

# Cardiovascular actions of angiotensin-(1-7)

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## Abstract

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Angiotensin-(1-7) (Ang-(1-7)) is now considered to be a biologically active member of the renin-angiotensin system. The functions of Ang-(1-7) are often opposite to those attributed to the main effector component of the renin-angiotensin system, Ang II. Chronic administration of angiotensin-converting enzyme inhibitors (ACEI) increases 10- to 25-fold the plasma levels of this peptide, suggesting that part of the beneficial effects of ACEI could be mediated by Ang-(1-7). Ang-(1-7) can be formed from Ang II or directly from Ang I. Other enzymatic pathways for Ang-(1-7) generation have been recently described involving the novel ACE homologue ACE2. This enzyme can form Ang-(1-7) from Ang II or less efficiently by the hydrolysis of Ang I to Ang-(1-9) with subsequent Ang-(1-7) formation. The biological relevance of Ang-(1-7) has been recently reinforced by the identification of its receptor, the G-protein-coupled receptor Mas. Heart and blood vessels are important targets for the formation and actions of Ang-(1-7). In this review we will discuss recent findings concerning the biological role of Ang-(1-7) in the heart and blood vessels, taking into account aspects related to its formation and effects on these tissues. In addition, we will discuss the potential of Ang-(1-7) and its receptor as a target for the development of new cardiovascular drugs.

### Key words

- Angiotensin-(1-7) receptor Mas
- Renin-angiotensin system
- Cardiac function
- Blood vessels
- Angiotensin-converting enzyme 2
- Transgenic models

## Introduction

The renin-angiotensin system (RAS) is a major regulator of renal and cardiovascular function, playing a pivotal role in the homeostasis of arterial pressure and of the hydro-electrolyte balance. In the past few years the combination of classical physiopharmacological techniques with modern genomics and protein chemistry methods has led to the identification of many novel components of the RAS: the angiotensin (Ang) IV binding site insulin-regulated aminopeptidase (1), angiotensin-converting enzyme 2 (ACE2)

(2,3), the renin receptor (4), and the Ang-(1-7) receptor Mas (5). Recent reports have also suggested that Des-Asp<sup>1</sup>-Ang I (Ang-(2-10)) has cardiovascular actions which may be direct or depend on its processing to smaller peptides (6). Ang-(1-7) is one of the most interesting peptide fragments of the RAS because it can be formed directly from Ang I independent of ACE (Figure 1) and because it has actions which are often opposite to those of Ang II (7). The recent identification of the Ang-(1-7)-forming enzyme ACE2 and of Mas as an Ang-(1-7) receptor has added further support and wider acceptance (8-10)



canine heart. In that study, immunoreactive Ang-(1-7) was demonstrated in the aortic root, coronary sinus, and right atrium under basal conditions. Ang-(1-7) was markedly reduced following treatment with the ACE inhibitor CGS-14,831 (18). In isolated rat hearts, Ang I is extensively metabolized during a single pass through the coronary bed, leading to the generation of Ang II, Ang III, Ang IV, and Ang-(1-7) (19,20). Ang-(1-7) formation in this model was not significantly changed by ACE inhibitors (19). Ang-(1-7) is also formed in the intact human myocardial circulation but, in contrast to the rat heart, ACE inhibitors markedly decrease Ang-(1-7) generation (21).

A novel ACE homologue (ACE2) was described a few years ago (2,3). ACE2 can form Ang-(1-7) from Ang II (22) or less efficiently by hydrolysis of Ang I to Ang-(1-9) (3,10,22) with subsequent Ang-(1-7) generation by ACE and neprilysin hydrolysis (23). ACE2 is expressed extensively in the heart but is also located in the endothelium (22). Recent studies have indicated that ACE2

is an important regulator of the RAS and apparently plays an important role in heart function (10,24). Interestingly, heart ACE2 is increased by treatment with AT<sub>1</sub> antagonists and in failing human heart ventricles (25,26). Averill et al. (27) reported that Ang-(1-7) immunoreactivity was limited to cardiac myocytes and absent in interstitial cells and vessels. Myocardial infarction induced by left coronary artery occlusion significantly increased Ang-(1-7) immunoreactivity in the ventricular tissue surrounding the infarcted area. These studies suggest that Ang-(1-7) is part of a functional RAS in the heart.

