Effects of Angiotensin II on the Cardiac Responses to Sympathetic Nerve Stimulation in Dogs
YASUYUKI FURUKAWA, M.D., PAUL SCIPIONE, AND MATTHEW N. LEVY, M.D.

SUMMARY In anesthetized dogs with the left cardiac sympathetic nerves and both vagal nerves intact, angiotensin II (All) induced a substantial, dose-dependent increase in arterial blood pressure and small increments in cardiac cycle length and ventricular contractile force. In dogs in which the cardiac sympathetic and vagal nerves had been interrupted, All produced similar increases in blood pressure and larger increases in contractile force, but it decreased the cardiac cycle length. In both groups of dogs, All produced similar increases in blood pressure and larger increases in contractile force, but it decreased the cardiac cycle length. In both groups of dogs, All augmented substantially the positive inotropic responses to sympathetic nerve stimulation, but it enhanced the positive chronotropic responses only slightly. However, All did not appreciably prolong the cardiac responses to sympathetic nerve stimulation, nor did it alter significantly the cardiac responses to norepinephrine infusions. Hence, at the dosage levels used, All probably did not inhibit the neuronal uptake of norepinephrine appreciably nor did it enhance the responsiveness of the cardiac effector sites to norepinephrine. Therefore, the potentiation of the cardiac responses to sympathetic nerve stimulation by All in these experiments was probably achieved principally by facilitating norepinephrine release from the adrenergic nerve terminals in the heart.

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KEY WORDS • arterial blood pressure • autonomic nervous system • heart rate • myocardial contractility

ANGIOTENSIN II (All) has several modes of action on the cardiovascular system, including those that involve an interaction between All and the adrenergic nervous system.1-2 Several types of such interactions have been described. All has been shown to facilitate the release of norepinephrine (NE) and dopamine β-hydroxylase from adrenergic nerve terminals,3-7 to enhance NE biosynthesis,8 to inhibit the neuronal uptake of NE9,10 and to increase the responsiveness of the adrenergic effector sites.11

It has been amply documented that All potentiates certain vascular responses to adrenergic stimulation.3,6,12-14 However, relatively little information has been obtained concerning the effects of All on the cardiac responses to sympathetic nerve stimulation, and the available data are contradictory. In isolated rabbit hearts, All augmented the release of NE in response to sympathetic nerve stimulation, but this was not usually accompanied by an increase of the chronotropic and inotropic responses.4,5,15 In two other studies also conducted on isolated hearts, however, All did potentiate the inotropic16 and chronotropic17 responses to sympathetic nerve stimulation. In intact, anesthetized dogs, the chronotropic responses to sympathetic nerve stimulation were not potentiated by All unless the neuronal uptake of NE had been suppressed by desipramine; the effects of myocardial contractility were not investigated.18

The present series of experiments were designed to determine the effects of All on the cardiac responses to sympathetic nerve stimulation and to infusions of NE in anesthetized, open-chest dogs.

Methods

Each dog was anesthetized with sodium pentobarbital, 30 mg/kg i.v. After a tracheal cannula was inserted, the chest was opened through a transverse incision in the fourth intercostal space, and artificial respiration was instituted.

Two series of experiments tested the effects of All on cardiac responses to sympathetic nerve stimulation, and to NE infusion.

Responses to Sympathetic Nerve Stimulation

We studied the effects of All on the cardiac responses to stimulation of the decentralized right ansa subclavia. The animals were divided into two groups. In Group 1 (8 dogs), the left cardiac sympathetic nerves and both vagal nerves remained intact. In Group 2 (8 dogs), both vagal nerves and the upper
poles of both stellate ganglia were crushed by means of tight ligatures in order to interrupt almost all of the tonic autonomic neural activity to the heart.19

