Selective ET\textsubscript{A} receptor blockade prevents left ventricular remodeling and deterioration of cardiac function in experimental heart failure

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Abstract

Background: Left ventricular (LV) dilation, which is a predictor of survival in humans with chronic heart failure (CHF), is limited by a mixed endothelin ET\textsubscript{A}–ET\textsubscript{B} antagonist. Whether selective ET\textsubscript{A} receptor blockade influences LV dilation is unknown. We determined, in a rat model of CHF, the effects of the ET\textsubscript{A} receptor blocker LU 135 252 on LV remodeling. Methods and Results: Rats were subjected to coronary artery ligation and treated for ten weeks with placebo or LU 135 252 (LU), at a dose of 10 or 30 mg kg\textsuperscript{-1} day\textsuperscript{-1}. Systolic blood pressure and heart rate (plethysmography) were determined in conscious animals before and after four and ten weeks of treatment. At these time points, cardiac output and LV dimensions were measured in anesthetized rats by transthoracic echocardiography. LV hemodynamics were determined in anesthetized rats after ten weeks. Pressor responses to ET-1 (1 nmol/kg, i.v.) and sarafotoxin S6c (0.3 ng/kg, i.v.) were measured, to assess the efficacy of ET receptor antagonism and the lack of blockade of ET receptor blockade, respectively. The pressor response to ET-1 was significantly reduced by LU (% change in systolic blood pressure: sham: 9±1; CHF: 5±1; CHF LU: 0±3 and −2±4% for the low and high dose, respectively). LU did not affect the response to sarafotoxin (CHF: −37±3; CHF LU: −29±3 and −28±2% for the low and high dose, respectively). Both doses of LU decreased systolic blood pressure, but only the high dose of LU reduced heart rate. Furthermore, LU restored cardiac output dose-dependently throughout the study. Both doses of LU limited LV dilation and deterioration of LV fractional shortening to the same extent. After ten weeks, LU normalized LV end-diastolic and central venous pressures, but did not affect LV dP/dt\textsubscript{max} or dP/dt\textsubscript{min}. LU did not prevent the development of cardiac hypertrophy, but reduced LV collagen density. Conclusions: In this rat model, the selective ET\textsubscript{A} receptor blocker LU, at the dose of 30 mg kg\textsuperscript{-1} day\textsuperscript{-1}, reduced blood pressure and heart rate, limited progressive left ventricular remodeling and improved cardiac hemodynamics and function. These effects of LU might have important clinical relevance in the treatment of heart failure. © 1998 Elsevier Science BV. All rights reserved.

Keywords: Heart failure; ET blockade; Cardiac remodeling; Rat; Echocardiography

1. Introduction

Congestive heart failure (CHF) is characterized, in humans and in experimental animal models [1–3], by progressive left ventricular (LV) dilation, which plays a key role in the deterioration of the pathophysiological status. Moreover, LV dilatation is inversely correlated with survival in humans [4], and prevention/limitation of LV remodeling is beneficial in CHF. Indeed, long-term therapy with angiotensin converting enzyme (ACE) inhibitor provokes, besides an improvement of systemic and cardiac hemodynamics, a limitation of cardiac remodeling in humans with CHF [5–7] and animal models [8,9] and these effects are associated with a reduced mortality rate. Increased endothelin (ET) plasma concentrations [10–
unknown. anesthetized with pentobarbital (50 mg kg⁻¹, i.p.). The progressive deterioration of LV remodeling in CHF is At the end of the study, the surviving rats were weighed every week and their food intake was measured in order to allow adjustment of the drug concentration of doses higher than 30 mg kg⁻¹ was associated with significant decreases in blood pressure, and that administration of doses higher than 30 mg/kg was associated with a decreased response to the ETb agonist sarafotoxin S6C, suggesting blockade of ETb receptors (K Münter, personal communication).

Treatment with LU was started seven days after ligation, in agreement with previous studies [8,9,16], in order to avoid interference with the healing process and/or the early distention of the infarct zone.

All treatments, provided by Knoll AG (Ludwigshafen, Germany), were given as food additive for ten weeks. Rats were randomly assigned to three groups (n=20 each), i.e. untreated, or treated with LU at a dose of either 10 mg kg⁻¹ day⁻¹ or 30 mg kg⁻¹ day⁻¹. These doses were chosen on the basis of preliminary short term experiments which showed that they were associated with significant decreases in blood pressure, and that administration of doses higher than 30 mg/kg was associated with a decreased response to the ETb agonist sarafotoxin S6C, suggesting blockade of ETb receptors (K Münter, personal communication).

