Angiotensin II receptor antagonists and sympathetic neurotransmission

Balt, J.C.

Citation for published version (APA):
CHAPTER 8

Decreased facilitation by angiotensin II of noradrenergic neurotransmission in the isolated mesenteric artery of rabbits with chronic heart failure

Accepted for publication, Journal of Cardiovascular Pharmacology
**Chapter 8**

**Introduction**

Various forms of congestive heart failure (CHF) are known to be accompanied by important neuro-endocrine changes, such as the activation of the renin-angiotensin system (RAS), the sympathetic nervous system, or the enhanced release of vasopressin [1]. In addition, the various influences of the RAS and SNS are subject to mutual interactions and potentiation. Although in the short term, these compensatory mechanisms help maintain blood pressure and tissue perfusion, in the long term, deleterious effects arise. Hence, sympathetic activation is now seen as a cardiovascular risk factor [1-3]. Additionally, blocking the RAS was shown to have favourable effects in both clinical and experimental heart failure [4-6].

Angiotensin II has a well known enhancing effect on the sympathetic neurotransmission at several sites, including the central nervous system, sympathetic ganglia, adrenal medulla and sympathetic varicosities [7]. The sympathetic nervous system in its turn stimulates the release of renin, via β-receptors in the juxtaglomerular apparatus in the kidney. Thus, there is important potential for this positive reciprocal feedback-loop between RAS and SNS, aimed at maintaining blood pressure, to be involved in the pathophysiology of heart failure. Evidence for this hypothesis was provided by the CONSENSUS trial, in which plasma NA-levels, were reduced by chronic ACE-inhibition [8]. More recently, reduction of plasma NA levels by AT₁-blockers has been shown in some [9,10] but not all [11] studies. In patients with CHF, chronic ACE-inhibition has been demonstrated to decrease sympathetic outflow, as measured by microneurography [12]. Similar findings were found for renal sympathetic nerve activity in a pacing-induced rabbit heart failure model [13]. In both studies, an impaired baroreflex control mechanism was demonstrated in HF, which was reversed by blockade of the RAS.

At the peripheral level, Ang II can enhance sympathetic neurotransmission by increasing the stimulation-induced noradrenaline release. This facilitating effect of Ang II has been shown to be mediated by prejunctionally located AT₁-receptors [14]. Eprosartan, a selective AT₁-antagonist, has been shown to very potently block the prejunctional AT₁-receptor [15].

Very little is known about the effects of Ang II on sympathetic neurotransmission at the peripheral level in congestive heart failure. Accordingly, the objective of the present study was to investigate the effects of Ang II on sympathetic neurotransmission in the isolated mesenteric artery taken from rabbits suffering from CHF, provoked by volume- and pressure overload. This
type of experimental heart failure was induced by aortic banding and destroying the aortic valve. Mesenteric arteries obtained from healthy, age matched controls were used in control experiments. We compared the sympato-inhibitory effects of the selective AT₁-receptor antagonist eprosartan between both groups.

Methods

Animals
Male New Zealand White Rabbits were used (9 months old, for body weights see table 1; N = 21 in the heart failure group, N = 17 in the control group). The guidelines were followed as presented in “The guide for the care and use of laboratory animals” published by the US National Institutes of Health. The Committee on Animal Experiments of the Medical Center Amsterdam approved of the protocol.

Procedure to induce heart failure
The experiment was performed in an animal model, where heart failure was induced as described by Bril et al. [16]. Accordingly, congestive heart failure was provoked in two stages.
In the first operation, the animals were subjected to general anaesthesia with ketamine 40 mg/kg body weight and xylazine 5 mg/kg. Volume overload was induced by provoking aortic valve insufficiency, by destroying the aortic valve by moving a fluid filled catheter across the valve. Insufficiency of the aortic valve was characterized by an increase in pulse pressure by more than 50%. In the second operation, three weeks after the first one, pressure overload was induced by aortic banding. In addition to the anaesthesia described above, inhalation-anesthesia with isoflurane 0.8 % was applied. Animals were ventilated with a mixture of 50% oxygen and 50% air, 2.5 l/min, 30 strokes/min. Via an abdominal incision, a ligature was placed around the aorta, just proximal of the renal arteries. Accordingly, a reduction of 50% of the aortic diameter was achieved.
Chapter 8

Assessment of heart failure

Approximately 3 months after the final procedure, at an age of 9 months, the rabbits were anaesthetized, the left carotid artery was cannulated with a 3F-microtip pressure transducer (Miller, Houston, Texas, USA) and passed into the left ventricle to measure left ventricular end-diastolic pressure (LVEDP). A bolus of 5000 IU of heparin was injected iv. Subsequently, the rabbits were killed with Nembutal® (pentobarbital) 60 mg/kg IV. The thorax was opened, and the heart and lungs were excised and weighed. The abdomen was opened to assess ascites and to remove the intestines.

