Journal of Cardiovascular Pharmacology
Issue: Volume 33(2), February 1999, pp 335-340

Publication Type: [Articles]
ISSN: 0160-2446
Accession: 00005344-199902000-00023
Keywords: Angiotensin II, AT1 receptor, AT1 receptor antagonist, Heart failure

[Articles]

The Role of Angiotensin II AT_1 Receptor in the Maintenance of Hemodynamics in a Canine Model of Coronary Microembolization-Induced Heart Failure

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Received September 4, 1997; revision accepted August 19, 1998.

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Summary:

The purpose of this study was to determine whether Angiotensin II (Ang II) contributes to the regulation of resting hemodynamics via Ang II type 1 (AT_1) receptors in awake dogs with coronary microembolization-induced heart failure. Six dogs were surgically instrumented for measurement of systemic hemodynamics and for coronary microembolization. The acute hemodynamic effects of a selective AT_1-receptor antagonist, GR138950 (1 mg/kg, i.v.), were determined before and after congestive heart failure (CHF). GR138950 had no effects on hemodynamics before CHF. Daily coronary microembolizations (through the previously implanted coronary catheter) resulted in CHF, as documented by hemodynamic measurements, a slight but significant increased Ang II plasma level (17.4 ± 1.6 vs. 23 ± 1.0 pg/ml; $p < 0.05$), and characteristic clinical signs of CHF. After CHF, GR138950 significantly increased left ventricular dP/dt_{max} ($LVdP/dt_{max}$) from 1,754 ± 68 to 2,347 ± 114 mm Hg/s and decreased LV systolic pressure (LVSP) from 118 ± 5 to 101 ± 7 mm Hg; meanwhile, heart rate (from 132 ± 4 to 102 ± 6 beats/min) and LV end-diastolic pressure (LVEDP; from 17 ± 3 to 9 ± 1.5 mm Hg) were significantly decreased. Mean arterial pressure (MAP) was not affected. The peak effects occurred 90 min after administration. Thus Ang II contributes significantly to resting hemodynamics via AT_1 receptors in this CHF model; that is, the specific AT_1 blocker inhibits the negative inotropic actions of Ang II in the CHF state.

The renin-angiotensin system (RAS) participates in a variety of homeostatic processes, including blood pressure regulation and the maintenance of fluid and electrolyte balances (1,2). The RAS not only is involved in regulating cardiac function in normal conditions, but also participates in the pathogenesis of cardiovascular diseases such as congestive heart failure (3). During the development of heart failure, the compensatory responses of the RAS cause vasoconstriction and retention of sodium and water, resulting in decreased cardiac output and increased ventricular preload and afterload. The intracardiac RAS may even directly elicit cardiac hypertrophy (4,5) and depress left ventricular contractility (6,7). Although initial stimulation of the system may be beneficial in the heart failure state, chronic activation of the RAS is believed to be detrimental by contributing to the progressive deterioration of cardiac pump performance characteristic of this disease.

The major effector of the RAS is angiotensin II (Ang II), which exerts its various physiologic and pathophysiologic actions throughout the body by binding to specific receptors (8). Two distinct receptor subtypes, AT_1 and AT_2, have been identified by binding studies with Ang II antagonists (9,10). Experimental data suggest that the major physiologic actions of Ang II are mediated by AT_1 receptors (8). Increasing knowledge of the role of RAS and Ang II in heart failure offers promising perspectives on the use of agents that interact with RAS to treat heart failure.

During the past 2 decades, several antagonists of the RAS have been developed. These antagonists act either by blocking Ang II-converting enzyme (ACE), which converts inactive angiotensin I into the active Ang II, or by blocking the AT_1 receptor. Although ACE inhibitors have been shown to be beneficial in heart failure, their ability to block the actions of AII is incomplete, because Ang II levels return significantly toward their elevated levels within weeks of instituting ACE inhibitor therapy. Accordingly, other actions of ACE inhibitor such as their effects on prostaglandin and bradykinin metabolism may contribute to their clinical benefits. Therefore, direct Ang II-receptor antagonism may offer additional benefits in heart failure (11,12).