Arterial blood pressure was measured from a femoral artery by means of a Statham transducer (P23 AA). A Walton-Brodie strain gauge arch was used to measure the myocardial contractile force. It was attached to the wall of the right ventricle, parallel and about 1.5 cm lateral to the anterior descending coronary artery, at a site about halfway between the apex and base of the heart. A bipolar recording electrode was inserted into the right ventricle through the right external jugular vein, to record the ventricular electrogram. Arterial blood pressure, right ventricular contractile force, and cardiac cycle length were recorded on a direct-writing Brush oscillograph (Mark 260). Angiotensin II (1-L-asparaginyl-5-valyl angiotensin octapeptide, Ciba), dissolved in saline, was infused intravenously at rates of 0, 1, 10, and 100 ng/kg/min, by means of an infusion pump (Harvard Apparatus, Millis, Massachusetts, Model 600-900). The order of infusion was randomized in each experiment. Each infusion of All was continued for 20 minutes, after which there was a 20-minute recovery period before the next infusion was begun. The changes in blood pressure evoked by the All infusion disappeared within 10 minutes after cessation of infusion. The cardiac responses evoked by the All infusion itself were measured 5 minutes after the beginning of each infusion. The cardiac responses to ansal nerve stimulation were then determined during the last 15 minutes of the All infusion.

In each animal, four different stimulation frequencies (0.5, 1, 2, and 4 Hz) were applied to the right ansa subclavia in a random sequence at each rate of All infusion. Each stimulation consisted of a 60-second train of square wave pulses (Grass Stimulator, Model S9); each pulse was 1 msec in duration and of supramaximal voltage (10V). Each stimulus train was delivered via shielded indium electrodes (Harvard Apparatus).

The responses to the various All infusions per se were analyzed by means of a three-way mixed model analysis of variance.20 The experimental groups and the All infusion rates were considered to be fixed factors. The individual dogs were considered to be a random effect factor. The "single degree of freedom" test was used for a priori comparisons,20 and Scheffé's test was used for all other comparisons.21

For the analysis of the effects of the All infusions on the cardiac responses to sympathetic stimulation, preliminary analysis revealed that the mean preinfusion levels of cardiac cycle length, cardiac contractile force, and arterial blood pressure were not significantly different in the two groups, and that the effects of All on the cardiac responses to sympathetic nerve stimulation were not significantly different in the two groups. Therefore, the data from both groups were combined. The composite data were analyzed by means of a three-way, mixed model analysis of variance. The All infusion rates and the stimulation frequencies were considered to be fixed factors. The individual dogs were considered to be a random effect factor.

Responses to Norepinephrine Infusions

The second series of experiments (four dogs) was conducted to determine the effects of All on the cardiac responses to norepinephrine (NE) infusions. The principal autonomic innervation of the heart was interrupted by tightly ligating both vagal nerves and the upper poles of both stellate ganglia.19 All was infused at rates of 0, 1, 10, and 100 ng/kg/min, according to the same protocol that was described for the preceding series. During each All infusion, norepinephrine bitartrate (Sigma Chemical Company, St. Louis, Missouri), dissolved in saline, was infused intravenously for 30 seconds at rates of 0.1, 0.2, 0.4, and 0.8 μg/kg/min. The various rates of NE infusion were given in a random sequence; a new random sequence of NE infusion rates was used for each All infusion. Each NE infusion was begun after all responses to the previous infusion had returned to their preinfusion levels.

The data were analyzed by means of a three-way, mixed-model analysis of variance. The All infusion rates and the NE infusion rates were considered to be fixed factors, and the individual dogs were considered to be a random effect factor.

Results

First Series: Responses to Sympathetic Nerve Stimulation

Effects of All Infusion Alone

The changes in cardiac cycle length, right ventricular contractile force, and mean arterial blood pressure produced by the infusion of All are shown in figure 1. In the dogs with the left sympathetic and both vagal nerves intact (Group 1), the cardiac cycle length increased slightly during the infusion of All; the extent of the increment in cycle length varied directly with the rate of infusion. In the dogs with the cardiac innervation interrupted (Group 2), however, the cycle length was virtually unaffected by the two lower rates of All infusion, and it decreased by 30 msec when All was infused at the highest rate (100 ng/kg/min). The changes in cycle length evoked by All were significantly different in the two groups of animals; that is, the interaction between groups and infusion rates was highly significant (p < 0.001; table 1).