Thus, the goal of our study was to determine, in a rat model of CHF, the effects of chronic treatment with the selective ETa blocker LU 135 252 on LV hemodynamics and remodeling.

2. Methods

The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.1. Animals and treatment

Myocardial infarction was produced in ten-week-old male Wistar rats by left coronary artery ligation [8,16,24]. For this purpose, animals were anesthetized with sodium methohexital (50 mg kg⁻¹, i.p.). The trachea was intubated and the animals were mechanically ventilated with air from the room. After a left thoracotomy, the proximal left coronary artery was occluded by a suture in order to induce myocardial infarction. Sham-operated rats were subjected to the same protocol, except that the snare was not tied. Fifteen min after occlusion, the chest was closed and the animals were allowed to recover from anesthesia. The 24-h mortality rate was about 20% for the infarction group. Fifteen sham-operated rats were used as controls.

Rats were randomly assigned to three groups (n=20 each), i.e. untreated, or treated with LU at a dose of either 10 mg kg⁻¹ day⁻¹ or 30 mg kg⁻¹ day⁻¹. These doses were chosen on the basis of preliminary short term experiments which showed that they were associated with significant decreases in blood pressure, and that administration of doses higher than 30 mg/kg was associated with a decreased response to the ETb agonist sarafotoxin S6C, suggesting blockade of ETb receptors (K Münter, personal communication).

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cannulated with a micromanometer-tipped catheter (SPR 407, Millar Instruments, USA) and advanced into the aorta and thoracic vena cava, respectively, for the recording of arterial and central venous pressures. The aortic catheter was then advanced into the left ventricle (LV) for the recording of LV pressure and its maximal rate of rise \( (dP/dt_{\text{max}}) \) and decrease \( (dP/dt_{\text{min}}) \). All tracings were recorded on a physiologic recorder (Windowgraph, Gould).

2.3. Echocardiographic studies

Transthoracic Doppler echocardiographic studies were performed in rats just before the start of the treatment (i.e., seven days after the surgical procedure) and after four and ten weeks of treatment. For this purpose, rats were anesthetized with methohexital (50 mg kg\(^{-1}\), i.p.), the chest was shaved and echocardiograms were performed with an echocardiographic system equipped with a 7-MHz transducer (Acuson 128 XP/10C), as described previously [16,25]. Briefly, a two-dimensional short axis view of the left ventricle was obtained at the level of the papillary muscle, in order to record M-mode tracings. Anterior and posterior end-diastolic and end-systolic wall thickness and LV diameters were measured using the American Society of Echocardiology leading-edge method from at least three consecutive cardiac cycles [26]. Measurements were performed by a single observer (P.M.) who was blinded to prior results and treatment groups.

Examples of M-mode recordings, obtained at the end of the ten week protocol, in sham and untreated myocardial infarcted rats are shown in Fig. 1. The diameter of the LV cavity and the thickness of the anterior and posterior walls were determined at the level of the papillary muscle [25]. LV posterior wall thickening was calculated as (posterior end-diastolic wall thickness—posterior end-systolic wall thickness)/posterior end-diastolic wall thickness, and was expressed as a percentage. Fractional shortening was calculated as \( \text{LV end-diastolic cavity diameter—LV end-systolic cavity diameter}/\text{LV end-diastolic cavity diameter} \), and was expressed as a percentage. In addition, LV outflow velocity was measured by pulsed-wave Doppler, and cardiac output was calculated as \( \text{CO}=\text{aortic VTI} \times \frac{\text{LV outflow diameter}^2}{2} \times \text{heart rate} \), where VTI is the velocity–time integral.

2.4. Efficacy of ET receptor antagonism and selectivity of \( \text{ET}_A \) receptor blockade

In order to assess the efficacy of ET receptor antagonism

![Sham vs. Myocardial Infarction](Image)

**Fig. 1.** Examples of M-mode recordings in a sham-operated rat and an untreated rat with myocardial infarction, at the end of the ten week protocol. In these typical examples, there is symmetric thickening of the anterior and posterior walls in the sham-operated rat. In contrast, the anterior wall is thinned and akinetic, while the posterior wall is hypokinetic, in the untreated myocardial infarcted rat. Moreover, the left ventricle cavity is significantly dilated.
and the selectivity of ET<sub>a</sub> receptor blockade, variations in systolic blood pressure, induced by an intravenous bolus injection of ET1 (1 nmol kg<sup>-1</sup>) and sarafotoxin S6c (0.3 ng kg<sup>-1</sup>), were determined.

