

CH, which induces hypertension of the upper part of systemic circulation, was produced by partial subdiaphragmatic aortic constriction, by a technique described previously. Briefly, under ether anesthesia, the rats were submitted to median laparotomy and isolation of the abdominal aorta just below the diaphragm and near the exit of the superior mesenteric artery. A cotton thread was used to constrict the aorta, the extent of narrowing being limited by a hypodermic needle (0.7 to 0.9 mm OD), according to the rat’s body weight. The needle was removed, and the abdomen was sutured. SH rats were submitted to the same surgical procedures, except for the narrowing of the abdominal aorta. All rats received 60 000 IU of penicillin (Pentabiotico Veterinário, Fontoura-Wyeth).

Pressure was measured by a tail-cuff technique (Programmed Sphygmomanometer, PE-300, Narco Bio-Systems) 7 to 10 days before starting the treatments and on day 4 of LOS or VEH therapy, immediately before CH or SH surgery. Arterial pressure (AP) was also measured directly (P23Db transducer, Gould-Statham) on day 5 of CH or SH. The right common carotid artery was cannulated and stored on a disk for offline analysis. Systolic and diastolic pressure and HR values were acquired on a computer and subjected to analog-to-digital conversion (Codas-Windaq, DI-200).

Data analysis was performed in beat-to-beat time series of raw data. Data series were inspected visually on the computer screen to guarantee the accuracy of the automatic detection; segments with artifacts were systematically discharged. Mean values and standard deviation of the mean of HR series were calculated as an index of artifacts were systematically discharged. Mean values and standard deviation of the mean of HR series were calculated as an index of variability of the heart rate on the time domain. The spectral density of the various frequency components of HR (frequency domain) was calculated by the autoregressive model (AR, model 12). The principles of the software for data acquisition and analysis have been described previously. AR power spectral analysis was made in short-term recording sequences (series of 512 and 1024 consecutive cardiac cycles) that allow for the detection of the central frequency and distribution of power of 2 main spectral components: low (LF) (0.25 to 0.75 Hz) and high frequency (HF) (0.75 to 3.00 Hz). AR analysis was repeated several times in stationary series (6 to 12) in the 60 to 70 minutes of continuous recording and the average central frequency (Hz) and power spectral density (in beats · min<sup>−1</sup> · Hz and mm Hg/Hz, or percentage of normalized units) used as natural values.

Other SH<sub>Veh</sub>, CH<sub>Veh</sub>, SH<sub>LOS</sub>, and CH<sub>LOS</sub> groups were used to record sympathetic nerve activity on experimental day 5. After measurement of AP in the conscious state, rats were intravenously anesthetized with a mixture of α-chloralose (50 mg/kg) and urethane (500 mg/kg), had the right jugular vein cannulated, and were prepared for recording splanchic sympathetic nerve activity (SSNA). The procedure used to record whole nerve SSNA was similar to that used in previous studies. Upper left lateral laparotomy allowed for isolation of the left splanchic nerve, which was placed on bipolar platinum electrodes; a third electrode, fixed in the muscle, served as reference. Whole SSNA was filtered (band pass of 100 to 3000 Hz), amplified (Differential Amplifier, 502A, Tektronix), full-wave rectified, and integrated (time constant of 3.9 milliseconds). The integrator output provides the nerve activity for each cardiac cycle (mV/cycle), continuously monitored on an oscilloscope (5115 Storage, Tektronix). SSNA was acquired online (computer, 3000 Hz sampling) with AP, subjected to analog-to-digital conversion (Codas), and stored. Because of great individual variability and multifiber preparation, SSNA was normalized and expressed as %/cardiac cycle. The experimental protocol consisted of measurements of SSNA/MAP relationship at basal condition (control, at least 20-minute record) and during MAP changes induced by intravenous infusions (100 μg/mL, 1 to 4 μL/h) and/or bolus injections (1 to 3 μg/kg) of phenylephrine and sodium nitroprusside. The data presented are the average of 2 to 3 consistent measurements made during each experimental situation for each rat. To represent SSNA responses during MAP changes the efferent discharge (%/cycle) was normalized, with the control SSNA value of 100%. Pressure-induced changes of SSNA were analyzed through logistic equations adjusted to data points:

\[
\text{SSNA} = P1 + \frac{P2}{1 + e^{-(x-P3)/P4}}
\]

where P1 is the lower SSNA plateau; P2, SSNA range, P3, curvature coefficient (which is independent of range); and P4, MAP<sub>50</sub> (ie, the MAP at half of SSNA range). The upper plateau is determined as P1 + P2, and the average gain (G) or slope of the curve between the 2 inflection points is given by G = (−P2 × P3)/4.