Earlier studies using the same model of CHF have demonstrated that there is no difference between the aforementioned parameters of the sham-operated rabbits or those which were not operated [16]. Therefore, in the present study, we used a control group of rabbits which were age-matched and that had not been subjected to surgery.

Mesenteric artery preparations

The mesentery and intestines were removed and placed in physiological salt solution (PSS) which was gassed with a mixture of 95% O2 and 5% CO2, at room temperature. Four segments of mesenteric artery with a length of ~2 mm each were dissected and a stainless steel wire with a diameter of 40 μm was inserted into the lumen of each vessel. The vessels were then transferred to organ baths of an isometric wire myograph. The organ bath contained PSS of the following composition (mM): NaCl 118.5, KCl 4.7, MgCl2 1.2, CaCl2 2.5, KH2PO4 1.2, NaHCO3 25, glucose 5.5, EDTA 0.024. Ascorbic acid (100 mg/l) was added to prevent oxidation of noradrenaline. Propranolol (1 μM), yohimbine (1 μM) and Nω-Nitro-L-Arginine (L-NNA) (0.1 mM) were added in order to exclude the β-adrenergic and α2-adrenergic effects of noradrenaline, and the influence of endothelium-derived NO, respectively. The preparations were attached to a micrometer screw and, after insertion of a second wire, to an isometric force transducer (Kister Morse, DSG 6, Redmond, WA, USA). The preparations were equilibrated for 15 minutes in PSS at 37 °C and the medium was gassed with a mixture of 95% O2 and 5% CO2 (pH 7.4). Subsequently, the vessels were subjected to a normalisation procedure according to Mulvany & Halpern [17]. The individual circumference was adjusted to 90% of the value that the particular vessel would have had at a transmural pressure of 100 mmHg.

Electrical field stimulation was applied using thin platinum wire electrodes positioned on either side of the vessel. Contractions were generated using an alternating current of 85/-85 mA, with a pulse width of 2 ms for 20 s per frequency step. The frequencies used were 1, 2 and 4 Hz.
Angiotensin II and sympathetic neurotransmission in experimental heart failure

respectively, applied in succession, in increasing order. Henceforth, the term EFS implies that the full range of frequency steps was applied.

In order to verify whether the stimulation-induced contractions were indeed neuronally mediated, control experiments with tetrodotoxin (1 µM) and prazosin (0.1 µM) were carried out.

Three different types of experiments were performed.

Experiment 1. Ang II + EFS and AT₁-blockade by eprosartan
After an equilibration period of 30 minutes, EFS was applied once as a priming procedure. Another 30 minutes later a second EFS was carried out as a reference procedure. After the second EFS (S2) had been completed, the vessels were left for another 30 minutes. Subsequently, a third EFS (S3) was applied in the presence of angiotensin II (0.5 nM) added to the organ bath 2 minutes before stimulation, or in the presence of the vehicle (control). Finally, a contraction with PSS containing 100 mM KCl (equimolar substitution for NaCl; KPSS) was generated to serve as a reference to quantify the contractions provoked by EFS.

In another group of preparations, several concentrations of the AT₁-receptor antagonist eprosartan were tested. Fifteen minutes after the reference EFS (S2) had been carried out, the medium was replaced by PSS containing one particular concentration of eprosartan. After an incubation period of 15 minutes a third EFS was applied in the presence of the AT₁-antagonist and angiotensin II 0.5 nM (added to the organ bath 2 minutes prior to stimulation).