Although insights into potential benefits of direct AT_1 blockade in heart failure are already being acquired in clinical studies, it may be through studies in the experimental setting that significant advances in understanding of mechanisms can be achieved. We have been developing and characterizing the features of a canine model of chronic, irreversible heart failure achieved by daily coronary microembolization. The purpose of this study was to test the effects of a new, selective nonpeptide AT_1-receptors antagonist, GR138950, in this model of chronic heart failure and, in so doing, to characterize the contributions of Ang II to the regulation of resting hemodynamics. The results show that whereas AT_1 blockade has no effect on hemodynamics in normal animals,

there are profound effects in the heart-failure state. The results demonstrate the utility of this model in studying the role of the neurohormonal axis in heart failure.

MATERIALS AND METHODS

Surgical procedure and measurements

Six adult mongrel dogs (four males and two females), weighing 26-30 kg, were used. Anesthesia was induced with 5-7 mg/kg of intravenously administered thiopental and maintained with 1.5-2.0% isoflurane. Animals were mechanically ventilated to maintain Pco_2 between 35 and 40 mm Hg. By using sterile technique, a thoracotomy was performed in the left fifth intercostal space. Two Tygon catheters (Cardiovascular Instrument Corp., Boston, MA, U.S.A.) were placed, one in the descending aorta and the second in the left atrial appendage. A solid-state pressure gauge (model P6.5; Koningsberg Instrument, Pasadena, CA, U.S.A.) was introduced into the left ventricle (LV) through the apical dimple and held in place with a purse-string suture. A flexible silicon catheter having an inner diameter of 0.04-0.05 inches and outer diameter of 0.07-0.09 inches (Cardiovascular Instrument Corp.) was implanted into the proximal portion of the dominant coronary artery for daily injection of microspheres. In five dogs, the left anterior descending coronary artery was dominant; in one dog, the left circumflex coronary artery was dominant. In each case, the wires and catheters were guided subcutaneously to the dog's back. The chest was closed in layers, and a chest tube was inserted to eliminate the pneumothorax. Antibiotics were given as necessary postoperatively. The dogs were allowed to recover fully from surgery and trained to lie quietly on a laboratory table.

Hemodynamic measurements and experimental protocols

For each experiment, the dog was placed on the laboratory table, and a 19-gauge intravenous catheter was inserted in a peripheral vein of a rear leg and attached to an extension tube for injection of drugs without perturbing the dog. The arterial and left atrial pressures were measured by attaching the implanted catheters to P23ID strain-gauge transducers (Statham Instruments, Inc., Rahway, NJ, U.S.A.). Systolic pressure in the LV was measured with the previously implanted solid-state pressure gauge. The LV pressure signal was differentiated to assess the myocardial contractility (LVdP/dt). The data were recorded on an eight-channel thermal writing chart recorder (model 30-V8808-10; Gould Electronics, East Rutherford, NJ, U.S.A.). The analog outputs of the data were sampled by using a Gateway 2000 486 computer equipped with an analog-to-digital conversion system (National Instruments, Austin, TX, U.S.A.). The digital data were stored on a Bernoulli disk for off-line analysis. Drift in the pressure gauges, amplifiers, and chart recorder was eliminated by frequent calibration during each experiment.

Previous study showed that GR138950 at dose range from 0.1 to 10 mg/kg exerts minimal to marked antagonistic effects on Ang II pressor response; in particular, GR138950 at dose of 1 mg/kg causes ~33-fold displacement of Ang II dose-pressor response curve at 1 h after intravenous administration in conscious dogs (13). Furthermore, in a preliminary study, we found that GR138950 at dose of 2 mg/kg was effective and caused profound hemodynamic effects in heart-failure state. Therefore, GR138950 (Glaxo Research & Development Limited, Stevenage, Herts, U.K.) was given intravenously at a dose of 2 mg/kg before and after establishment of a stable heart failure. Systemic hemodynamics were examined before and at 30, 60, 90, 120, and 180 min after the drug administration.