Results are presented as mean±SEM. For all parameters, differences between groups (CH and SH) and treatments (LOS and VEH) were analyzed by 2-way ANOVA, followed by Student-Newman-Keuls multiple comparison test. Differences were considered significant at P<0.05.

**Results**

**Blood Pressure Changes**

In the control period, the 4-day LOS treatment caused a significant reduction of tail pressure (93±4 versus 112±3 mm Hg in the VEH-treated rats, Table). On experimental day 5, direct measurements of pressure in the conscious state confirmed that both CH<sub>Veh</sub> and CH<sub>LOS</sub> groups were hypertensive (154±3 and 133±3 mm Hg) (Table) compared with respective controls (120±3 and 107±4 mm Hg in SH<sub>Veh</sub> and SH<sub>LOS</sub>, corresponding to equal pressure loads of 28% and 24%, respectively).

**HR Variability**

Figure 1 illustrates the power spectral density of HR variability in 4 rats representative of the 4 groups. For SH<sub>Veh</sub> and SH<sub>LOS</sub>, the dominant frequency (with a higher fractional power) was found in the HF range (0.75 to 3.00 Hz). In CH<sub>Veh</sub> but not in CH<sub>LOS</sub>, the dominant frequency moved to the LF range (0.25 to 0.75 Hz). Group means showed that baseline HR variability was characterized by 2 major spectral
components at LF (~0.4 Hz) and HF (~1.2 Hz), with similar central frequencies among groups (Table 1). However, the fractional power differed markedly between groups: whereas in the SH groups HF predominates (33% to 35% of total power spectrum) over LF (smaller fractional power, in the range of 16% to 19%), in CH VEH rats there was a marked predominance of LF over HF (54±6% versus 14±1%, respectively) (Table), determining a marked increase in LF/HF ratio (from 0.90±0.42 to 4.66±1.12). On the other hand, the establishment of CH in LOS-treated rats did not change the HF or LF component and the LF/HF ratio (0.30±0.04 versus 0.46±0.10). Therefore, both LF and HF/HF ratio were significantly smaller in CH LOS versus CH VEH (Table).

Splanchnic Sympathetic Nerve Responses

At the conscious state, MAP of SH VEH, CH VEH, SH LOS, and CH LOS groups used for SSNA experiments were 111±2, 151±9, 104±2, and 128±5 mm Hg, respectively. Anesthesia did not change significantly MAP levels (values on the Table). At the control period, basal integrated SSNA (mV/cardiac cycle) (Table) was similar for all groups, corresponding to 29±4, 28±3, 28±5, and 30±2%/cycle in SH VEH, CH VEH, SH LOS, and CH LOS, respectively. Normalized basal SSNA (15-minute recording period) showed large variability but a negative relationship with spontaneous fluctuations of MAP. The slope of the regression lines were not different among groups, although sensitivity was 61% and 53% smaller in CH VEH and CH LOS versus respective controls (Table).

Figure 2 illustrates groups average sigmoidal logistic equations adjusted to SSNA responses during pressure changes, and the Table shows the equations parameters for the 4 groups of rats. In VEH- and LOS-treated groups, establishment of hypertension caused a right-hand displacement of normalized curves toward higher MAP levels (both control MAP and MAP50 were increased) (Table). The slope of the curve (−10.36±1.05% · cycle−1 · mm Hg−1) and the lower plateau (45±5%/mm Hg) were only increased in CH VEH group (versus SH VEH group) (Figure 2). These effects were not present when hypertension developed in the presence of chronic AT1 receptor blockade. Because in the CH model of hypertension the narrowing of the aorta was not exactly the same in all animals (the extent of narrowing was based on body weight, an approximate index), hypertensive levels attained showed a continuous distribution with 2 subgroups exhibiting higher (153±3 mm Hg) and lower control MAP levels (123±3 mm Hg, a value similar to that of CH LOS group). The comparison of normalized SSNA/MAP curves in the CH VEH subgroups (Figure 2, lower panel) corroborates the observation that reflex gain and lower plateau displacement were not conditioned by the existing pressure level, because they were similarly increased in the higher (−9.49±1.27% · cycle−1 · mm Hg−1 and 45±6%/cycle, n=7) as well as in the lower MAP subgroups (−11.60±1.79% · cycle−1 · mm Hg−1 and 46±9%/cycle, n=6, respectively). Figure 2 also discriminates between the different effects of chronic LOS treatment on SSNA: (1) the pressure-lowering effect demonstrated by the displacement of the SH LOS and CH LOS curves to the left, according to the reduction in the respective control MAP, and (2) the restoration of efferent gain and normalization of the lower plateau during establishment of CH. On the other hand, LOS did not change SSNA/MAP relationship in SH rats.