Experiment 2. Ang II + Noradrenaline
The priming procedure consisted of two subsequent applications of KPSS, a single concentration of phenylephrine (3 µM) and again KPSS. Subsequently, after an equilibration period of 30 minutes, a concentration-response curve (CRC) was constructed for the effects of noradrenaline (concentration range 3 nM – 30 µM) in the presence of either angiotensin II 0.5 nM (added to the organ bath 2 minutes before the CRC was started) or the vehicle (control). Non-linear regression was carried out to calculate maximal effect (E_max) and the concentration of NA that caused half-maximal effects (EC₅₀).

Experiment 3. Concentration-response curves to Ang II.
The priming procedure was performed as described for experiment 2. Subsequently, after an equilibration period of 30 minutes, a concentration-response curve (CRC) was constructed for the effects of Ang II (concentration range 0.1 nM – 0.3 µM). Non-linear regression was carried
out to calculate maximal effect ($E_{\text{max}}$) and the concentration Ang II that caused half-maximal effects ($EC_{50}$).

**Drugs**

Angiotensin II (Bachem, Bubensdorf, Switzerland), (±)-propranolol HCl (Research Biochemical Incorporated, Natick, USA), yohimbine hydrochloride (Sigma Chemical, St. Louis, USA) and Nω-nitro-L-arginine (Sigma) were dissolved in distilled water. Eprosartan (Solvay, Hannover, Germany) was dissolved in NaOH 1 M. Using HCl 1 M, the pH of the solutions was lowered to 7.5. (-)-Noradrenaline bitartrate (Sigma, USA) was dissolved in distilled water containing L(+)ascorbic acid 100 μg/ml.

**Statistical analysis**

All data are expressed as means ± SEM. Comparison of means was performed using Student's $t$-test. Multiple means were compared with ANOVA and Dunnett's post-test. For comparison of the sympatho-inhibitory potency of eprosartan between vessels derived from heart failure and controls, linear regression calculations were performed. Linear regression lines were compared using analysis of covariance. The incidence of ascites was compared between HF-rabbits and controls with the Chi-square test.
Angiotensin II and sympathetic neurotransmission in experimental heart failure

Results

Heart weight and lung weight (both related to body weight) and LVEDP were significantly enhanced in heart failure rabbits, as well as the incidence of ascites (see table 1). A total number of 112 and 99 artery preparations were used in the HF-group and the control animals, respectively. The vessel diameter, normalised passive tension and the active force induced by potassium depolarisation were the same in heart failure and control rabbits (table 1).

Table 1. Baseline characteristics of heart failure rabbits and control animals. LVEDP-measurements were performed in all heart failure rabbits and 7 control animals.

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 17)</th>
<th>Heart Failure (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>4.3 ± 0.2</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>Relative heart weight (g/kg)</td>
<td>2.1 ± 0.3</td>
<td>5.3 ± 0.4 *</td>
</tr>
<tr>
<td>Relative lung weight (g/kg)</td>
<td>2.4 ± 0.1</td>
<td>4.4 ± 0.5 *</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>3.4 ± 0.3</td>
<td>16.8 ± 2.2 *</td>
</tr>
<tr>
<td>Ascites (ratio)</td>
<td>0/17</td>
<td>10/21 *</td>
</tr>
<tr>
<td>Diameter mesenteric artery (μm)</td>
<td>637 ± 30</td>
<td>632 ± 25</td>
</tr>
<tr>
<td>Tension (mN)</td>
<td>4.4 ± 0.3</td>
<td>4.7 ± 0.3</td>
</tr>
<tr>
<td>Contractile Force K 100 mM (mN)</td>
<td>25.8 ± 1.5</td>
<td>29.1 ± 1.2</td>
</tr>
</tbody>
</table>

Electrical field stimulation caused an increase in contractile force, which could be abolished by tetrodotoxin in both groups (1 μM) (N = 3). Prazosin (0.1 μM) abolished the responses to 1 Hz and blocked the responses to 2 and 4 Hz by 95 ± 3 and 96 ± 4 % (N = 4). Responses to EFS were similar in control rabbits and animals with HF (fig 1). In both control rabbits and rabbits with HF, the second (S2) and third (S3) stimulation resulted in virtually superimposable contractions, leading to an S3/S2 ratio of almost unity at each stimulation-frequency in both HF rabbits and controls (see table 1). From these results we concluded that S2 was suitable as a reference contraction for S3 in the presence of Ang II and the AT1-receptor antagonist eprosartan.
Figure 1. Contractile responses induced by the second (S2) and third (S3) period of electrical field stimulation in the isolated mesenteric artery, taken from rabbits with heart failure and age-matched controls, respectively. Stimulation frequencies are plotted on the abscissa, contractions (expressed as % of a standard contraction to KPSS) on the ordinate. Values are shown as means ± SEM. N = 10 in both groups.