Coronary microsphere embolization

Heart failure was induced by daily injection of glass microspheres (Spheriglass, ~90-μm mean diameter) through the catheter implanted in the dominant coronary artery. Details of this model were described previously (14,15). In brief, the microspheres were agitated in a saline suspension (25,000 microspheres/ml, 50,000 microspheres/day) and injected daily until resting LVEDP was >=15 mm Hg and resting heart rate (HR) was >=120 beats/min. Stable heart failure (i.e., persistent elevation of LVEDP) occurs after 3-5 weeks of daily embolization.

Assessments of ANG II level in plasma

Blood samples were drawn through the implanted aortic catheter before and after establishment of heart failure to determine the Ang II concentration in the plasma. A commercially available radioimmunoassay (RIA) kit (Peninsula Laboratory, Belmont, CA, U.S.A.) was used for this measurement. Blood samples were spun with angiotensin inhibitor (125 m*M* EDTA and 25 m*M* *o*-phenanthroline) at 2,500 *g* at 4°C for 15 min, and the plasma was withdrawn. An equal amount of 1% trifluoroacetic acid in distilled water was added to the plasma, which was then centrifuged at 8,100 *g* at 4°C for 20 min. The supernatant was loaded on a sep-column C18 and washed with 1% trifluoroacetic acid, and the wash was discharged. The column was washed again with 60% acetonitrile in 1% trifluoroacetic acid, and the eluate was collected in a polypropylene tube. The eluate was evaporated to dryness by using a lyophilizer. The residue was dissolved with 300 μg RIA buffer and centrifuged at 8,100 *g* at 4°C for 10 min.

For RIA, the samples or standards were incubated overnight with polyclonal rabbit antibody at 4°C. ^{125}I-labeled Ang II was added to each tube and incubated at 4°C overnight. Separation of free and bound fractions was accomplished by adding 50 μl of goat antirabbit [gamma]-globulin and 50 μl of normal rabbit serum, and then incubating for 90 min at room temperature. The precipitate was counted with a gamma counter. The standard curve ranged from 1 to 128 pg per tube. The mean recovery for Ang II was >95%. The minimal concentration of Ang II was 1 pg/tube and expressed as picograms of immunoreactive Ang II per milligram plasma. All reagents, antibodies, and columns used in this assay were purchased from Peninsula Laboratory.

This study was approved by the Institutional Animal Care and Use Committee of Columbia-Presbyterian Medical Center, and animals were cared for in accordance with the Guiding Principles for the Use and Care of Laboratory Animals (NIH publication no. 82-23, 1985).

Statistical analysis

All data were expressed as means ± SEM. Two-way analysis of variance (ANOVA) was used for multiple comparisons between control values and hemodynamic responses at 5 time points after the administration of GR138950. For other comparisons between groups, one-way ANOVA with Tukey's post hoc test was used. A value of $p < 0.05$ was considered significant.

RESULTS

Coronary microembolization produces heart failure

The effects of daily coronary microembolization on resting hemodynamics in dogs during the awake state are summarized in Table 1. After 31.3 ± 4.0 days of microembolization with an average total microsphere dose of 1,057,500 ± 260,086 microspheres, LVSP, LV dP/dt_{max}, and mean arterial pressure (MAP) were significantly decreased, whereas LVEDP, left atrial pressure, and HR were significantly increased. The hemodynamic abnormalities were accompanied by clinical signs of heart failure. Dyspnea at rest, decrease in body weight, and ascites demonstrated the establishment of heart failure. These observations were consistent with our previous report (14,15).

	Control	Heart failure
LVSP (mm Hg)	124 ± 9	118 ± 7
LV dP/dt (mm Hg/s)	2,531 ± 304	1,802 ± 45[a]
LVEDP (mm Hg)	5.2 ± 0.7	17 ± 2[a]
MAP (mm Hg)	97 ± 5	95 ± 5
LAP (mm Hg)	6 ± 1.3	16 ± 1.2[a]
HR (beats/min)	88 ± 3	132 ± 3[a]

LVSP, left ventricular systolic pressure; LV dP/dt, left ventricular dP/dt; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; LAP, left atrial pressure; HR, heart rate.
[a]$p < 0.05$ compared with control state.