2.5. Cardiac morphometry

Morphometric analyses were performed as described previously [27,28]. The atria, left and right ventricles were weighed separately, and the left ventricle was immersed in Bouin's fixative solution. After fixation, the heart was cut perpendicular to the apex to base axis into three sections of approximately identical thickness. Sections were dehydrated and embedded in paraffin. From these sections, 3 μm thick histologic slices were obtained and were stained with Sirius Red.

For the measurement of infarct size, slices were placed under a video microscope (Microwatcher VS-30H, Mitsubishi Kasei Cooperation) with a 20-fold enlargement lens. The endocardial and epicardial circumferences of the infarcted tissue and of the left ventricle were determined using image analysis software (CYBERVIEW, Cervus International). Infarct size was calculated as (endocardial + epicardial circumference of the infarcted tissue)/(endocardial + epicardial circumference of the left ventricle) and the result was expressed as a percentage.

For the determination of cardiac collagen density, images (500-fold enlargement) were obtained in the noninfarcted subepicardial region of the left ventricle on Sirius Red-stained slides. The volume of the collagen fraction was calculated as the sum of the surface of all connective tissue areas divided by the total surface of the image. Perivascular collagen was excluded from this measurement. It has been shown that the total volume fraction, as determined by this morphometric approach, is closely related to the hydroxyproline concentration of the ventricle [29,30].

2.6. Statistical analysis

All results are given as the mean±SEM. Intergroup differences were evaluated by ANOVA and were followed by a Tukey test for multiple comparisons, using BMDP software, if ANOVA revealed significant differences. Differences were considered to be significant at the level of p<0.05.

3. Results

3.1. Infarct size and mortality

Infarct sizes in the surviving animals that were sacrificed after ten weeks were identical in the groups treated with LU at both low and high doses (30±3 and 33±2%, respectively) and were comparable to those of the untreated CHF control group (33±2%). During the treatment period, four untreated CHF rats, four CHF rats treated with LU at 10 mg kg<sup>-1</sup> day<sup>-1</sup> and three CHF rats treated with LU at 30 mg kg<sup>-1</sup> day<sup>-1</sup> died.

3.2. Systemic hemodynamic measurements in conscious rats

One week after coronary artery ligation, systolic blood pressure in untreated CHF rats was significantly lower than that of sham-operated rats, whereas heart rate was significantly augmented (Fig. 2). At this time (i.e. immediately before the onset of treatment), both systolic blood pressure and heart rate in the low and high dose LU treated groups were not different from those of the untreated CHF rats. Compared to untreated CHF rats, both the low and high dose of the ET<sub>a</sub> antagonist LU induced a decrease in systolic blood pressure after four weeks (W<sub>4</sub>: −13 and −18 mmHg, both p<0.05 vs. time-matched untreated CHF). While this effect remained significant throughout the study for the high dose of LU (−12 mmHg at W<sub>10</sub>, p<0.05 vs. time-matched untreated CHF rats), it did not reach statistical significance for the low dose (−6 mmHg at W<sub>10</sub>). Simultaneously, only LU at the dose of 30 mg kg<sup>-1</sup> day<sup>-1</sup>, reduced heart rate throughout the study (−26 and −14 beats min<sup>-1</sup> at W<sub>4</sub> and W<sub>10</sub>, p<0.05 vs. time-matched untreated CHF rats).

3.3. Echographic measurements in anesthetized rats

One week after surgery, LV end-diastolic and end-systolic diameters were significantly increased in infarcted animals (Fig. 3). While both left ventricular end-diastolic and end-systolic diameters remained stable throughout the study in sham animals, they significantly increased over
time in untreated infarcted animals. Immediately before the onset of treatment, left ventricular diameters were similar and not different from those of the untreated CHF rats. Both the low and high doses of LU limited, but did not completely prevent, the subsequent increase in LV end-diastolic and end-systolic diameters.

One week after surgery, LV fractional shortening was significantly diminished in infarcted animals compared to sham-operated rats and continued to decrease afterwards, reaching a plateau after four weeks (Fig. 4). LU at the doses of 10 and 30 mg kg⁻¹ day⁻¹ prevented the decrease in LV fractional shortening. Furthermore, seven days after surgery, ligation induced a depression of LV posterior wall thickening and this slightly worsened over time. LU prevented this worsening, however, compared to time-matched CHF control rats, this effect reached statistical significance only for the high dose.