Table 2. Ratio between the contractile responses to the third (S3) and second (S2) period of stimulation.

<table>
<thead>
<tr>
<th>Ratio S3/S2</th>
<th>Control (N = 10)</th>
<th>HF (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hz</td>
<td>1.05 ± 0.04</td>
<td>1.08 ± 0.03</td>
</tr>
<tr>
<td>2 Hz</td>
<td>1.06 ± 0.04</td>
<td>0.98 ± 0.04</td>
</tr>
<tr>
<td>4 Hz</td>
<td>1.04 ± 0.02</td>
<td>0.94 ± 0.04</td>
</tr>
</tbody>
</table>

Responses were very similar at each frequency in both groups, resulting in a Ratio S3/S2 of around 1. (N = 10 in both groups).

Ang II 0.5 nM caused a significant enhancement of responses to EFS at 1, 2 and 4 Hz. In control rabbits, S3/S2-ratios at 1 Hz, 2 Hz and 4 Hz were 3.2 ± 0.5, 2.4 ± 0.3 and 1.5 ± 0.08, respectively (p<0.05 at all frequencies compared to vehicle). In rabbits with heart failure, S3/S2-ratios at 1 Hz, 2 Hz and 4 Hz were 2.1 ± 0.2, 1.7 ± 0.1 and 1.2 ± 0.04, respectively (p<0.05 compared to vehicle at all frequencies).
Accordingly, the enhancing effect of Ang II was more pronounced in the control group compared to rabbits with HF (p<0.05 at each frequency) (fig. 2).

The enhancement could be concentration-dependently antagonized by eprosartan (1 nM – 0.1 μM) in both HF- as well as in control rabbits (see fig. 3A-B). While a low concentration of eprosartan (0.1 nM) was ineffective, the highest concentration of eprosartan (0.1 μM) abolished the enhancing effect of Ang II; Responses to EFS in the presence of Ang II + eprosartan 0.1 μM were almost the same as responses without Ang II, resulting in a S3/S2 ratio of approximately 1 at each stimulation frequency.

**Figure 2.** Contractile responses to electrical field stimulation in the presence and absence of Ang II (0.5 nM) in rabbits with heart failure and age-matched controls. Ang II or vehicle was added to the organ bath 2 minutes before the third period of EFS (S3). The ratio between forces induced by S2 and S3 (S3/S2) is shown at the ordinate and stimulation frequencies at the abscissa. Values are given as means ± SEM. * p<0.05 compared to vehicle. # p<0.05 between HF and controls at each stimulation frequency. N = 12 in both groups.
Figure 3. Inhibitory effect of eprosartan (0.1 nM-0.1 μM) on the facilitation by Ang II of stimulation-induced contractions. A: heart failure rabbits. B: age-matched controls. Ang II (0.5 nM) in the presence or absence of one concentration of eprosartan was added to the organ bath 2 minutes prior to the third electrical field stimulation (S3). The ratio between contractile forces induced by S2 and S3 (S3/S2) is shown at the ordinate and stimulation frequencies at the abscissa. Values are given as means ± SEM. * p<0.05 compared to responses in presence of Ang II (0.5 nM) + vehicle at 1, 2 and 4 Hz. # p<0.05 compared to responses in presence of Ang II (0.5 nM) + vehicle at 1 and 2 Hz. (N = 7-12 per group).
We compared the sympatho-inhibitory potency of eprosartan between HF and the control group at a stimulation frequency of 2 Hz (see fig. 4). We calculated the percentage of inhibition by each concentration of eprosartan in both groups. 0% inhibition is defined as a S3/S2 ratio of 2.3 and 1.7 in the control group and HF group, respectively; these were the ratios obtained in the presence of Ang II (0.5 nM) at a stimulation frequency of 2 Hz. 100% inhibition is defined as a S3/S2 value of 1. Linear regression calculations adequately described the relationship between inhibition (in terms of percentage) and the concentrations of the AT₁-antagonist. R²-values of the regression lines were 0.99 (p<0.05) both groups. LR-lines did not differ significantly (p>0.05, analysis of covariance).