TABLE 1. The resting hemodynamics in awake condition

Alterations of Ang II plasma concentrations

To test whether alterations of the RAS occurred in this model of heart failure, plasma concentrations of Ang II level were assessed. There was a statistically significant increase in the Ang II plasma level from 17.4 ± 1.6 pg/ml in the normal state to 23.0 ± 1.0 pg/ml after the establishment of heart failure.

AT_1 receptor-mediated mechanisms contribute to regulation of resting hemodynamics during heart failure

The hemodynamic effects of GR138950 in normal dogs and dogs with heart failure are summarized in Fig. 1. In normal animals, there were no significant changes in LVSP, $LVdP/dt_{max}$, MAP, HR, or LVEDP at any time after the administration of GR138950. In contrast, after the development of heart failure, GR138950 caused significant hemodynamic responses. LVSP decreased from a resting value of 118 ± 5 mm Hg to a minimum of 101 ± 7 mm Hg ($p < 0.05$). LVEDP decreased from a resting value of 17 ± 3 mm Hg to a minimal value of 9 ± 1.5 mm Hg ($p < 0.05$). MAP decreased from a resting value of 95 ± 5 mm Hg to a minimal value of 82 ± 4 mm Hg, but this was not statistically significant. Aortic diastolic pressure also was not affected. HR decreased from 132 ± 4 to 102 ± 6 beats/min. In contrast, and despite the reduction in HR and LVEDP, dP/dt_{max} increased from 1,754 ± 68 to 2,347 ± 114 mm Hg/s. The hemodynamic effects of GR138950 began 30 min after administration of the drug and peaked at 90 min after administration. All significant hemodynamic effects of GR138950 except the changes in LVEDP disappeared within 180 min after administration of the drug.

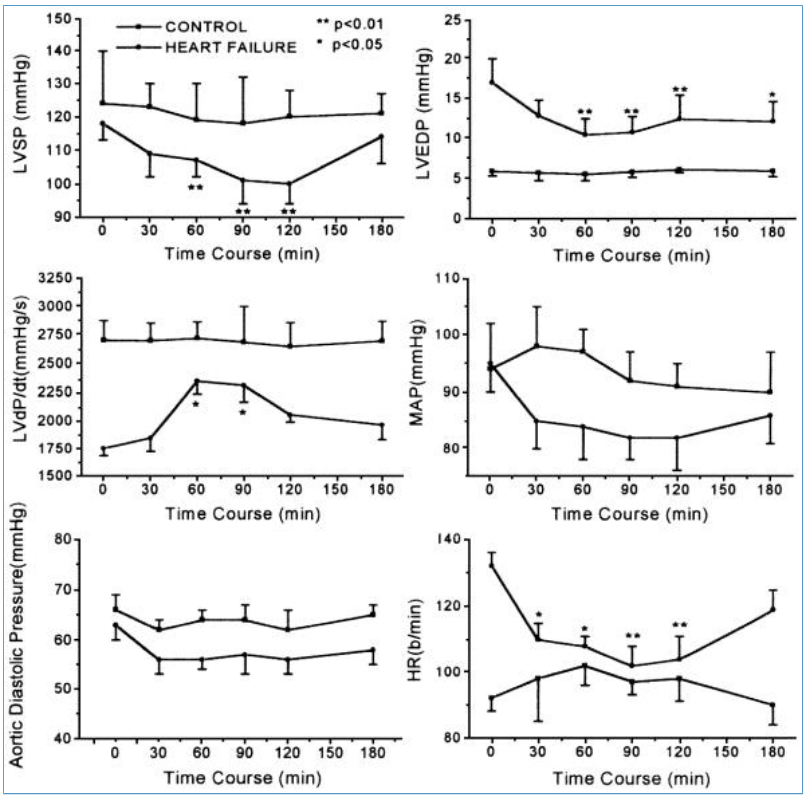

FIG. 1. Responses of left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), LVdP/dt, mean arterial pressure (MAP), aortic diastolic pressure, and heart rate (HR) after administration of GR138950 (i.v.) in control state and after heart failure.

