Intravenous Angiotensin II Does Not Affect Dynamic Baroreflex Characteristics of the Neural or Peripheral Arc

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Abstract: Although the elevation of angiotensin II (Ang II) associated with cardiovascular diseases has been considered to suppress the arterial baroreflex function, how Ang II affects dynamic arterial pressure (AP) regulation remains unknown. The aim of the present study was to elucidate the acute effects of Ang II on dynamic AP regulation by the arterial baroreflex. In seven anesthetized Japanese white rabbits, we randomly perturbed intra-carotid sinus pressure (CSP) according to a binary white noise sequence while recording renal sympathetic nerve activity (RSNA) and AP. We estimated the neural arc transfer function from CSP to RSNA and the peripheral arc transfer function from RSNA to AP before and after 30-min intravenous administration of Ang II (100 ng/kg/min). Ang II increased mean

AP from 75.7 ± 3.1 to 95.5 ± 5.1 mmHg ($p < 0.01$), while it did not affect mean RSNA (from 5.9 ± 1.3 to 5.7 ± 1.2 a.u.). The neural arc transfer functions did not differ before or after Ang II administration (dynamic gain: -0.94 ± 0.04 vs. -0.94 ± 0.13 , corner frequency: 0.06 ± 0.01 vs. 0.06 ± 0.01 Hz, pure delay: 0.16 ± 0.01 vs. 0.17 ± 0.02 s). The peripheral arc transfer function did not differ before or after Ang II administration (dynamic gain: 1.18 ± 0.05 vs. 1.06 ± 0.11 , natural frequency: 0.07 ± 0.01 vs. 0.08 ± 0.01 Hz, damping ratio: 1.19 ± 0.06 vs. 1.24 ± 0.19 , pure delay: 0.83 ± 0.06 vs. 0.78 ± 0.05 s). Intravenous Ang II hardly affects the dynamic characteristics of neural and peripheral arc around the physiological operating pressure. [The Japanese Journal of Physiology 53: 135–143, 2003]

Key words: renal sympathetic nerve activity, transfer function, systems analysis, rabbits, carotid sinus baroreflex.

The arterial baroreflex system is one of the most important negative-feedback systems that stabilizes arterial pressure (AP) against exogenous pressure perturbation. The arterial baroreflex may be divided into the neural and peripheral arc subsystems [1–3]. The neural arc represents the signal transduction pathway from baroreceptor pressure input to efferent sympathetic nerve activity (SNA). The peripheral arc represents the regulatory pathway from SNA to AP. Static characteristics of the two arcs provide information on

the operating point of AP regulation [2, 4]. The dynamic characteristics of the two arcs determine the stability and quickness of AP regulation [1, 5]. Because the baroreflex operates dynamically under the ordinary conditions of daily activity, changes in baroreflex dynamic characteristics critically affect the performance of AP regulation and consequently have an impact on quality of life. An assessment of baroreflex dynamic characteristics in conjunction with altered hormonal regulation of the cardiovascular sys-

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tem could be important in gaining a better understanding of the pathophysiology of AP regulation associated with cardiovascular diseases.

Angiotensin II (Ang II) is known to have a variety of effects on the cardiovascular system [6]. Ang II acts on the vascular beds and increases peripheral vascular resistance. It also acts on the adrenal cortex and causes volume retention. These direct effects of Ang II contribute to maintaining AP [7]. Aside from these direct effects, Ang II is thought to modulate both neural and peripheral arcs of the arterial baroreflex system. In terms of neural arc modulation, Ang II acutely attenuates the range of arterial baroreflex control of renal SNA (RSNA) [8, 9]. Ang II also plays a role in the attenuation of baroreflex sensitivity observed in animal models of heart failure [10, 11]. In a previous study performed at our laboratory [12], intracerebroventricular administration of angiotensin converting enzyme (ACE) inhibitor exerted a preventive effect on cardiac remodeling in rats with chronic heart failure, suggesting that the brain is a possible target of ACE inhibitor. In the peripheral arc modulation, Peach *et al.* [13, 14] reported that large doses of intravenous Ang II increased plasma norepinephrine (NE) levels in anesthetized dogs. Szabo *et al.* [15] demonstrated that NE levels were increased disproportionately in relation to RSNA after the intravenous administration of Ang II.

