Effect of Angiotensin-(1-7) and Bradykinin in Patients With Heart Failure Treated With an ACE Inhibitor

Andrew P. Davie, John J.V. McMurray

Abstract—Angiotensin-(1-7) is a product of angiotensin processing that has been proposed to have vasodepressor effects, both on its own and in combination with bradykinin, which may be pathophysiologically and therapeutically important. Despite this, there has been very little examination of its effects in humans and none in heart failure patients or in other patients treated with ACE inhibitors. We therefore sought to determine the effects of angiotensin-(1-7) in patients with heart failure treated with an ACE inhibitor, as well as any interaction with the effects of bradykinin. A locally active dose of angiotensin-(1-7), alone and in combination with bradykinin, was infused into the nondominant brachial artery while forearm blood flow was measured by venous occlusion plethysmography in 8 patients with heart failure treated with ACE inhibitors. Although bradykinin on its own caused profound vasodilation, there was no effect of angiotensin-(1 to 7) on its own or any effect of angiotensin-(1-7) on the response to bradykinin. We conclude that angiotensin-(1-7) is biologically inactive in the forearm circulation of patients with heart failure treated with an ACE inhibitor. The contrast between these findings and previously reported preclinical findings calls into question the relevance of angiotensin-(1-7) to the hemodynamic effects of ACE inhibitors. (Hypertension. 1999;34:457-460.)

Key Words: angiotensin ■ bradykinin ■ angiotensin-converting enzyme inhibitors ■ heart failure ■ renin-angiotensin system

Angiotensin-(1-7) [Ang-(1-7)] was originally regarded as a biologically inactive degradation product of the renin-angiotensin system (RAS). An early study reported pressor effects in humans in vivo but used such large doses that it was regarded as confirmation of biological inactivity (0.028% of the activity of Ang II). It has since emerged that Ang-(1-7) is biologically active in the central nervous system and indeed in the circulation. It has also emerged that not only are Ang-(1-7) levels not reduced by inhibition of ACE but that they may actually be increased, which suggests that Ang-(1-7) is derived directly from Ang I, and that the effect of Ang-(1-7) itself is potentiated by ACE inhibition, which suggests that Ang-(1-7) is inactivated by ACE. It is therefore hypothesized that Ang-(1-7) may contribute toward the “non–angiotensin-II–ergic” effects of ACE inhibitors and even that this may be one way in which inhibitors of prostaglandin synthesis could interfere with the action of ACE inhibitors. The situation is further complicated by the fact that Ang-(1-7) has been shown to interact closely with the effects of bradykinin. It is clear that Ang-(1-7) potentiates the effect of bradykinin and even that the effects of Ang-(1-7) may be mediated by bradykinin. Given that the effects of bradykinin are also potentiated by ACE inhibitors, this reiterates the potential importance of Ang-(1-7) (and bradykinin) in the effects of ACE inhibitors. It is hardly surprising that it has even been suggested that Ang-(1-7) may be functioning as an ACE inhibitor itself.

With a single exception, these studies were conducted in animals, not humans, and many were in vitro rather than in vivo. Furthermore, despite the potential importance of Ang-(1-7) in the effects of ACE inhibitors, there has been no examination of the effects of Ang-(1-7) in heart failure, a syndrome in which the RAS is of enormous importance and ACE inhibitors are extraordinarily clinically useful. We therefore sought to discover the effects of Ang-(1-7) in patients with heart failure treated with an ACE inhibitor, as well as any interaction with the effects of bradykinin.

Patients

The study was conducted with the approval of the West Ethics Committee. All patients gave written informed consent.

Eight patients with chronic heart failure secondary to left ventricular systolic dysfunction confirmed by echocardiography were studied (left ventricular ejection fraction <40%). All patients were clinically stable and taking fixed doses of cardioactive medication for ≥3 months, with no peripheral edema or pulmonary congestion, and none had uncontrolled hypertension, untreated hypercholesterolemia, or diabetes mellitus requiring insulin. All patients were undergoing treatment with an ACE inhibitor (5 patients taking enalapril 10 mg BID, 1 patient lisinopril 10 mg QD, 1 patient captopril 25 mg TID, and 1 patient perindopril 4 mg BID). All medications other than aspirin were continued throughout the period of study. Patient characteristics are summarized in the Table.