The infusion of All caused dose-dependent increases (p < 0.001) in contractile force and mean arterial blood pressure (fig. 1). The increments in contractile force were significantly greater (p = 0.01) in Group 2 than in Group 1 (table 1). The changes in mean arterial blood pressure, on the other hand, were not significantly different in the two groups of animals.

Effects of All on the Cardiac Responses to Sympathetic Nerve Stimulation; Representative Experiment

Figure 2 illustrates the hemodynamic changes elicited by stimulation of the right ansa subclavia in a repre-
FIGURE 1. Mean changes in the cardiac cycle length, right ventricular contractile force, and mean arterial blood pressure in response to angiotensin II infused at rates of 0, 1, 10, and 100 ng/kg/min in two groups of dogs. Each response is expressed as a change from the preinfusion control level. In Group 1 (n = 8), the left ansa subclavia and both vagal nerves were intact. In Group 2 (n = 8), the cardiac autonomic nerves were transected.

Control levels of cycle length, contractile force, and mean arterial blood pressure were as follows: Group 1 = 489 ± 57 (mean ± SD) msec, 12.2 ± 3.06 mm, and 120 ± 24.6 mm Hg, respectively; Group 2 = 527 ± 101 msec, 12.6 ± 2.20 mm, and 122 ± 21.9 mm Hg, respectively.

TABLE 1. Analysis of Variance of the Chronotropic, Inotropic, and Pressor Responses Evoked by the Infusion of Angiotensin II Itself and by Stimulation of the Right Ansa Subclavia during Angiotensin II Infusions

<table>
<thead>
<tr>
<th>Infusion of angiotensin II</th>
<th>Chronotropic</th>
<th>Inotropic</th>
<th>Pressor</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF</td>
<td>MS</td>
<td>F ratio</td>
<td>MS</td>
</tr>
<tr>
<td>Groups</td>
<td>1.7</td>
<td>3291</td>
<td>13.92*</td>
</tr>
<tr>
<td>All</td>
<td>3.21</td>
<td>420</td>
<td>2.54</td>
</tr>
<tr>
<td>Interaction</td>
<td>3.21</td>
<td>2168</td>
<td>16.02*</td>
</tr>
<tr>
<td>Stimulation of the ansa subclavia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3.45</td>
<td>2175</td>
<td>1.42</td>
</tr>
<tr>
<td>Symp. stim.</td>
<td>3.45</td>
<td>68676</td>
<td>54.83‡</td>
</tr>
<tr>
<td>Interaction</td>
<td>9,135</td>
<td>482</td>
<td>2.02*</td>
</tr>
</tbody>
</table>

DF = degrees of freedom; MS = mean square.

*p = 0.05.

†p = 0.01.

‡p ≤ 0.001.
When All was infused at a rate of 10 ng/kg/min (fig. 2, right panel), ansal stimulation evoked hemodynamic responses that were similar directionally to those obtained before the All infusion. The magnitudes of these responses were greater than they were under control conditions (left panel), but the decay times of these responses were not appreciably different from the respective control values.

**Effects of All on the Cardiac Responses to Sympathetic Nerve Stimulation; Composite Data**

**Chronotropic Responses.** The positive chronotropic responses to ansal stimulation varied significantly ($p < 0.001$) with the frequency of stimulation (fig. 3; table 1). The main effect of the All infusions on the chronotropic responses was not significant (table 1). However, the responses to ansal stimulation did vary significantly with the rate of All infusion; i.e., the interaction between infusion rate and stimulation frequency was significant ($p = 0.05$; table 1). For example, the decrease in cycle length tended to be greater when All was infused at a rate of 10 ng/kg/min than when it was infused at a rate of 0 or 1 ng/kg/min. Furthermore, at the highest infusion rate (100 ng/kg/min), the responses to ansal stimulation appeared to be depressed, especially those responses to the two highest stimulation frequencies.

