

Vasopressor Response to Angiotensin II Infusion in Patients With Chronic Heart Failure Receiving β -Blockers

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Background—A synergistic interaction between the angiotensin II (Ang II) type 1 receptor and α_1 -adrenergic receptors has been described. We hypothesized that the nonselective β -antagonist carvedilol, through its α_1 -adrenergic blocking properties, may modulate vascular reactivity to Ang II in patients with chronic heart failure (CHF). Accordingly, we compared the vasopressor response to infused Ang II in patients treated with carvedilol and metoprolol, a selective β -antagonist.

Methods and Results—All subjects were treated with carvedilol or metoprolol for at least 3 months. ACE inhibitor therapy was standardized to enalapril 40 mg/d or the maximally tolerated dose. Exogenous Ang II was administered as sequential intravenous bolus injections (2.5 to 30 ng/kg) titrated to a rise in radial artery systolic pressure of ≥ 20 mm Hg. The dose of Ang II required to elicit a change of 20 mm Hg in radial artery systolic pressure (PD20) defined the vasopressor response to Ang II. Twenty subjects with CHF (mean left ventricular ejection fraction $28 \pm 9\%$, New York Heart Association class II [$n=13$] and III [$n=7$]) were studied. There was no correlation between plasma Ang II levels and PD20. However, the PD20 was significantly higher in patients treated with carvedilol than in those treated with metoprolol (20 [range 2.5 to 30] versus 5 [range 2.5 to 10] ng/kg, $P=0.019$).

Conclusions—The vasopressor response to Ang II infusion in patients treated with carvedilol was significantly lower than in patients treated with metoprolol. Whether this is due to the α_1 -adrenergic blocking or other ancillary properties of carvedilol warrants further investigation. (*Circulation*. 2003;107:290-293.)

Key Words: congestive heart failure ■ angiotensin ■ adrenergic receptors

It is known that α_1 -adrenoceptors mediate vasoconstriction in many vascular beds¹ and promote proximal tubular sodium reabsorption.² These physiological actions are attributable in part to interactions with the renin-angiotensin system. Specific to α_1 -adrenergic receptors, there are several lines of evidence to suggest that there is a synergistic interaction between the vascular angiotensin II type 1 receptor (AT₁-R) and α_1 -adrenergic receptors. In vivo animal studies have shown that angiotensin (Ang) II enhances adrenergic receptor function, which results in increased vasoconstriction and myocardial damage.³⁻⁵ In healthy volunteers, Seidelin and colleagues⁶ showed that low physiological doses of Ang II and norepinephrine interacted synergistically to produce an enhanced vasopressor response. Also in healthy volunteers, Lang and colleagues⁷ showed that the α_1 -adrenoceptor blocker prazosin blunted the antinatriuretic effect of Ang II. Finally, a recent study has shown that Ang II induces transcription and expression of α_1 -adrenergic receptors in rat vascular smooth muscle cells.⁸ Whether the interaction between vascular AT₁-R and α_1 -adrenergic receptors modulates vasomotor function in patients with chronic heart failure (CHF) is unknown.

Accordingly, the present study was undertaken to compare the vasopressor response to intravenous administration of Ang II in subjects with CHF receiving chronic treatment with carvedilol or metoprolol. We hypothesized that the α_1 -adrenoceptor-blocking effects of carvedilol would be associated with a decreased pressor response to Ang II infusion compared with metoprolol.

Methods

Study Population

Subjects were recruited from the Columbia-Presbyterian Medical Center Heart Failure Center. All subjects were taking β -adrenoceptor blockers for at least 3 months and had undergone a stable medical regimen for 1 month or more. All subjects were taking ACE inhibitors, and an attempt was made to standardize ACE inhibitor therapy to enalapril 40 mg/d for 1 month before study. Subjects intolerant of ACE inhibitors, treated with Ang receptor blockers and other α_1 -adrenoceptor blockers, with baseline resting systolic blood pressure >140 mm Hg or <90 mm Hg, acute coronary syndromes within the past 3 months, serum creatinine >2.5 , or hospitalization within the past 1 month were excluded. The Medical Center Institutional Review Board approved the study protocol, and all subjects signed an informed consent form before study.