Patients were studied after 14 days of abstinence from aspirin. They took their usual medications other than aspirin 6 hours before

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Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>Gender, n</td>
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</tr>
<tr>
<td>Age, y (mean±SD)</td>
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<tr>
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<td>LVEF, % (mean±SD)</td>
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<tr>
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<tr>
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<tr>
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<td>Calcium antagonist use, n</td>
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<tr>
<td>Amiodarone use, n</td>
<td>2</td>
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<tr>
<td>Baseline BP, mm Hg (mean)</td>
<td>124±67</td>
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</table>

IHD indicates ischemic heart disease; IDC, idiopathic dilated cardiomyopathy; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; and BP, blood pressure.

Attendance on the day of study. Patients abstained from alcohol, tobacco, and caffeine for ≥24 hours before each study and fasted for ≥3 hours before the study. Bradykinin was infused at 3, 10, and 30 pmol/min for 3 minutes at each dose. Ang-(1-7) was then infused at 5, 50, 500, 5000, and 50 000 pmol/min for 6 minutes at each dose. Finally, bradykinin was reinfused as before while a coinfusion of Ang-(1-7) at 50 000 pmol/min continued. Measurements of pulse, blood pressure, and blood flow were made continuously throughout the study.

Measurements

Studies were performed with patients lying supine in a quiet clinical laboratory in which the temperature was maintained between 23°C and 25°C. After local anesthesia with 1% lidocaine (Astra Pharmaceuticals), a 27-gauge steel needle (Terumo Medical Corp) was placed in the nondominant brachial artery and connected to a constant-rate infusion pump (IVAC P1000, Alaris Medical Systems) via a 16-gauge epidural catheter (Portex Ltd). Physiological saline solution (0.9%, Baxter Healthcare Ltd) was infused at 1 mL/min for ≥20 minutes before drug infusion.

Blood flow was measured simultaneously in the infused and noninfused arms by venous occlusion plethysmography with indium/gallium-in-Silastic strain gauges applied to the widest aspect of each forearm. To obtain blood flow measurements, hand circulation was excluded by inflation of wrist cuffs to 220 mm Hg, and upper-arm cuffs were inflated to 40 mm Hg to obstruct venous outflow for 12 of every 16 seconds. Voltage output from a plethysmograph (Hokanson Corp) was transferred via an analog-to-digital converter (MacLab 4e, AD Instruments) to a personal computer (PowerMac, Apple Computer Inc) for analysis (Chart version 3.2.8; AD Instruments). Plethysmographic recordings were made for a period of 2.5 minutes at 10-minute intervals during saline infusion and at 3- to 5-minute intervals during drug infusion. The last 5 measurements from each 2.5-minute recording period were further analyzed (Excel version 7.0, Microsoft Corp) and averaged, and the mean percentage change from baseline in the ratio of flow between the infused and noninfused arms was calculated. Provided blood pressure remains constant, increases in blood flow can be taken to represent vasodilation and decreases in blood flow to represent vasoconstriction. This method is extremely well validated and uses the noninfused arm as a contemporaneous control and a means of distinguishing the effects of drug infusion from any other external or environmental factors. Blood pressure and pulse rate were manually recorded in the noninfused arm at 5- to 10-minute intervals throughout each study.

Drugs

Bradykinin (purity 99.4% by high-performance liquid chromatography [HPLC]) was obtained from Clinalfa AG and dissolved in normal saline. Ang-(1-7) (purity 99.9% by HPLC) was obtained from Clinalfa AG and dissolved in normal saline. All drugs were used within 2 hours of final preparation and destroyed thereafter.

Data Analysis

All results are expressed as mean values with 95% CIs in the text and mean values with SEs in the figures. All results were compared by use of 2-tailed paired t tests. Differences were considered statistically significant at a value of P<0.05.

Results

Local infusion of bradykinin and Ang-(1-7) caused no adverse or systemic effects, and patients reported no discomfort. Pulse rate, blood pressure, and forearm blood flow in the noninfused forearm did not change significantly during the initial infusions of bradykinin and Ang-(1-7). In addition, there was no significant hemodynamic change during coinfusion of bradykinin and Ang-(1-7), by the end of which coinfusion, 0.78 μmol Ang-(1-7) had been administered in total, a dose that might have been expected to be systemically active.

Effect of Bradykinin Infusion

Bradykinin caused marked vasodilation that was rapid in onset (~1 minute) and almost as rapid in offset (~5 minutes). There was a clear dose-response relationship, with peak vasodilation at the highest dose of 30 pmol/min (Figure 1).

There was no sign of the development of tachyphylaxis.