Concerning the effects of Ang-(1-7) in the coronary bed there are marked differences related to dose and species. In isolated canine coronary artery rings precontracted with the thromboxane A<sub>2</sub> analogue U46,619, Ang-(1-7) elicited a dose-dependent vasorelaxation (10 nM to 100 µM). This effect was completely blocked by the nonselective Ang II antagonist (Sar<sup>1</sup>, Thr<sup>8</sup>)-Ang II, but not by the selective AT<sub>1</sub> or AT<sub>2</sub> Ang II antagonists CV11974 and PD123319, respectively, sug-

Table 1. Cardiovascular effects mediated by angiotensin receptors.

Angiotensin	Receptor	Actions
Ang II	AT <sub>1</sub>	Vasoconstriction and pressor effect Increase of inotropism and chronotropism Arrhythmogenic effect Remodeling and cell proliferation Thrombosis and inflammation
Ang II	AT <sub>2</sub>	Inhibition of cell proliferation Apoptosis Vasodilation (?)
Ang-(1-7)	AT <sub>1-7</sub> (Mas)*	Vasodilation Potentiation of BK-induced vasodilation Anti-arrhythmogenic effect Improvement of post-ischemic contractile function Inhibition of cell proliferation
Ang-(3-8) (Ang IV)	AT <sub>4</sub> (IRAP)?	Vasodilation Inhibition of cell proliferation
Des-Asp <sup>1</sup> -Ang I	AT <sub>1</sub> /?	Inhibition of Ang II-induced cell proliferation

\*Mas-mediated actions were listed based on direct or indirect evidence (blocked by A-779). Ang = angiotensin; BK = bradykinin; IRAP = insulin-regulated aminopeptidase.

gesting the existence of a specific ligand site for Ang-(1-7) in dog coronary vessels (15). Moreover, the vasorelaxant activity of Ang-

(1-7) was markedly attenuated by the nitric oxide (NO) synthase inhibitor L-NA and by the specific kinin B<sub>2</sub> receptor blocker Hoe 140, but not by the cyclooxygenase inhibitor indomethacin (15). On the other hand, Neves et al. (28) found that Ang-(1-7) induced a concentration-dependent (27, 70, and 210 nM) decrease in coronary flow in isolated perfused rat hearts, and effect that was not accompanied by consistent changes in inotropism or heart rate. A similar result was observed in isolated hamster hearts (29).

According to Loot et al. (17), chronic infusion (8 weeks) of Ang-(1-7) improved endothelial aortic function and coronary perfusion and preserved cardiac function in an experimental rat model of heart failure induced by ligation of the left coronary artery. The vascular endothelial dysfunction observed in aortic rings from rats with myocardial infarction was also markedly reversed by chronic infusion of Ang-(1-7) (17). The mechanisms of the coronary vascular actions of Ang-(1-7) have not been fully characterized, but probably involve release of prostacyclin and/or NO (11). One possible pathway involved in the coronary effects of Ang-(1-7) is the amplification of the vasodilator effects of BK. The vasodilator effect produced by BK injected in bolus into isolated perfused rat hearts or into isolated canine coronary arteries was potentiated by Ang-(1-7) (15,30).

Ang-(1-7) produced a significant increase in cardiac output and stroke volume in anesthetized Wistar rats as assessed by a fluorescent microsphere methodology. These effects were partially attenuated by the Ang-(1-7) antagonist, A-779 (31). We have shown that Ang-(1-7) at 220 pM concentration decreased the incidence and duration of ischemia-reperfusion arrhythmias in isolated perfused rat hearts (16). These cardioprotective effects were blocked by A-779 and by the cyclooxygenase inhibitor indomethacin. Furthermore, at the same low concentration, Ang-(1-7) improved the post-ischemic con-