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Study Protocol

All subjects were studied after an 8-hour fast, and all received their usual daily medications, including enalapril and β -adrenoceptor blocker, 3 hours before study. All studies were performed in a quiet, temperature-controlled room. An intravenous angiocatheter was inserted into a forearm vein in the antecubital fossa. After 30 minutes of supine rest, venous blood was drawn for a basic metabolic panel and Ang II levels. Blood for the measurement of plasma Ang II was collected into vials containing neutral endopeptidase–ACE and renin inhibitors. Plasma was separated by cold centrifugation and assayed by radioimmunoassay at the Cardiorenal Research Laboratories, Mayo Clinic, Rochester, Minn.⁹

Heart rate and cuff blood pressure were then measured. Radial artery waveform was calibrated to cuff pressure and recorded continuously with a Colin Pilot Monitor 9200 high-fidelity arterial tonometer system (Colin Instruments Corp). Data were stored on a notebook computer with an analog-digital converter (TDA program version 2, Colin Instruments Corp). Analysis of the change in radial artery systolic pressure (RASP) was subsequently performed by an investigator (C.C.L.) who was blinded to the dose of Ang II, dosing sequence, and subject treatment status.

Vasopressor Response to Ang II

The vasopressor response to Ang II was determined by examining the RASP response to intravenous Ang II as described previously.¹⁰ In brief, ascending sequential doses of Ang II (Clinalfa AG) were administered intravenously to increase RASP by ≥ 20 mm Hg. The first dose was 2.5 ng/kg, and the subsequent doses were 5, 7.5, 10, 15, 20, and 30 ng/kg. The RASP was allowed to return to baseline between injections. The primary outcome variable for assessment of vasopressor response was defined as the dose of Ang II required to increase RASP by 20 mm Hg (PD20), determined as an average of 15 beats at the peak of the response.

Statistical Analysis

Comparisons of PD20 values and other variables between treatment groups (carvedilol versus metoprolol) were analyzed with independent-sample 2-tailed Student's *t* test for continuous variables and χ^2 test for categorical variables. A probability value <0.05 was used to infer statistical significance. Values are expressed as mean \pm SEM or median (range).

Results

Twenty subjects with CHF were studied. Baseline clinical characteristics are summarized in the Table. All patients had been taking β -adrenoceptor blockers for at least 3 months; 13 were treated with carvedilol (mean dose 38 ± 19 mg) and 7 with metoprolol (4 were taking metoprolol XL, and 3 were taking immediate-release metoprolol). Because oral bioavailability of the sustained-released metoprolol succinate formulation is 75% of the immediate-release metoprolol tartrate,¹¹ the derived equivalent mean dose of metoprolol tartrate of the metoprolol group was 83 ± 54 mg. All patients were treated with a daily dose of enalapril 40 mg except for 4 patients in the carvedilol group, with 2 patients receiving 20 mg/d and 2 receiving 10 mg/d. Plasma Ang II levels did not differ between the 2 groups. With respect to other cardiovascular medications, 95% were receiving diuretics, 75% digoxin, and 40% spironolactone, with no differences between the 2 groups.

Administration of Ang II was well tolerated and followed by a characteristic rise and plateau of blood pressure ≈ 60 to 90 seconds after injection. Blood pressure returned to baseline after 2 to 5 minutes.

Baseline Characteristics of Patients in Carvedilol and Metoprolol Pretreatment Groups

	Carvedilol (n=13)	Metoprolol (n=7)
Age, y	54 \pm 9	53 \pm 12
Sex, M/F, n	11/2	7/0
Pathogenesis, n		
Ischemic	4	4
Nonischemic	9	3
New York Heart Association class II/III, n	9/4	4/3
Systolic blood pressure, mm Hg	106 \pm 18	111 \pm 11
Diastolic blood pressure, mm Hg	63 \pm 9	67 \pm 10
Heart rate, bpm	65 \pm 10	68 \pm 13
Left ventricular ejection fraction, %	26 \pm 11	30 \pm 6
Left ventricular end-diastolic dimension, cm	6.4 \pm 0.7	6.1 \pm 0.6
Serum sodium, mmol/L	136 \pm 5	138 \pm 3
Serum creatinine, mg/dL	1.3 \pm 0.5	1.1 \pm 0.2
Mean β -blocker dose, mg	38 \pm 19	83 \pm 54
Mean enalapril dose, mg	34 \pm 10	40
Mean diuretic dose, mg	90 \pm 90	100 \pm 72
% Digoxin	77	71
% Spironolactone	38	43
Plasma Ang II, pg/mL	9.6 \pm 5.5	9.8 \pm 5.8

The PD20 to Ang II ranged from 2.5 to 30 ng/kg body weight and was significantly higher in patients treated with carvedilol (PD20=20 [range 2.5 to 30] ng/kg) than in those treated with metoprolol (PD20=5 [range 2.5 to 10] ng/kg; $P=0.019$ by χ^2 analysis; Figure 1). A 20-mm Hg increase in systolic blood pressure was accompanied by an increase in radial artery diastolic pressure of 16.6 ± 2.9 mm Hg in the carvedilol and 14.2 ± 5.6 mm Hg in the metoprolol group. The relationship of systolic and diastolic pressure increase was not different between groups.