Discussion

The present new set of data demonstrates that Ang II, activated by CH, acts on AT1 receptors to cause both marked increase in basal sympathetic tone to the heart and facilitation of SSNA responses during pressure challenges. The complete normalization of these responses with chronic AT1 receptor blockade, in the presence of similar pressure load, indicates the observed effects are not dependent of the pressure load. Several studies have linked Ang II with altered cardiovascular functions in different models of hypertension. On day 5 of CH, previous studies from our laboratory have shown overactivation of the RAS and increased baseline HR, depression of both reflex bradycardia and tachycardia, and increased variability of aortic nerve activity associated with reduction in the gain of afferent discharge/presure relationship. What we show in the present study is that part of the depression of baroreflex control could be attributed to the effects of Ang II on efferent pathways, by changing the sympathovagal balance to the heart, by reducing peripheral sympathetic inhibition during pressure increases, and by facilitating sympathetic outflow during pressure decreases. It is interesting to note that in the CH model of hypertension, as showed before in the sponta-
neous hypertension. Ang II has an important role in influencing both baroreceptor reflex sensitivity and sympathetic outflow.

Several pieces of experimental evidence show that elevated Ang II levels are associated with increased sympathetic activity. Although the interaction between Ang II and peripheral sympathetic activity in hypertensive individuals has been extensively investigated, there are some controversies: increased, decreased, or unchanged sympathetic activity has been described. Other works point out that increased sympathetic activity was not constant but transiently elevated at early hypertensive stages. Apart of the transient characteristic, the discrepant findings are certainly owing to the available methods to measure sympathetic activity (magnitude of pressure fall after sympathetic blockade, measurements of plasma norepinephrine release and turnover, direct neuronal recordings). Most of these techniques allow the determination of an indirect index of sympathetic activity, whereas sympathetic nerve traffic recording can measure it directly, but only in a specific region of anesthetized animals. Actually, our recordings of SSNA in anesthetized rats showed similar basal values in all groups, although the pressure-induced SSNA response was increased by CH and normalized by LOS. On the other hand, our results with power spectral analysis on spontaneous fluctuations of HR (and MAP) clearly showed the predominance of LF over HF components, indicative of an increased sympathetic tone after the establishment of hypertension in VEH-treated rats. It is possible to reconcile these apparently discrepant experimental findings in CHVEH rats. Similar basal SSNA (total discharge in mV/cardiac cycle) is a good index for the presence of baroreceptors resetting to hypertensive levels and permits the normalization of sympathetic inhibition in the chronic phase of CH, besides the maintenance of high pressure. On the other hand, the predominance of LF component indicates that the sympathetic inhibition in the

<table>
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<th>Values of MAP, HR, LF, and HF Components of HR Variability and SSNA in VEH- and LOS-Treated Groups Submitted to CH or SH</th>
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<td><strong>VEH-Treated</strong></td>
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<td>Tail pressure, mm Hg</td>
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Values are mean±SEM.
<sup>*</sup>P<0.05 vs SH; <sup>†</sup>P<0.05 vs VEH.
CH\textsubscript{VEH} was not exactly similar but smaller than that of other groups, besides the similar total neural efferent activity. Actually, it is well documented in hypertension that in the presence of baroreceptors resetting, both baroreceptor reflex control of HR and total peripheral resistance were significantly depressed (smaller gain\textsuperscript{11,21,24,30}). This could facilitate an increase in the sympathetic tone, as we show in the CH\textsubscript{VEH} group. The new observation was possible because of employment of the spectral analysis on spontaneous HR and MAP variability, a very sensitive method to distinguish even mild changes, not detected by the conventional methods.\textsuperscript{15,34}

Power spectral analysis also revealed that not only the LF was favored, but the HF component was markedly reduced in CH\textsubscript{VEH}, thus contributing to alter sympathovagal balance to the heart. LF/HF ratio, used as an index of sympathovagal activity,\textsuperscript{15,32} showed that establishment of hypertension was accompanied by a huge control in the autonomic control of the heart from a vagal predominance to an intense sympathetic activity. This change may explain the marked depression of both reflex bradycardia (less efficient inhibition of sympathetic plus smaller response of the already depressed vagal tone) and reflex tachycardia (small range for further sympathetic increase) we observed previously in the chronic phase of CH.\textsuperscript{11} Our results with direct SSNA recordings also showed increased peripheral sympathetic outflow during loading/unloading of baroreceptors in the CH\textsubscript{VEH}. The significant displacement of lower plateau to high SSNA levels revealed a deficient withdrawal of sympathetic during transient pressure increases, which is consistent with reduced gain of sympathetic response described earlier in the chronic phase of CH.\textsuperscript{11} On the other hand, the larger gain of SSNA/MAP relationship was consistent with a potentiation of sympathetic response during transient pressure decreases. Ang II–induced depression of vagal afferents\textsuperscript{25,35} and attenuation of sympathetic vasoconstrictor responses to sympathetic nerve stimulation, hypothalamic simulation and intravenous norepinephrine injections in SHR chronically treated with captopril\textsuperscript{22} have been described previously.