![Graph showing inhibitory effects of eprosartan in heart failure rabbits and age-matched controls on facilitation by Ang II (0.5 nM) of stimulation-induced contractions, observed at a stimulation frequency of 2 Hz. The % inhibition is shown on the ordinate. The concentrations of eprosartan, expressed as log M, shown on the abscissa. Values are given as means ± SEM. Linear regression lines are shown. No statistically significant difference exists between regression lines (p > 0.05, analysis of covariance). (N = 7-12 per group).](image-url)
Concentration response curves to noradrenaline were very similar in rabbits with heart failure and control rabbits (fig. 5 and table 3). Ang II (0.5 nM), the concentration that caused facilitation in stimulation experiments, did not affect the CRC to NA, neither in control rabbits, nor in heart failure rabbits (see table 3). EC\(_{50}\)-values and E\(_{\text{max}}\)-values did not significantly differ between controls and HF-rabbits, and were unaffected by the presence or absence of Ang II (p>0.05).

**Figure 5.** Contractile response to noradrenaline in the isolated mesenteric artery of rabbits with heart failure and age-matched controls. Values are shown as means ± SEM. N = 8 in both groups. No differences were observed between EC\(_{50}\) and E\(_{\text{max}}\) values between groups.

**Table 3.** Effects of Ang II (0.5 nM) on the sensitivity (EC\(_{50}\)-values, expressed as -log M), and maximal response (E\(_{\text{max}}\)-values, % of contraction to K 100 mM) to noradrenaline in the isolated mesenteric artery of rabbits with heart failure and age-matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Control rabbits (N = 8)</th>
<th>HF-rabbits (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC(_{50})</td>
<td>E(_{\text{max}})</td>
</tr>
<tr>
<td>control</td>
<td>6.1 ± 0.04</td>
<td>113.2 ± 3.2</td>
</tr>
<tr>
<td>+ Ang II (0.5 nM)</td>
<td>6.0 ± 0.05</td>
<td>111.5 ± 2.8</td>
</tr>
</tbody>
</table>

Values are shown as means ± SEM. N = 8 per group. No differences were observed between EC\(_{50}\) and E\(_{\text{max}}\) values in the presence or absence of Ang II.
Ang II caused a concentration-dependent increase in contractile force in both rabbits with heart failure and control animals (Fig. 4). EC$_{50}$ values were 8.2 ± 0.04 and 8.2 ± 0.06 -log M in HF-rabbits and controls, respectively (p>0.05); E$_{\text{max}}$ values were 71.6 ± 6.8 and 68.7 ± 6.9 in HF-rabbits and controls respectively (p>0.05).

**Figure 6.** Contractile response to Ang II in the isolated mesenteric artery of rabbits with heart failure and age-matched controls. Values are shown as means ± SEM. N = 8 per group. No differences were observed between EC$_{50}$ and E$_{\text{max}}$ values between the two groups.
Discussion

The rabbits subjected to volume- and pressure overload in the present study developed a significant degree of heart failure, as reflected by the increased heart weight, the increased lung weight, and the increased incidence of ascites (table 1). In a previous study using this HF-model was studied, a HW/BW ratio (mg/kg) of > 4.6 and a LW/BW ratio of > 3.5 was taken to indicate heart failure [18]. For that study, an increased myocyte length and width was reported, indicating left ventricular hypertrophy. In the present study, the LVEDP was significantly increased, which is a general indicator of left heart failure. In this model, however, this increase was probably partly caused by the experimentally induced aortic insufficiency.

Receptor-independent contractile force, as provoked by KCl (100 mM) depolarization was similar in both groups. Hence, the contractile capacity of the vessels as such was unchanged. The stimulation-induced contractions could be abolished by both prazosine and TTX, indicating that the contractions are mainly caused by stimulation-induced release of noradrenaline from the sympathetic nerve terminals. Stimulation-induced contractions were not different in vessels from HF-rabbits compared to controls. This is in accordance with a previous study, where stimulation-induced contractions did not differ between subcutaneous arteries derived from HF-patients and healthy controls [19]. In both clinical and experimental HF, alterations in both α- (and β) adrenergic responses have been described [20], which are believed to be caused by the increased plasma catecholamine-levels. In the present study, like in other studies in which α-adrenergic responses were studied in heart failure [19,21,22] responses to exogenous NA were the same in both groups. Taken together, these findings indicate that EFS caused a similar NA-release (per pulse) in both groups. In the present investigation, propranolol was added to the medium, thus excluding β-receptor mediated effects.