DISCUSSION

GR138950 is a bromobenzofuran trifluorosulphonamide that is a selective nonpeptide Ang II AT_1-receptor antagonist. In previous studies, GR138950 reduced diastolic blood pressure in spontaneously hypertensive rats but not in normal rats (16); In normal anesthetized dogs, GR138950 reduced arterial blood pressure by reducing total peripheral resistance (13). Despite the expectation of a potential use of Ang II AT_1-receptor antagonists for the treatment of heart failure, the hemodynamic effects of GR138950 in a clinically relevant experimental model of heart failure have not been determined. In this study GR138950 was tested on a canine model of multimicroinfarct-induced heart failure (14,15). Although the degree of heart failure achieved with embolization is moderate compared with rapid cardiac pacing-induced heart failure, we believe that this serves as a more stable and more clinically relevant model, as it mimics the most common clinical etiology of chronic heart failure. We demonstrated here and elsewhere that this model leads to a persistent heart failure state (15) characterized by increased LVEDP, reduced LVdP/dt and ejection fraction, tachycardia (14), impaired LV mechanics (17), and clinical signs of heart failure (14,15). With this ischemic heart failure model, we showed that GR139950 had no significant effects on resting hemodynamics in normal conscious dogs; in the heart-failure state, LVSP and LVDP, as well as HR, were significantly reduced. $LVdP/dt_{max}$, an index of ventricular contractility, was significantly increased in response to intravenous bolus injection of GR138950. The peak hemodynamic effects of GR138950 occurred between 60 and 90 min after administration. We believe that our measurements of hemodynamics in the conscious state, although limited by not measuring cardiac output and by the use of load and HR-dependent indices of contractile function, permitted the assessment of heart failure and the hemodynamic responses to GR138950 without the interference of the negative inotropy of sedation or anesthesia.

Clinical and experimental evidence demonstrated involvement of the RAS in the natural history and pathogenesis of heart failure. For instance, ACE inhibitors prevented the progression of experimental heart failure in rats with ascending aortic stenosis (18) and in dogs with rapid ventricular pacing (19). These results suggested that Ang II might have actions that are detrimental to the cardiovascular system and therefore contribute to the progression of heart failure. With respect to its effects on normal LV contractile function, Ang II was reported to act as either a negative or as a positive inotropic agent (20), an agent without inotropic effects (21), or an agent with biphasic inotropic effects (22). Our study showed no demonstrable effect on contractile performance in normal dogs.

However, one postulated mechanism through which Ang II is involved in the development of heart failure is that Ang II acts as a negative inotropic agent. After the establishment of heart failure, a negative inotropic effect of Ang II was shown in one study in which both whole-animal and isolated myocyte experiments were performed (6). In this same study, it was demonstrated that the Ang II-mediated depression of myocardial contractile in heart failure is mediated by AT_1 receptors, because the affect is reversed by losartan, an Ang II AT_1-receptor blocker. Our results confirm these observations; in the heart-failure state, GR1389050 produced an ~17% increase in LVdP/dt; meanwhile, HR and LVEDP were significantly decreased.

According to the hemodynamic data presented in Table 1, our model produces a state of mild heart failure. Associated with this, there was a mild, statistically significant increase in plasma Ang II levels comparable to that observed in human heart failure (23,24) and moderate cardiac dysfunction in dogs (3), although less than reported in some studies using canine models of more severe heart failure (3). Local Ang II concentration, not examined in our study, could be higher. Therefore, based on these results and previous work, although GR1389050 does not appear to be a direct positive inotropic agent, its positive inotropic effects in heart failure are likely to be exerted through blockade of the direct negative effects of endogenous Ang II, and this is mediated by AT_1 receptors.

In association with the increase in ventricular contractile performance, we observed a significant decrease in LVEDP. Although a decrease in LVEDP can be caused by an increase in ventricular contractility, results of recent studies suggest that the degree of LVEDP reduction noted in our study (>7 mm Hg) is too large to be explained simply on the basis of the change in contractile performance. Rather, the results of previous studies suggested that changes in LVEDP of this magnitude are mediated by venodilation; thus we postulate that, as in other models of heart failure (25), Ang II causes venoconstriction in chronic heart failure via AT_1 receptors, and this can be blocked by GR1389050.