Despite the above-mentioned modulation of the arterial baroreflex function by Ang II, the acute effects of intravenous Ang II on the dynamic characteristics of arterial baroreflex remain unknown. In order to test the hypothesis that exogenous Ang II modulates the dynamic characteristics of the neural and/or peripheral arc of the arterial baroreflex, we performed an open-loop experiment of the carotid sinus baroreflex in anesthetized rabbits using a white noise analysis [1, 3, 16]. The results of the present study indicate that intravenous Ang II does not acutely affect either the neural or the peripheral arc when baroreflex dynamic characteristics are estimated near physiological operating pressure.

MATERIALS AND METHODS

Surgical preparations. The investigation conformed with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Seven Japanese white rabbits weighing 2.4–2.7 kg were anesthetized via intravenous injection (2 ml/kg) using a mixture of urethane (250 mg/ml) and α -chloralose (40 mg/ml), and mechanically ventilated

with oxygen-enriched room air. Supplemental doses of these anesthetics were administered continuously (0.2–0.3 ml/kg/h, I.V.) to maintain the appropriate level of anesthesia. AP was measured using a high-fidelity pressure transducer (Millar Instruments, Houston, TX, USA) inserted from the right femoral artery. A double-lumen catheter was introduced into the right femoral vein for drug administration. Through a mid-line cervical incision, the bilateral vagal and aortic depressor nerves were sectioned to eliminate the reflex effects from the cardiopulmonary region and the aortic arch. To isolate the bilateral carotid sinuses from the systemic circulation, the external and internal carotid arteries and other small branches originating from the carotid sinus regions were ligated. The isolated carotid sinuses were filled with warmed physiological saline through catheters inserted via the common carotid arteries. The intracarotid sinus pressure (CSP) was controlled by a servo-controlled piston pump. We exposed the left renal sympathetic nerve retroperitoneally and attached a pair of stainless steel wire electrodes (Bioflex wire AS633, Cooner Wire) to record RSNA. The nerve fibers peripheral to the electrodes were crushed by tight ligature to eliminate afferent signals from the kidney. To insulate and fix the electrodes and prevent the nerve from drying, the nerve and electrodes were soaked in a silicone gel (Semicosil 932A/B, Wacker Silicones). The preamplified nerve signal was band-pass filtered at 150–1,000 Hz. It was then full-wave rectified and low-pass filtered with a cutoff frequency of 30 Hz to quantify the nerve activity. Pancuronium bromide (0.3 mg/kg, I.V.) was given to prevent the contamination of muscular activity in the RSNA recordings prior to each experimental protocol. Body temperature was maintained at around 38°C with a heating pad.

Protocols. After completing the surgical preparation, the baroreflex negative-feedback loop was closed by adjusting CSP to AP for 20 min. Mean AP (and thus mean CSP) at the steady state was treated as the operating pressure (P_{OP}). To assess the dynamic characteristics of the carotid sinus baroreflex, we randomly assigned CSP to either high ($P_{OP}+20$ mmHg) or low ($P_{OP}-20$ mmHg) pressure every 500 ms according to a binary white noise sequence [16, 17]. The power spectral density of CSP was reasonably constant up to 1 Hz. Because the total baroreflex from CSP to AP had low-pass characteristics and its dynamic gain at 1 Hz was less than one-tenth that at 0.01 Hz in rabbits [5], we focused on the dynamic characteristics in the frequencies up to 1 Hz. Conversely, baroreceptors are normally exposed to pressure perturbation above 1 Hz associated with heart

rate (4–5 Hz in rabbits) and its harmonics. The possible effects of Ang II on the baroreflex relating to such high-frequency pressure perturbation could not be assessed by the present protocol.