Interestingly, the development of hypertension in the presence of chronic LOS treatment completely blocked all the observed effects, thus abolishing evidence of sympathetic overactivity. These results clearly indicated that Ang II triggers the sympathetic tone to the heart and splanchnic bed, via activation of AT\textsubscript{1} receptor. Both AT\textsubscript{1} and AT\textsubscript{2} receptors subtypes have been mapped in the central nervous system of rats, but most of the functional Ang II effects are mediated by the G protein–coupled AT\textsubscript{1} receptor.\textsuperscript{8,36} In addition, brain structures involved in cardiovascular control such the nucleus tractus solitarii, dorsal motor nucleus of the vagus, hypothalamic nuclei, and circumventricular organs have been shown to contain AT\textsubscript{1}–Ang II receptors exclusively.\textsuperscript{36} We showed before that Ang II has important effect on baroreflex control by altering aortic baroreceptor discharge,\textsuperscript{13} by acting in the nucleus tractus solitarii,\textsuperscript{37} and by changing sympathetic outflow (present results). Apart of these results and the central distribution of AT\textsubscript{1} receptors,\textsuperscript{36} we still do not have experimental evidence on which areas are actually involved in the mediation of Ang II effects on sympathetic outflow during the establishment of CH.

It should be stressed that all the observed responses are due to the modulatory effect of Ang II and not to simultaneous pressure changes. Independent of LOS-induced MAP decreases (−17% by tail pressure, −11% and −12% in the conscious and anesthetized SH rats, respectively) (Table), establishment of CH caused similar pressure loads in VEH- or LOS-treated groups (+28% and +24%, respectively). In addition, the significant differences of lower plateau and SSNA/MAP gain between CH\textsubscript{LOS} and CH\textsubscript{VEH} low-pressure subgroup (presenting the same absolute MAP levels) clearly showed that the observed effects are not dependent on maintained pressure levels. Dissociation between pressure levels/plasma renin activity\textsuperscript{23} and between plasma renin activity/lower brain stem angiotensinogen mRNA levels\textsuperscript{38} has
been demonstrated in rats made hypertensive by ligation of the aorta between the renal arteries. In accordance, we have previously shown that the modulatory effect of central Ang II on baroreceptor reflex control of heart rate was not dependent of the pressure level. Subpressor doses of Ang II administered into the nucleus tractus solitarius of normotensive rats depressed the reflex bradycardia\(^7\) and CH rats treated chronically with LOS showed normalization of reflex responses and aortic nerve activity even in the persistence of hypertension.\(^12,13\)

Collister et al\(^8\) reported that chronic treatment with LOS was able to lower pressure of normotensive rats on normal-sodium diet. Accordingly, a similar daily dose of LOS caused a reduction of pressure levels in SH as CH groups, with similar magnitude and maintained throughout the experiment. The LOS-induced reduction in MAP emphasizes the importance of endogeneous Ang II levels in the maintenance of basal vasocostriction and in the determination of basal pressure in both groups. In the CH groups treated or not treated with LOS, the huge constriction of the upper abdominal aorta, imposing a large resistance to blood circulation (mechanical factor\(^10\)) determined a similar increase in MAP, showing that the mechanical factor was not altered by LOS treatment. Another finding of the present study is that chronic AT\(_1\) receptor blockade did not change the sympathovagal balance and SSNA/MAP relationship in normotensive groups. Accordingly, LOS has been shown to not alter the basal firing pattern of Ang II–sensitive neurons in the medial neural tractus solitarii but only to reverse the increased firing and to block the excitation induced by Ang II administration.\(^39\)

In summary, our data show that Ang II, activated by CH, has multiple effects on the effenter pathways. It acts on AT\(_1\) receptors to change sympathovagal balance, producing a marked increase in sympathetic outflow while inhibiting vagal outflow to the heart, to cause a deficient pressure-induced sympathetic withdrawal and to increase sympathetic tone to splanchnic circulation during unloading of baroreceptors. Chronic AT\(_1\) receptor blockade, not changing the pressure load but normalizing sympathovagal balance and sympathetic tone to the periphery, indicates that these effects are not conditioned by the pressure levels.

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