Effect of Ang-(1-7) Infusion

There was evidence of slight vasoconstriction to Ang-(1-7) at 500 pmol/min (4.3±3.0%) and 5000 pmol/min (6.7±3.8%) but not at lower or higher doses. Even this effect was so
Effect of Ang-(1-7) Infusion on Response to Bradykinin Infusion

Confusion of bradykinin and Ang-(1-7) after 30 minutes of Ang-(1-7) infusion gave very similar results to the initial infusion of bradykinin alone. If anything, there was a slight reduction in response, although this was not significant (Figure 1).

Discussion

In this study in the forearm of patients with heart failure treated with an ACE inhibitor, we have shown that exogenous bradykinin causes vasodilation, that Ang-(1-7) has no significant effect on its own (except, if anything, a tendency to slight vasoconstriction), and that Ang-(1-7) does not potentiate the response to exogenous bradykinin (if anything, it inhibits it). These findings do not agree with previously reported findings in animals (many of them in vitro rather than in vivo) and therefore deserve further consideration.

This is the first study of the effects of bradykinin in patients with heart failure. Bradykinin has been well studied in healthy volunteers and in patients with endothelial dysfunction but not in patients with heart failure, despite the importance of ACE inhibitors and the potential importance of bradykinin potentiation in the treatment of heart failure. Our findings confirm that bradykinin is a potent vasodilator in patients with heart failure, as it is in subjects without heart failure. Furthermore, they generate the hypothesis that this may be an endothelin-dependent response that is not impaired in heart failure. Although it is possible that an impaired response to bradykinin might be improved by ACE inhibitor treatment (especially given that ACE inhibitors do potentiate bradykinin), our findings were remarkably similar to those in healthy volunteers also treated with an ACE inhibitor (albeit acutely rather than chronically). Interestingly, it has very recently been reported that responses to bradykinin are indeed unimpaired in heart failure, albeit in an animal model.

It was surprising that Ang-(1-7) had so little hemodynamic effect on its own and even more surprising that what effects it did have tended toward vasoconstriction rather than vasodilator effects. At first glance, this appears to contradict the substantial body of evidence reviewed in our introduction. Again, however, we point to the potential importance of the species gap. We find that our findings are consistent with the only 2 human studies in the literature. First, it was shown that a systemic infusion of Ang-(1-7) has pressor effects, albeit at a dose 24 times higher than the total dose we gave and 3600 times higher than an equipotent dose of Ang II. Second, there is 1 human study that is frequently cited as evidence that ACE inhibitors increase Ang-(1-7) levels. Although that study showed that Ang-(1-7) levels were increased by a last dose of captopril at the end of 6 months of treatment with captopril, even that increased level was not as high as the pretreatment level, which was itself unaffected by the first dose of captopril. This was in marked contrast to the effects of captopril on Ang I levels. We contend that the available evidence suggests that Ang-(1-7) is biologically inactive in the circulation of humans (certainly in the forearm of patients with heart failure treated with an ACE inhibitor).

We could find no evidence of any influence of quite massive doses of Ang-(1-7) on the response to bradykinin. It was important to demonstrate this in humans given the very clear demonstration that Ang-(1-7) potentiates the effects of bradykinin in animal models. Indeed, it has been reported that the effects of Ang-(1-7) itself are mediated by bradykinin. It has also been reported that Ang-(1-7) acts as an ACE inhibitor. It is obviously possible that a bradykinin-potentiating effect of Ang-(1-7) was obscured by the fact that all our patients were already taking an ACE inhibitor [if Ang-(1-7) is an ACE inhibitor, it is certainly not as powerful as enalapril and related drugs]. A lack of effect of Ang-(1-7) on the response to bradykinin, however, is compatible with the lack of effect of Ang-(1-7) alone, which we have also demonstrated.

We have demonstrated that Ang-(1-7) has no significant effect on its own or on the response to bradykinin in the forearm arteries of patients with heart failure treated with an ACE inhibitor (who otherwise have quite impressive responses to bradykinin). These are patients in whom the RAS is of supreme pathophysiological and therapeutic importance. Ang-(1-7) has gained some currency as a potential mediator of the “nonangiotensinergic” (or more properly, “non–angiotensin-II–ergic”) effects of ACE inhibitors and, perhaps, other modulators of the RAS, such as Ang II type I receptor blockers. Our results argue against any such role for Ang-(1-7) and suggest both that it will be necessary to look elsewhere for mediators to explain the complexity of this system and that it may be a fruitless task to look for a pathophysiological role of Ang-(1-7) in humans with heart failure.

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References


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