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) 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.

Methods

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 BD, 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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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
small, however, that it was not significantly different from baseline (Figure 2).

**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 endothelium-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 vasopressor rather than vasodepressor 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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