The decay time of the chronotropic response, as assessed by the 50% recovery time, varied directly with the frequency of sympathetic nerve stimulation (fig. 4, left panel; table 2). The decay time of the chronotropic response was not significantly influenced by the rate of All infusion. At the highest infusion rate, the decay time of the chronotropic response tended to be slightly curtailed, but the change was not significant.

**Figure 2.** Changes in the cardiac cycle length, right ventricular contractile force, and arterial blood pressure produced by a 1-minute train of supramaximal stimuli (10 V, 1 msec duration, 2 Hz) to the right ansa subclavia during the infusion of a small volume of saline (left panel) or of angiotensin II (right panel) at a rate of 10 ng/kg/min. Arrows denote the beginning and end of the sympathetic stimulation period.

**Figure 3.** Effects of angiotensin II infusions on the magnitudes of the cardiac cycle length (left panel), right ventricular contractile force (middle panel), and mean arterial blood pressure (right panel) responses to ansal stimulation. Each response is expressed as the mean change from the pre-stimulation control level.
**Inotropic Responses.** The positive inotropic response to ansal stimulation (fig. 3, middle panel) varied directly with the frequency of ansal stimulation \((p < 0.001\); table 1) and with the rate of All infusion \((p < 0.001)\). Furthermore, the effects of the All infusions varied with the frequency of sympathetic stimulation; i.e., the interaction between infusion rate and stimulation frequency was significant \((p = 0.05)\). Note that All exerted its most pronounced enhancement of the inotropic responses at the highest stimulation frequency.

The decay time of the positive inotropic response increased \((p < 0.001)\) with the frequency of ansal stimulation (fig. 4, right panel; table 2). The decay time of this response was also slightly, but significantly, more prolonged as the rate of the All infusion was increased \((p = 0.05)\).

**Blood Pressure Responses.** The increment in mean arterial blood pressure evoked by ansal stimulation (fig. 3, right panel) increased with the stimulation frequency \((p < 0.001)\) and with the All infusion rate \((p < 0.001);\) table 1). The blood pressure change evoked by ansal stimulation increased significantly as the rate of All infusion was raised; the interaction between stimulation frequency and infusion rate was significant \((p = 0.01)\).

**Second Series: Responses to Norepinephrine Infusion**

The effects of the infusion of All on the cardiac responses to the infusion of exogenous NE are shown in figure 5, and the analysis of variance is presented in table 2. The NE infusions evoked significant, dose-dependent decreases in cycle length \((p = 0.01)\) and increases in contractile force \((p < 0.001)\). However, neither the chronotropic nor inotropic responses to the NE infusions varied significantly with the rate of All infusion; i.e., neither the main effects of the All infusions nor the effects of their interactions with the NE infusions were significant (table 2). The decay times of the cardiac responses to the NE infusions were also not influenced by the rate of All infusion.

**Discussion**

**Effects of All Infusion Alone**

In the dogs with most of the efferent autonomic nerves intact (Group 1), infusion of All caused an appreciable, dose-dependent elevation of blood pressure, but only slight increases of cardiac cycle length and ventricular contractile force (fig. 1). In the dogs with virtually all of the efferent nerves to the heart intact (Group 2), infusion of All caused only slight increases of blood pressure, but significant decreases of cardiac cycle length and increases of contractile force.