It is noteworthy that significant bradycardia occurs after the administration of GR138950 during heart failure, with no effect in normal animals. This bradycardia seems not to be mediated by the reflexes, given the fact that there was no significant effect of GR138950 on MAP. Several investigators reported that Ang II increases blood pressure without decreasing HR because it either resets the baroreflex control of HR to a higher pressure or decreases the sensitivity of the baroreflexes (26). This resetting is mediated by central AT_1 receptors (27). The principal action of Ang II is to suppress cardiac vagal efferent activity (28). Therefore blockade of the RAS system with Ang II-receptor antagonists resets the baroreflex to a lower pressure, even in normal animals (29). In our experimental condition, the inhibition of cardiac vagal tone produced by the higher circulating Ang II levels may have been relieved by GR138950. The facilitated vagal activity might then have resulted in bradycardia.

Limitations of the study

One limitation of this study was that cardiac output was not measured, and total peripheral resistance was not calculated. This is because our experimental protocol requires survival for almost 10 weeks (3 weeks for surgical recovery, training, and initial experiment, 4-5 weeks for embolization, 1 week for terminal experiment), and implantation of the aortic flow probe for calculation of systemic vascular resistance significantly jeopardizes the survival of the animal because of the risk of rupture of the pulmonary artery or aorta. Therefore the effects of GR138950 on cardiac output and systemic vasomotion were not determined in the study. Because Ang II level was significantly increased in our experimental CHF model and both MAP and LVEDP were decreased after administration of GR138950 (although the decrease in LVEDP may simply result from the increase in cardiac pump function, detail earlier), the beneficial effects of GR138950 in CHF state may be also via its vasodilator mechanisms. However, to confirm this expectation, further studies are needed to determine the effects of GR138950 on cardiac output and vasomotor properties in various vascular beds in both normal and CHF state. The second concern of this study is whether the beneficial effects of GR138950 via its effects on cardiac diastolic properties. It has been shown that both ACE inhibitor and Ang II AT_1-receptor antagonist significantly improve LV stiffness constants in dogs with LV hypertrophy (29). Whether such effects play a role in the improved resting hemodynamics in heart failure was not addressed by our study because the direct indexes of LV diastolic function, such as LV chamber stiffness constant, were not measured. Although LVEDP, which was measured in our study, may indirectly reflect LV diastolic function, available information suggests that even large changes in [tau] (the time constant of LV relaxation) do not have a significant effect on LVEDP (30); furthermore, LVEDP was influenced by several factors such as LV contractility, preload, afterload, and vascular vasodilator capacities. Therefore the role of GR138950 on LV diastolic properties in the improved resting hemodynamics in our canine model of ischemic heart failure must be further studied. Finally, our results might be restricted to the CHF model used in this study. Although Cheng et al. (6) showed that another AT_1-receptor blocker, losartan, has comparable effects on LVdP/dt in a canine model of rapid cardiac pacing-induced heart failure, the effects of losartan on LVEDP were not so striking as GR138905. The mechanisms responsible for the discrepancy between their study and our study must be further elucidated.

In summary, Ang II contributes significantly to resting hemodynamic parameters in our canine model of moderate heart failure induced by daily coronary microembolization. This was manifest not only as changes in LV peak systolic pressure or LVEDP, but also as a significant increase in $LVdP/dt_{max}$, thus indicating a significant indirect inotropic action of GR138950. That is, GR138950, a specific AT_1 blocker, inhibits the negative inotropic actions of Ang II. Also identified was a prominent negative chronotropic effect of GR138950. On the whole, these data, although limited to physiologic measurements, provide important new information showing that Ang II plays an important role in modulating hemodynamics in this clinically relevant model of heart failure. Accordingly, this will be a useful model for studying the role of Ang II in the pathophysiology and progression of heart failure.

Acknowledgment: This work was supported, in part, by a Grant-In-Aid from the American Heart Association (National Center) and a grant from Glaxo-Wellcome Research and Development, Stevenage, UK. J.W. and D.B. were supported in part by Investigatorship Award from the American Heart Association, New York City Affiliate, Inc.

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Key Words: Angiotensin II; AT_1 receptor; AT_1 receptor antagonist; Heart failure

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