After recording the control data of CSP, RSNA, and AP for 10 min (the control condition), we administered Ang II (100 ng/kg/min, I.V.) for 40 min. The binary CSP perturbation continued throughout the experiment using the same P_{OP} determined under the control condition. The dose of Ang II was chosen based on the maximum dose used in previous studies [15, 18]. Although Ang II of this dose may have increased plasma Ang II concentration ten times higher than the physiologically relevant concentration [19, 20], it would be beneficial for uncovering the effects of intravenous Ang II on the baroreflex transfer characteristics. Because Ang II of this dose did not affect the baroreflex transfer characteristics in a preliminary study, we did not examine lower doses of Ang II. Although carotid sinus isolation might have affected the distribution of central blood flow, the central sites perfused by the vertebral arteries are at least involved in developing the central effects of Ang II on the arterial baroreflex [21]. Because bilateral vertebral arteries were kept intact in the present study, we assumed that intravenous Ang II administration acted centrally as well as peripherally. We recorded CSP, RSNA, and AP for the last 10 min of 40-min Ang II administration (the Ang II condition). Data were sampled at 200 Hz using a 12-bit analog-to-digital converter and stored on the hard disk of a dedicated laboratory computer system for later analysis.

Data analysis. To estimate the neural arc transfer function, we treated CSP as the input and RSNA as the output of the system. To estimate the peripheral arc transfer function, we treated RSNA as the input and AP as the output of the system. We resampled input–output data pairs at 10 Hz and segmented them into 10 sets of 50% overlapping bins of 1,024 data points each. For each segment, a linear trend was subtracted and a Hanning window was applied. We then performed a fast Fourier transform to obtain frequency spectra of the input and output. We ensemble averaged the input power [$S_{xx}(f)$], output power [$S_{yy}(f)$], and cross-power between the input and output [$S_{yx}(f)$] over the 10 segments, where f represents frequency. Finally, we calculated the transfer function [$H(f)$] from the input to output using the following equation [22].

$$H(f) = \frac{S_{yx}(f)}{S_{xx}(f)}$$

We obtained the modulus [$|H(f)|$] and phase [$\theta(f)$] of the transfer function using the following equations [22]:

$$|H(f)| = \sqrt{H_{Re}(f)^2 + H_{Im}(f)^2}$$

$$\theta(f) = \tan^{-1} \frac{H_{Im}(f)}{H_{Re}(f)}$$

where $H_{Re}(f)$ and $H_{Im}(f)$ are the real and imaginary parts of $H(f)$, respectively. Hereafter, we denote the modulus as dynamic gain of the transfer function. To quantify the linear dependence between the input and output signals in the frequency domain, we calculated a magnitude-squared coherence function [$Coh(f)$] using the following equation [22].

$$Coh(f) = \frac{|S_{yx}(f)|^2}{S_{xx}(f)S_{yy}(f)}$$

The coherence value ranges from zero to unity. A unity coherence indicates a perfect linear dependence between the input and output signals, whereas zero coherence indicates total independence between the two signals.

Statistical analysis. We normalized the neural arc transfer functions using a mean value of dynamic gain below 0.03 Hz obtained under the control condition. We then parameterized the neural arc transfer function [$H_N(f)$] using a band-pass filter based on a previous study [5] as follows:

$$H_N(f) = K \frac{1 + \frac{f}{f_{c1}} j}{\left(1 + \frac{f}{f_{c2}} j\right)^2} \exp(-2\pi f j L)$$

where f and j represent the frequency (in Hz) and imaginary units, respectively; K is the gain; f_{c1} and f_{c2} ($f_{c1} < f_{c2}$) are the frequencies (in Hz) for derivative and high-cut characteristics, respectively; and L is the pure delay (in s). The numerical analysis for fitting the model to the transfer function data was performed using MATLAB (Math Works, Natick, MA, USA).

We normalized the peripheral arc transfer functions using a mean value of dynamic gain below 0.03 Hz that was obtained under the control condition. We then parameterized the peripheral arc transfer function [$H_P(f)$] using a second-order low-pass filter as in previous studies [1, 23]:

$$H_P(f) = \frac{K}{1 + 2\zeta \frac{f}{f_N} j + \left(\frac{f}{f_N} j\right)^2} \exp(-2\pi f j L)$$

where K , f_N , and ζ represent the gain, natural frequency (in Hz), and damping ratio, respectively; L shows the pure delay (in s).