**Table 2. Analysis of Variance of the Effects of Angiotensin II on the Decay Times of the Chronotropic and Inotropic Responses to Stimulation of the Right Ansa Subclavia; and on the Magnitudes of the Chronotropic and Inotropic Responses to Exogenous Norepinephrine**

<table>
<thead>
<tr>
<th></th>
<th>Chronotropic</th>
<th>Inotropic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ansal stimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infusion</td>
<td>3.45</td>
<td>189</td>
</tr>
<tr>
<td>Symp. stim.</td>
<td>3.45</td>
<td>1176</td>
</tr>
<tr>
<td>Interaction</td>
<td>9.135</td>
<td>7</td>
</tr>
<tr>
<td>Exogenous norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infusion</td>
<td>3.9</td>
<td>50</td>
</tr>
<tr>
<td>NE infusion</td>
<td>3.9</td>
<td>2664</td>
</tr>
<tr>
<td>Interaction</td>
<td>9.27</td>
<td>79</td>
</tr>
</tbody>
</table>

DF = degrees of freedom; MS = mean square.

\(p = 0.05\)

\(p = 0.01\)

\(p < 0.001\)
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Effects of All on the Cardiac Responses to Sympathetic Stimulation

In the present study (fig. 3, middle panel), All augmented the inotropic responses that were evoked by ansal stimulation, and the degree of enhancement varied directly with the rate of All infusion. This influence was more pronounced the greater the frequency of sympathetic stimulation. In isolated, perfused rabbit hearts, the positive inotropic effects of sympathetic stimulation were significantly augmented by All, but only over a limited range of infusion rates.4 Iven et al.16 also found that All enhanced the positive inotropic responses that were evoked by field stimulation in the isolated guinea-pig left atrium; these responses were blocked by a beta adrenergic antagonist. In other isolated heart preparations, however, the inotropic responses to sympathetic stimulation were not potentiated significantly by All.28

The effects of All on the chronotropic responses to ansal stimulation (fig. 3, left panel) were less pronounced and less consistent than were the effects on the inotropic responses. At an infusion rate of 10 ng/kg/min, All tended to augment the chronotropic responses, but its influence was negligible at the higher and lower infusion rates. Thompson17 reported previously that the positive chronotropic responses to sympathetic nerve stimulation were augmented by angiotensin infusions in isolated rabbit hearts. However, in other studies,4,5 the chronotropic responses to sympathetic nerve stimulation were not enhanced by All in isolated hearts. Similarly, in the studies conducted on intact, anesthetized dogs by Lokhandwala et al.,18 the chronotropic responses to sympathetic nerve stimulation were not potentiated by All infusion alone, although the responses were potentiated after the neuronal uptake mechanism had been blocked by desipramine.

The following mechanisms have been proposed to explain the influence of All on the various responses to

interrupted (Group 2), however, infusion of All caused not only a rise in blood pressure, but also a significant increase in contractile force and a substantial reduction in cycle length.

The increase in cycle length observed in the animals in Group 1 was probably a baroreflex response to the associated rise in arterial blood pressure. The baroreceptor reflex probably also acted to attenuate the inotropic response to the All infusion.

In the animals in group 2, the baroreflex influence on the heart was abolished, because most of the efferent fibers to the heart involved in this reflex had been transected.19 The increases in cardiac contractile force and the reductions in cardiac cycle length at the higher rates of All infusion were probably ascribable to the direct effects of All on the cardiac effector sites,22-24 and to certain indirect actions of All. The indirect effects of All on the heart were probably mediated through certain interactions with the autonomic nervous system; i.e., by an increased release of catecholamines from the adrenal medulla,25 by exciting efferent cardiac sympathetic nerves by an action on the postganglionic neuronal cell bodies located in the peripheral sympathetic ganglia,26 or by releasing NE from the adrenergic nerve endings in the heart.27
sympathetic nerve stimulation: All inhibits the neuronal uptake of NE; All increases the responsiveness of the effector cells; and All augments the rate of NE release from the sympathetic nerve endings.