A concentration of Ang II that caused no vasoconstriction (0.5 nM), enhanced stimulation-induced contractions in both groups. This concentration did not alter the CRC for NA, excluding an interaction at the level of vascular smooth muscle cells, as described by some authors [23,24]. The facilitation by Ang II could be inhibited by the selective AT1-receptor antagonist eprosartan (1 nM – 0.1 μM) in vessels derived from HF-rabbits and controls, respectively. Thus, in the present study, the facilitating effect was mediated by prejunctionally located AT1-receptors in HF-
Angiotensin II and sympathetic neurotransmission in experimental heart failure

rabbits as well as in control animals. These findings are in accordance with previous findings by us and others in isolated arteries from healthy rats and rabbits [14,25]. The enhancing effect of Ang II (0.5 nM) was weaker in the HF-rabbits, compared to the controls. This may have been caused by down-regulation or an uncoupling/desensitization of pre-junctionally located AT₁-receptors. Data on alterations in the number of AT₁-receptor are mainly derived from myocardial tissue: in general, the number of AT₁-receptors is decreased in heart failure [26,27]. This may be caused by the increased levels of Ang II, that have been reported to decrease the number of AT₁-receptors [28]. Whether these alterations in the number of AT-receptors also apply to the vasculature is uncertain. Functional studies on Ang II-induced vasoconstriction in HF have yielded many conflicting results [19,29-32]. In a pithed rabbit model, in which HF was induced with doxorubicine, an unchanged facilitating prejunctional effect as well as an unchanged vasoconstrictor tone caused by Ang II were reported [33].

In the present study, concentrations of eprosartan, required to inhibit Ang II - induced facilitation were the same in preparations from HF- and control animals (fig. 4). Accordingly, the decreased effect of Ang II on noradrenergic neurotransmission via pre-junctional AT₁-receptors in heart failure did not alter the sympato-inhibitory potency of eprosartan.

The CRC for the vasoconstrictor effect of Ang II was not different between preparations from HF-rabbit and controls, as reported by others [19,29,31]. Thus, regarding the postsynaptic receptor, no changes in receptor affinity or density are apparent. In the present study, the alterations regarding the pre-junctional receptor do not occur with respect to the AT₁-receptor on vascular smooth muscle. Receptor reserve has been described regarding the AT₁-receptor on vascular smooth muscle [34]. For the prejunctional receptor, receptor reserve has not been studied. It may therefore be possible that down-regulation, caused by increased levels of Ang II, occurred for both the pre- and postjunctional receptors, whereas this phenomenon only influences the effects mediated by the prejunctional receptors.

In rabbits with pacing induced-heart failure, sympathetic nerve terminals at the level of the myocardium display abnormalities, such as reduced myocardial NA uptake and reduced tyrosine hydroxylase profiles [35]. Although in the present study stimulation-induced contractions under control circumstances were not different between HF-rabbits and controls, such changes in function of the sympathetic nerve terminal, as well as changes in the signaling pathway, cannot be excluded to play a role in the decreased facilitation by Ang II in HF-rabbits.
Chapter 8

Some of the changes in vascular responses to various stimuli in heart failure have been attributed to a decreased endothelial function [36]. In the present study, we ruled out the influence of endothelium derived NO, by adding L-NNa (0.1 μM) to the medium.

From the present findings we conclude that HF as well as in control rabbits, Ang II facilitates the stimulation-induced vasoconstrictor response by prejunctionally mediated AT\textsubscript{1}-receptor. The facilitating effect was decreased in HF, while responses to exogenous Ang II were unchanged. These findings may be explained by a down-regulation or uncoupling of the prejunctional AT\textsubscript{1}-receptor. The sympatho-inhibitory potency of eprosartan proved unchanged in vessels obtained from rabbits with CHF compared to controls.
References


Angiotensin II and sympathetic neurotransmission in experimental heart failure