Levels of circulating Ang II ranged from 2.3 to 19 pg/mL and were not correlated with the pressor response to Ang II in the carvedilol and metoprolol treatment groups ($r=0.08$, $P=NS$; Figure 2).

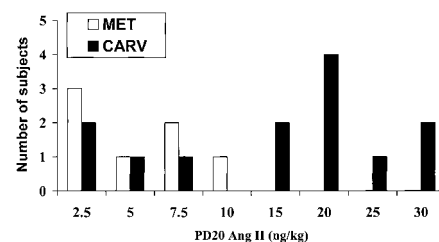


Figure 1. Vasopressor response to Ang II, determined by PD20 to Ang II, in groups treated with carvedilol (CARV; n=13) or metoprolol (MET; n=7). PD20 is pressor dose of Ang II to elicit change of 20 mm Hg (PD20) in systolic blood pressure taken as average of 15 beats at peak of this rise. PD20 to Ang II was significantly higher in carvedilol-treated group (carvedilol median PD20 Ang II of 20 [range 2.5 to 30] ng/kg vs metoprolol median PD20 Ang II of 5 [range 2.5 to 10] ng/kg, $P=0.019$ by χ^2 analysis).

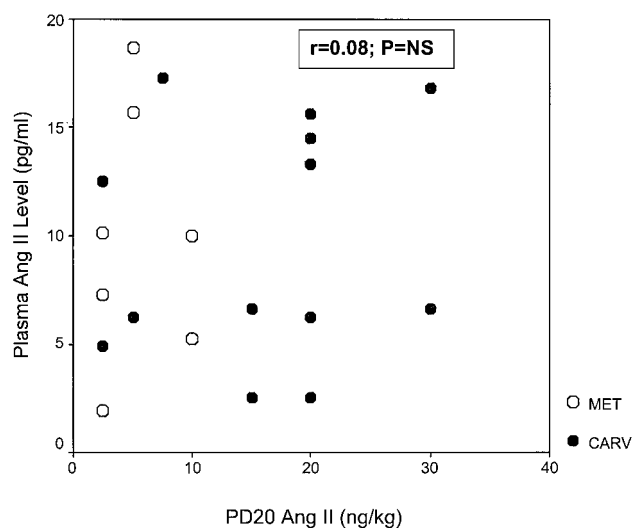


Figure 2. Vasopressor response or PD20 of Ang II is shown in ng/kg on x-axis. Plasma levels of Ang II (in pg/mL) are shown on y-axis. There was no correlation ($r=0.08$; $P=NS$). Levels of circulating Ang II ranged from 2.3 to 19 pg/mL and were not correlated with pressor response to Ang II in carvedilol ($n=13$) and metoprolol ($n=7$) treatment groups. CARV indicates carvedilol; MET, metoprolol.

Discussion

Considerable evidence supports the existence of an interaction between the renin-angiotensin system and the sympathetic nervous system.¹² Ang II facilitates sympathetic neurotransmission at several sites, including the central nervous system,¹³ adrenal medulla,¹⁴ sympathetic ganglia,¹⁵ and pre-synaptic sympathetic nerve terminals.¹⁶ Stimulation of the sympathetic nervous system leads to renin secretion and Ang II generation.¹⁷ Furthermore, vascular AT₁-R and α_1 -adrenergic receptors sensitize each other to produce an enhanced response to their respective substrate. Experimental studies have also investigated the molecular basis of this interaction. Activation of both AT₁-R and α_1 -adrenergic receptors involves G proteins, and G-protein-coupled receptor cross-talk pathways have been described.¹ Hu and colleagues⁸ have shown that Ang II induces transcription and expression of α_1 -adrenergic receptors in rat vascular smooth muscle cells. These actions of Ang II were associated with an enhanced activation of α_1 -adrenergic receptors to induce the protooncogene c-fos. Interestingly, other investigators have also suggested that the interaction between α -adrenoceptors and AT₁-R may be specific to α_1 -adrenoceptors.¹⁸

The main finding of the present study is that the vasopressor response to intravenous administration of Ang II in patients with CHF was significantly decreased in those subjects treated with an α,β -blocker compared with those treated with a β -selective agent. Our observation suggests that the above-reviewed interaction between AT₁-R and α_1 -adrenergic receptors might be relevant in CHF, ie, α_1 -adrenoceptor blockade leading to a reduced vasopressor response to Ang II via downregulation of AT₁-R.