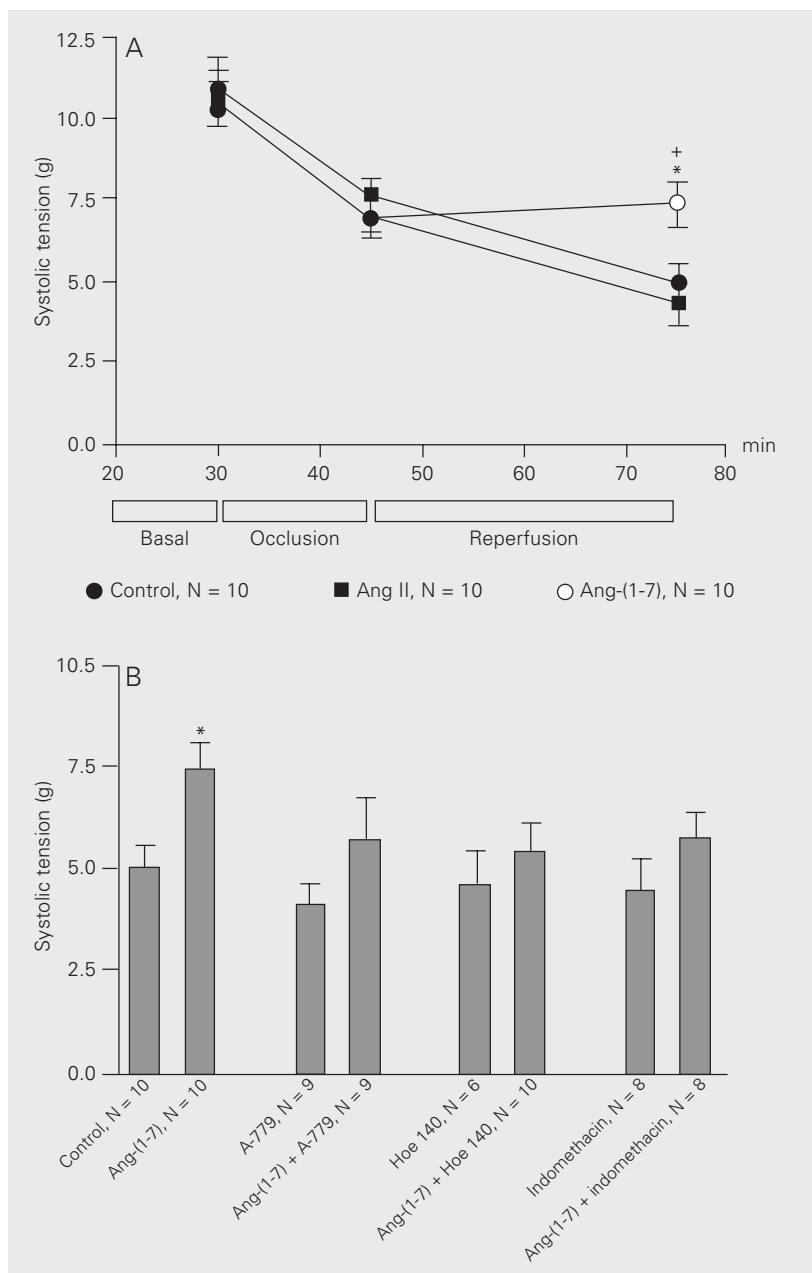


Figure 2. Time course of changes in systolic tension in isolated perfused rat heart submitted to temporary coronary occlusion. The hearts were perfused with Krebs-Ringer solution (KRS, control), KRS containing 0.22 nM angiotensin (Ang)-(1-7), or KRS containing 0.20 nM Ang II. The systolic tension was preserved in hearts perfused with Ang-(1-7) in the reperfusion period (A). This effect was completely blocked by A-779 (2 nM), Hoe 140 (100 nM), and pretreatment with indomethacin (5 mg/kg, *ip*, 1 h before heart removal) (B). \* $P < 0.05$  compared to the control group and \* $P < 0.05$  compared to the Ang II group (Student *t*-test).

tractile function in isolated perfused rat hearts by a mechanism apparently involving its receptor Mas (5) and release of BK and prostaglandins (Figure 2) (32). Of note is the fact that at higher concentration (27 nM) Ang-(1-7) exerts an opposite effect. Neves et al. (28) reported that Ang-(1-7) facilitated reperfusion arrhythmias in isolated perfused rat hearts. Accordingly, transgenic mice over-expressing ACE2 in the heart presented sudden death due to cardiac arrhythmias (33). These observations suggest that high local concentrations of Ang-(1-7) have deleterious effects on the heart.