All data are expressed as means $\pm$ SEM. To examine the differences between the control and Ang II conditions, average CSP, RSNA, AP, and each parameter of the fitted models were examined by a paired t -test [24]. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Time series data

Figure 1 shows typical time series of CSP, RSNA, and AP obtained under control (left) and Ang II (right) conditions. CSP was perturbed according to a binary white noise sequence. Mean CSP was kept unchanged between the two conditions. The perturbation of CSP resulted in RSNA and AP being changed

through the carotid sinus baroreflex. Ang II increased mean levels of AP, whereas its effect on mean levels of RSNA was unclear.

Mean levels of CSP, RSNA, and AP averaged from seven rabbits under the control and Ang II conditions are summarized in Fig. 2. Mean levels of CSP were kept unchanged. Mean levels of AP were significantly higher in the rabbits administered Ang II than under the control conditions ($p < 0.01$). In contrast, the mean levels of RSNA did not change significantly between the control and Ang II conditions.

Neural and peripheral arc transfer functions

Figure 3 shows the averaged neural arc transfer functions under the control (left) and Ang II (right) conditions. Gain plots (top), phase plots (middle), and coherence functions (bottom) are shown. As the dynamic gain was normalized, the gain value at 0.01 Hz approximated unity under the control condition. The dynamic gain was relatively constant below 0.03 Hz and increased above this frequency up to 1 Hz under both control and Ang II conditions. The phase value approached $-\pi$ radians at the lowest frequency, reflecting the negative feedback of the baroreflex neural

Fig. 1. Typical time series of carotid sinus pressure (CSP), renal sympathetic nerve activity (RSNA), and arterial pressure (AP) obtained in the absence (left) and presence (right) of angiotensin II (Ang II). CSP was perturbed according to a binary white noise sequence. The perturbation resulted in RSNA and AP being changed through the baroreflex.

Fig. 2. Mean levels of CSP, RSNA, and AP before and during the administration of Ang II. * $p < 0.01$ by a paired t -test. Data are means $\pm$ SEM.

Fig. 3. Transfer functions of the baroreflex neural arc from CSP to RSNA averaged from all animals. Gain, phase, and coherence function before (**left**) and during (**right**) the administration of Ang II. Solid lines are mean values of the transfer functions and dashed lines are $\pm$ SEM.

arc. The neural arc transfer functions did not differ in their fitted parameters before or during Ang II administration (Table 1). The coherence was approximately 0.5 at the lowest frequency and increased to approximately 0.7 at frequencies between 0.04 and 0.8 Hz under the control condition. The coherence function under the Ang II condition showed values similar to the control condition.

Figure 4 shows the averaged peripheral arc transfer functions under the control (left) and Ang II (right) conditions. Gain plots (top), phase plots (middle), and coherence functions (bottom) are shown. As the dynamic gain was normalized, the gain value at 0.01 Hz approximated unity under the control condition. The dynamic gain was relatively constant below 0.04 Hz and decreased above this frequency up to 1 Hz under both control and Ang II conditions. The peak around 0.58 Hz corresponded to the artificial ventilation frequency. The phase value approached zero radians at the lowest frequency, reflecting the fact that an increase in RSNA increased AP. The peripheral arc transfer functions did not change in their fitted parameters before or during Ang II administration (Table 2). The coherence was approximately 0.5 at the lowest frequency, and increased to approximately 0.7 at frequencies between 0.05 and 0.4 Hz under the control condition. The coherence function under the Ang II condition showed values similar to the control condition.

Table 1. Parameters of the neural arc transfer functions.

	Control	Ang II
K (a.u./mmHg)	-0.94 ± 0.04	-0.94 ± 0.13
f_{C1} (Hz)	0.06 ± 0.01	0.06 ± 0.01
f_{C2} (Hz)	0.44 ± 0.06	0.43 ± 0.05
L (s)	0.16 ± 0.01	0.17 ± 0.02

DISCUSSION

In the present study, we used RSNA to decompose the carotid sinus baroreflex into the neural and peripheral arcs. This does not mean, however, we regarded RSNA as a main efferent pathway to regulate AP. A principal role of RSNA may be renal control [25]. Nevertheless, high coherence values between RSNA and AP (Fig. 4) suggest a tight relation between RSNA and AP. RSNA may regulate AP via renal function [26]. Further, RSNA should convey general information to regulate AP as well as specific information to regulate renal function. Because the transfer function analysis retrieved a linear input–output relationship even in the presence of significant noise components, the estimated neural arc transfer function might represent transfer characteristics between baroreceptor pressure input and the general information in RSNA. Similarly, the peripheral arc transfer

Fig. 4. Transfer functions of the baroreflex peripheral arc from RSNA to AP averaged from all animals. Gain, phase, and coherence function before (left) and during (right) the administration of Ang II. Solid lines are mean values of the transfer functions and dashed lines are $\pm$ SEM.