It has been documented that All suppresses the neuronal uptake mechanism for NE, although the effect varies with the experimental conditions and with the tissue being investigated. Peach et al. found that All inhibited the uptake of NE in isolated rabbit hearts, and that it potentiated the positive chronotropic responses to exogenous NE. Khairallah et al. administered All intravenously to anesthetized, intact rats, and observed that it inhibited the uptake of NE in various tissues, including the heart and kidneys. However, other investigators did not detect any appreciable inhibition of the neuronal uptake of NE by All.

Substances that inhibit the neuronal uptake of NE increase the decay times of the cardiac responses to sympathetic nerve stimulation in intact, anesthetized dogs. The prolongations of the chronotropic responses are especially pronounced, and therefore the decay time of the chronotropic response serves as a sensitive index of the extent of neuronal uptake blockade. The decay times of the chronotropic responses to anal stimulation were not prolonged significantly by All in the present series of experiments (fig. 4, left panel). Therefore, it is unlikely that the neuronal uptake mechanism for NE was depressed appreciably at the rates of All infusions that were used in the present study.

The decay times of the inotropic responses to anal stimulation were slightly prolonged by All (fig. 4, right panel). However, these small changes were probably ascribable to the All-induced increase in the magnitude of the contractile force responses to anal stimulation (fig. 3, middle panel). An increase in the magnitude of the inotropic response per se has been shown to be accompanied by a prolongation of that response.

With respect to the second possible mechanism noted above, namely, an increase in the responsiveness of the effector cells, it has been reported that All potentiates the vasoconstrictor responses to injected NE in the canine vascular bed perfused in situ. Similarly, in isolated canine vascular tissues the contractile responses to field stimulation, to exogenous NE, and to Ba2+ were all augmented by All. Therefore, suggested that All augments the vasoconstrictor responses to NE by enhancing effector responsiveness, rather than by inhibiting the neuronal uptake mechanism. Conversely, All did not potentiate the cardiac responses to NE infusion in isolated rabbit hearts or in the open-chest, anesthetized dog. In the present study, also, All did not augment the cardiac responses to NE infusion (fig. 5). Therefore, it is unlikely that the responsiveness of the cardiac effector cells was appreciably enhanced by All under the conditions of our study.

By exclusion, therefore, the most likely explanation for the All-induced enhancement of the inotropic responses to sympathetic stimulation in our study (fig. 3, middle panel) is a facilitation of the release of NE from the sympathetic nerve endings. In isolated, perfused rabbit hearts, the rate of NE release from the sympathetic nerve terminals during sympathetic nerve stimulation was significantly augmented by angiotensin, even when its effects on the chronotropic and inotropic responses were imperceptible. Hughes and Roth also found that All augmented the vasoconstriction and the efflux of labelled catecholamines in isolated vascular tissues. Therefore, it is likely that the facilitatory effects of All on the inotropic responses to sympathetic nerve stimulation in our study were also achieved through an enhancement of NE release, rather than through either an inhibition of the neuronal uptake mechanism or an increase of effector responsiveness.

If this conclusion is correct, then it is likely that All would facilitate the release of NE from the sympathetic nerve endings in the sinus node region as well as in the ventricular myocardium. Yet, in our experiments, All did augment the inotropic, but not the chronotropic, responses to sympathetic stimulation (fig. 3). Perhaps such disparate effects might be related to the pronounced differences in the dimensions of the neuroeffector gaps in the sinus node and ventricular myocardial regions. The mean width of the neuroeffector gap in the sinus node region is about 100 Å, whereas the mean gap width in the ventricular myocardium is about 20 times as great. It is possible that All does facilitate NE release in both regions, but that the effects of the enhanced release are masked in the sinus node region by the more effective neuronal reuptake mechanism, by virtue of the greater proximity of the nerve endings to the effector cells. This hypothesis is supported by the data of Lokahandwala et al., cited above. In their experiments, the chronotropic responses to sympathetic stimulation were indeed augmented by All, but only after the neuronal uptake mechanism had been suppressed by desipramine.

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