Using the engineered fusion protein strategy, we have generated a transgenic rat model expressing an Ang-(1-7)-producing fusion protein (34). These TGR(A1-7)3292 rats presented a 2.5-fold increase in plasma Ang-(1-7) concentration. Radiotelemetry measurements showed that transgenic rats presented a slight but significant increase in diurnal and nocturnal dP/dt measurements. TGR(A1-7)3292 rats were significantly more resistant than control animals to induction of cardiac hypertrophy by isoproterenol. Moreover, these transgenic rats showed a reduced duration of reperfusion arrhythmias and an improved post-ischemic function in isolated perfused hearts. Therefore, this model provided further evidence for an important role of Ang-(1-7) in cardiac function (34).

### **Ang-(1-7) formation and actions in blood vessels**

Endothelial cells are an important site for the formation (35) and metabolism (36) of Ang-(1-7). It has been shown that Ang-(1-7) produces relaxation in several vascular beds, including canine and porcine coronary arteries, canine middle cerebral artery, piglet pial arterioles, feline systemic vasculature, rabbit renal afferent arterioles, rat aortic rings, and mesenteric microvessels of normotensive and hypertensive rats (37,38; see also Ref. 7 for a review). In human vessels, con-

tradictory results have been reported. Sasaki and co-workers (39) reported vasodilation in the human forearm while Davie and McMurray (40) did not observe any effect of Ang-(1-7) in the same territory in ACEI-treated patients. In keeping with previous reports by Ferrario's group (41), a role for Ang-(1-7) in mediating the chronic hypotensive effect of losartan in normal rats has been proposed by Collister and Hendel (42).

Many studies have shown that the vascular actions of Ang-(1-7) appear to involve increased production of vasodilatory prostanooids, NO and endothelium-derived hyperpolarizing factor (15,43,44). Moreover, some vascular effects involve simultaneous participation of these vasodilator mediators. A crosstalk between AT<sub>1-7</sub> and other receptors such as kinin B<sub>2</sub> and AT<sub>2</sub> receptors may also activate these pathways in blood vessels. For example, it has been demonstrated that the vasodilator action of Ang-(1-7) can be blocked by the B<sub>2</sub> receptor antagonist Hoe 140 (7,15). Moreover, a recent study showed that the link between Ang II and BK in endothelium-dependent vasorelaxation could involve receptors that bind the AT<sub>2</sub> and Ang-(1-7) receptor antagonists, PD123319 and A-779, respectively (45). The participation of vasodilating prostanoids in the vascular actions of Ang-(1-7) is not restricted to vasorelaxation, since they are also apparently involved in the antiproliferative actions of Ang-(1-7) in vascular smooth muscle cells and cardiomyocytes (44,46). Recently, it has been demonstrated that Ang-(1-7) inhibits vascular growth by the production of prostaglandin-mediated intracellular events, which include cAMP production and reduction of Ang II-stimulated ERK1/2 activities (47).

An important subset of cardiovascular actions of Ang-(1-7) is related to its BK-potentiating activity. Ang-(1-7) potentiates the vasodilator and hypotensive effects of BK in normotensive (48) and hypertensive (38) rats, in the human forearm (49), and in porcine (50), dog (15) and rat coronary

vessels (30). As mentioned above for vasodilation, the BK-potentiating activity of Ang-(1-7) is controversial in humans. Ueda et al. (49) reported BK potentiation while Wilsdorf et al. (51) were unable to show an effect at supraphysiological doses. Several mechanisms have been proposed to explain the BK-potentiating activity of Ang-(1-7) including ACE inhibition (50), non-hydrolytic interaction with ACE favoring a crosstalk between ACE and the BK-B<sub>2</sub> receptor (52), and AT<sub>1-7</sub> receptor-mediated changes in the coupling and/or signaling of BK (7,16,38,48). The recent observation that the Ang-(1-7) antagonist D-Ala<sup>7</sup>-Ang-(1-7) reverses the potentiation of BK in mesenteric microvessels by enalapril or enalaprilat (38) or attenuates the potentiated hypotensive response to BK in captopril-treated rats (53) indicates that an Ang-(1-7)-related mechanism is importantly involved in the effects of ACEI. In addition, the vascular actions of Ang-(1-7) could involve modulation of Ang II-induced changes in vascular resistance (13,54).