Table 2. Parameters of the peripheral arc transfer functions.

	Control	Ang II
K (mmHg/a.u.)	1.18 ± 0.05	1.06 ± 0.11
f_N (Hz)	0.07 ± 0.01	0.08 ± 0.01
ζ	1.19 ± 0.06	1.24 ± 0.19
L (s)	0.83 ± 0.06	0.78 ± 0.05

function might represent transfer characteristics between the general information in RSNA and AP. Therefore, changes in the baroreflex dynamic characteristics by intravenous Ang II, if any, might have been detected by the transfer function analysis using RSNA.

Effects of Ang II on the neural arc transfer function. The sites of action of Ang II modulation in the central nervous system include the rostral ventrolateral medulla [27] and nucleus tractus solitarius [28, 29]. Destruction of the area postrema eliminated the attenuation of baroreflex sensitivity induced by acute and/or chronic intravenous infusion of Ang II in conscious rats [30]. Intravertebral or intravenous Ang II decreases the maximum RSNA at AP ranges below approximately 80 mmHg in conscious rabbits [11, 21]. Although these lines of evidence indicate that Ang II modulates the baroreflex neural arc, to the best of our knowledge, no studies have focused on the effects of

Ang II on the dynamic characteristics of the arterial baroreflex.

In the present study, intravenous Ang II did not modulate the neural arc transfer function (Fig. 3, Table 1). The apparent contradiction between our results and previous studies may be explained as follows. We fixed mean input pressure during Ang II administration at P_{OP} (approximately 90 mmHg) in order to avoid differences in mean CSP affecting dynamic baroreflex characteristics (Fig. 2). Therefore, the present protocol might not have detected the changes in RSNA induced by Ang II that have previously been reported mainly for the low-input pressure range [11, 19]. Nevertheless, the present study provides an important perspective on the involvement of Ang II in the pathophysiology of cardiovascular diseases in the following respect. Although Ang II is elevated in several cardiovascular diseases, mean AP may not necessarily be low enough to allow the modulation of the baroreflex function by Ang II. In other words, the elevated Ang II associated with several cardiovascular diseases may not modulate the baroreflex function when normal AP is maintained.

Effects of Ang II on peripheral arc transfer function. Previous studies indicated that Ang II modulates not only the neural arc, but also the peripheral arc. Campbell and Jackson [31] reported that Ang II possesses the capacity of both increasing NE release from sympathetic nerve terminals during sympa-

thetic nerve stimulation and decreasing neuronal uptake of NE. Szabo *et al.* [15] reported that exogenous Ang II activates release-facilitating receptors at postganglionic sympathetic neurons in anesthetized rabbits with ongoing SNA. However, whether or not the enhanced NE released by Ang II plays a significant role in dynamic AP regulation by the sympathetic system remained unknown. Although Ang II increased the mean level of AP (Fig. 2), the modulation of the peripheral arc by Ang II is insignificant in terms of dynamic AP regulation, at least in the frequency range of the present study (0.01–1 Hz). Therefore, the effects of Ang II on NE kinetics at neuro-effector junctions may play only a slight role in dynamic AP regulation.

Although we determined P_{OP} by imposing native AP on CSP, mean AP during binary CSP perturbation was lower than P_{OP} under the control condition (Fig. 2). The phenomenon may be explained by the difference in the input amplitude [32]. Mean SNA and AP decrease as the input amplitude of CSP perturbation increases when mean CSP is lower than the midpoint pressure (P_{MID}) of the static CSP-SNA relationship [33]. When we directly estimated P_{MID} using experimental settings similar to the present study, P_{MID} was approximately 115 mmHg [16]. P_{OP} might have been lower than P_{MID} owing to the anesthetic condition. Taken together, the peak-to-peak amplitude of CSP perturbation (40 mmHg) was greater than the native pulse pressure (20–30 mmHg), lowering mean AP below P_{OP} .