There is some debate as to whether the α_1 -adrenoceptor blockade by carvedilol persists during long-term therapy. Some investigators report a reduction in systemic vascular

resistance with chronic treatment,^{19,20} but this has not been a consistent finding.²¹ Recently, Kubo and colleagues²² reported that 4 months of treatment with carvedilol did not blunt the hemodynamic response to handgrip exercise, which possibly suggests that the peripheral α_1 -adrenoceptor blocking property of carvedilol is not functionally important during long-term treatment. However, only 18 of 36 patients recruited for this study actually performed isometric handgrip exercise, an indirect assessment of α_1 -adrenoceptor blockade. Furthermore, interpretation of handgrip exercise may be problematic in CHF, because baroreceptor function is altered in this condition.²³ Using direct α_1 -adrenoceptor stimulation with intravenous phenylephrine, Giannattasio et al²⁴ demonstrated sustained α_1 -adrenoceptor blockade with carvedilol in patients with hypertension after several weeks of therapy. The findings of the present study are consistent with a persistent α_1 -adrenoceptor blocking action of carvedilol during long-term treatment.

Other possible explanations for the present findings need to be considered. First, baroreflex dysfunction is present in CHF and enhances the vasopressor response to Ang II.²⁵ Treatment with carvedilol has been shown to improve arterial baroreceptor function in patients with CHF and might thereby blunt the vasopressor response to Ang II by this mechanism.²⁶ Second, carvedilol is capable of inhibiting biosynthesis of endothelin, which has vasoconstrictive and proliferative actions on vascular smooth muscle and may enhance the effects of Ang II.^{27,28} However, improvement of baroreceptor gain in CHF and a reduction of endothelin release has also been demonstrated with metoprolol,²⁹ and it is unknown whether a quantitative difference exists between these 2 agents with respect to improving autonomic dysfunction or downregulation of endothelin. Third, the β_2 -adrenergic blocking property of carvedilol has been shown to have a sympathoinhibitory effect.³⁰ This sympathoinhibitory effect would result in less norepinephrine to act on other adrenergic receptors that were not blocked by the β -blocker, such as extrasynaptic α_2 -adrenergic receptors that can cause vasoconstriction. Besides inhibiting norepinephrine release, carvedilol may also reduce the release of other vasoactive neurotransmitters such as neuropeptide Y.³¹ Finally, it has recently been shown that Ang II-induced NAD(P)H oxidase-dependent superoxide production contributes importantly to its acute vasoconstrictor effects.³² Carvedilol dose dependently modulates generation of superoxide ions by NADPH oxidase³³ and may thus interfere with the vasoconstrictor response to Ang II.

Several limitations of the present study should be acknowledged. Our study did not prospectively randomize patients to selected doses of carvedilol and metoprolol. Consequently, there may have been unforeseen bias in the selection and dosing of the β -adrenoceptor blockers. The mean dose of carvedilol was 38 mg/d, which is 84% of the mean dose that was achieved in the US Carvedilol Multicenter Trial Program.³⁴ The mean dose of metoprolol tartrate in the present study was 83 mg/d, which is 72% of the mean dose used in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial.³⁵ Thus, the relative dose of carvedilol might have been slightly higher. However, there was no significant difference in heart rate

between the 2 groups, and results of a separate post hoc analysis that excluded the 4 patients taking the highest dose of carvedilol, which made the average dose equivalent to 73% of the US Carvedilol Study, did not differ from those reported here.

In addition, 4 subjects in the carvedilol group did not receive the 40 mg of enalapril. Theoretically, this lower dosage of ACE inhibition may make patients more sensitive to infused Ang II. However, when these 4 subjects were excluded from the analysis, the difference between the 2 treatment groups was still significant ($P=0.024$). Finally, we did not control the sodium balance status of patients in the present study before testing, which might have influenced the vasopressor response to Ang II.

In conclusion, we have shown that the vasopressor response to Ang II infusion in CHF patients treated with carvedilol was significantly lower than that in patients treated with metoprolol. These differences could be related to the α_1 -adrenoceptor blocking effects or other ancillary pharmacological properties of carvedilol and need to be confirmed in a randomized study. The clinical significance of these findings is unknown.

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