### **Ang-(1-7) and its receptor in the heart and blood vessels**

Many of the cardiovascular effects of Ang-(1-7) are completely blocked by the selective Ang-(1-7) antagonist A-779, suggesting that the effects of Ang-(1-7) on the heart and blood vessels are mediated by a specific receptor sensitive to A-779 (16,30-32,37,38; see also Ref. 7 for a review). Recently, Santos et al. (5) reported that Ang-(1-7) is an endogenous ligand for the G-protein-coupled receptor Mas. The specific binding of <sup>125</sup>I-Ang-(1-7) in mouse kidney slices was abolished by genetic deletion of Mas while the binding of <sup>125</sup>I-Ang II and <sup>125</sup>I-Ang IV was fully preserved. Furthermore, <sup>125</sup>I-Ang-(1-7) bound with high affinity to Mas-transfected COS cells and Ang-(1-7) treatment elicited arachidonic acid release from CHO and COS cells transfected with the Mas re-

ceptor. The binding of <sup>125</sup>I-Ang-(1-7) and the effect of Ang-(1-7) on arachidonic acid release were blocked by the Ang-(1-7) antagonist A-779. Mas mRNA was detected in the heart, testis, kidney, and brain (55). In keeping with the putative cardioprotective role of Ang-(1-7), isolated hearts of Mas-deficient mice presented marked changes in cardiac function. The systolic tension and positive and negative dT/dt were importantly decreased. Furthermore, a significant decrease in heart rate and an increase in coronary vascular resistance were also observed (56). In addition, the left ventricular pressure, positive dP/dt, and cardiac output were significantly lower in Mas-knockout mice assessed by means of a micro-conductance catheter placed inside the left ventricle (57). A reduced heart rate variability associated with an increased sympathetic tone was also found in Mas-deficient animals (58). These findings indicate that the Ang-(1-7) receptor Mas plays an important role in cardiac function and that the interaction of Ang-(1-7) with its specific receptor Mas is an important step for the actions of this peptide in the heart.

Evidence for a role of the Ang-(1-7) receptor Mas in the vascular effects of Ang-(1-7) was also obtained. Experiments on aortic rings derived from Mas-deficient mice demonstrated that the Ang-(1-7)-induced endothelium-dependent relaxation was abolished (5). This observation agrees with the results observed in Mas-transfected CHO cells, where Ang-(1-7), as well as its non-peptide agonist, AVE 0991 (59), cause a concentration-dependent increase in NO release (14). This effect was also blocked by A-779 but not by AT<sub>1</sub> or AT<sub>2</sub> antagonists. The Mas receptor appears to be also involved in the antiproliferative effect of Ang-(1-7) in vascular smooth muscle cells (47). It should be pointed out that, besides a Mas-Ang-(1-7) interaction, other mechanisms may be involved in the Ang-(1-7) vasodilatory effect, depending on the vessel diameter and the vascular regional bed (31).



## Perspectives

Considering our current knowledge of the actions of Ang-(1-7), we could divide its cardiovascular actions into Mas-mediated and non-Mas-mediated ones. The fact that some actions of Ang-(1-7) are also blocked by AT<sub>1</sub> or AT<sub>2</sub> antagonists (7,11,60) is in favor of this hypothesis and may represent an indirect interaction of Ang-(1-7) with AT<sub>1</sub> and AT<sub>2</sub> receptors via Mas. In addition, the possibility of Ang-(1-7) directly interacting with AT<sub>1</sub> or AT<sub>2</sub> receptors as it does with

ACE (7,53), cannot be excluded, especially at high Ang-(1-7) concentrations. The availability of non-peptide Ang-(1-7) receptor agonists, such as AVE 0991 (59), is a novel and important tool that will permit us to better understand its biological role and to clarify its complex mechanism of action (14). More importantly, these drugs may represent a new possibility for the development of novel therapeutic strategies for the treatment of cardiovascular diseases by interfering with the ACE2-Ang-(1-7)-Mas axis.

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