Despite a significant change in the mean levels of AP (Fig. 2), changes in the fitted parameters of the peripheral arc transfer function by Ang II did not reach statistical significance (Fig. 4, Table 2). According to an open-loop study in rats, the static characteristics of the peripheral arc have a much wider linear range than those of the neural arc [4]. In the present study, changes in the mean levels of AP were approximately 20 mmHg. Although Ang II significantly increased the mean levels of AP independently of the mean levels of RSNA, the changes in the operating point might have been within a quasi-linear portion of the RSNA-AP relationship. The modeling study by Ringwood *et al.* [34] also suggested an insignificant non-linearity in peripheral arc transfer characteristics around the physiological operating pressure.

Open-loop vs. closed-loop experiments.

Many investigators have examined the effects of Ang II on the arterial baroreflex function under baroreflex closed-loop conditions. Under closed-loop conditions, changes in AP affect SNA via the baroreflex, whereas changes in SNA, in turn, alter AP. The closed-loop

conditions have two major problems. First, the rate of AP change by pharmacological agents such as phenylephrine and nitroprusside cannot be controlled precisely. As a result the difference in the rate of AP change may have affected the estimation of baroreflex sensitivity [3]. Secondly, changes in AP via the direct effect of Ang II inevitably affected the mean input pressure to baroreceptors. Because the baroreflex neural arc has a sigmoidal input-output relationship with threshold and saturation, changes in the mean input pressure may also have affected the estimation of baroreflex gain. To circumvent these problems associated with the baroreflex closed-loop conditions, we performed an open-loop experiment where the input pressure to the baroreceptors was precisely controlled independent of AP. The open-loop baroreflex conditions were essential to estimate baroreflex dynamic characteristics using a conventional transfer function analysis [35].

Limitations. There are several limitations in the present study. First, we performed the experiments in anesthetized rabbits. As the anesthesia affects autonomic nervous activity [36], the results might have been different had we performed the experiment without anesthesia. Second, Ang II affects the baroreflex not only acutely, but also chronically [37]. As Ang II is chronically elevated in heart failure, further studies focusing on the effects of chronic Ang II administration on the baroreflex are clearly required to extend the interpretation of the pathophysiological meaning of elevated Ang II in cardiovascular diseases. Third, the intracarotid sinus fluid was free of Ang II. As intravenous Ang II normally reaches the baroreceptors, it may affect baroreceptor transduction properties [38]. To elucidate the effects of Ang II on baroreceptor transduction, experiments in which the intravascular content of the isolated carotid sinuses contains Ang II might be required.

With respect to chemoreceptors, small branches supplying carotid bodies might have been ligated during vascular isolation of the carotid sinuses. When the small branches supplying carotid bodies were patent, the servo-controller replenished a small leak from the carotid sinus regions (less than 1 ml/h). Under both circumstances, the extent of chemoreceptor activation might not change acutely. In experimental settings similar to the present study, SNA and AP responses to stepwise CSP perturbation were reproducible for an hour or more [4].

Finally, we estimated the neural and peripheral arc transfer functions using RSNA as an efferent pathway. As noted in the discussion, examining the effects of Ang II on the baroreflex dynamic characteristics using

RSNA was reasonable. At the same time, however, derivative characteristics were different between the neural arc transfer functions using cardiac SNA and RSNA [16]. Therefore, using SNA other than RSNA, such as that controlling the vascular bed, should reveal somewhat different transfer characteristics of the baroreflex neural and peripheral arcs.

In conclusion, exogenous Ang II acutely affected neither the neural nor the peripheral arc transfer function of the carotid sinus baroreflex, while increasing AP independent of RSNA. The dynamic characteristics of the arterial baroreflex were optimal in achieving quick and stable regulation of AP under normal physiological conditions [1]. The present results suggest that the intravenous administration of Ang II may not acutely disrupt the optimality of the dynamic AP regulation by the arterial baroreflex.

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