One week after surgery, cardiac output was significantly diminished in infarcted animals compared to sham-operated rats and remained lower throughout the study (Fig. 5). Immediately before the start of treatments, cardiac output in the low and high dose LU groups were not different from that of the untreated CHF rats. Throughout the treatment period, cardiac output was increased by both the low and high doses of LU, however, this effect was more marked with the high dose. Finally, one week after surgery, stroke volume was significantly decreased in infarcted animals compared to sham-operated rats. Compared to untreated CHF animals, LU improved stroke volume, and even normalized it in the group treated with the high dose.

3.4. Cardiac hemodynamic measurements in anesthetized rats

After ten weeks and as compared to sham-operated animals, CHF decreased LV systolic pressure, LV dP/dt_max and LV dP/dt_min, and caused a significant increase in LV end-diastolic pressure (LVEDP) and central venous pressure (Table 1). Compared to untreated CHF rats, both the low and the high dose of LU reduced LV systolic pressure, and normalized both LVEDP and central venous pressure, without affecting LV dP/dt_max or LV dP/dt_min.

3.5. Efficacy of ET receptor antagonism and selectivity of ET₄ receptor blockade

The ET₄ agonist sarafotoxin S6c induced a transient decrease in systolic blood pressure in all groups (sham: 31±4; CHF control: 37±3; CHF LU: 29±2 and 28±2% for doses of 10 and 30 mg kg⁻¹ day⁻¹, respectively). The variations among the different groups did not reach statistical significance.
Table 1
Cardiac hemodynamics after ten weeks of treatment

<table>
<thead>
<tr>
<th>Chronic heart failure</th>
<th>Sham</th>
<th>Control</th>
<th>LU 10 mg/kg/day</th>
<th>LU 30 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP (mmHg)</td>
<td>161±5</td>
<td>145±7(^a)</td>
<td>147±4(^b)</td>
<td>122±6(^#)</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>3.2±0.4</td>
<td>15.1±2.7(^a)</td>
<td>8.1±3(^b)</td>
<td>6.2±1.2(^#)</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>1.9±0.4</td>
<td>7.7±1.4(^b)</td>
<td>3.0±0.6(^b)</td>
<td>3.4±0.6(^#)</td>
</tr>
<tr>
<td>LV dP/dt(_{max}) (10(^2) mmHg s(^{-1}))</td>
<td>10.0±0.7</td>
<td>7.3±0.4(^a)</td>
<td>7.2±0.4(^b)</td>
<td>6.4±0.3(^#)</td>
</tr>
<tr>
<td>LV dP/dt(_{min}) (10(^2) mmHg s(^{-1}))</td>
<td>10.5±0.8</td>
<td>5.1±0.4(^a)</td>
<td>4.9±0.5(^b)</td>
<td>4.2±0.3(^#)</td>
</tr>
</tbody>
</table>

LVSP, left ventricular systolic pressure (mmHg); LVEDP, left ventricular end diastolic pressure (mmHg); CVP, central venous pressure (mmHg). *p<0.05 vs. sham; \(^a\) p<0.05 vs. CHF control; \(^\#\) p<0.05 vs. CHF LU at 10 mg kg\(^{-1}\) day\(^{-1}\).

The non-selective ET agonist ET-1 induced an increase in systolic blood pressure in the sham and CHF control group (9±1 and 5±1\%, respectively, NS). Compared to the CHF control value, LU, at doses of 10 and 30 mg kg\(^{-1}\) day\(^{-1}\), reduced the increase in systolic blood pressure induced by ET-1 (0±2 and −4±2\%, respectively), but this effect reached statistical significance (p<0.05) only for the dose of 30 mg kg\(^{-1}\) day\(^{-1}\).

3.6. Cardiac morphology

Heart weight, LV and right ventricular (RV) weights as well as LV collagen density were significantly increased in untreated CHF rats. LU never affected heart weight, LV and RV weights, but it significantly reduced LV collagen density (Table 2).

4. Discussion

In this study, the effects of the ET\(_A\) receptor antagonist LU 135 252 on systemic and cardiac hemodynamics in a rat model of CHF, as well as its impact on the progression of post-infarction left ventricular remodeling, using serial echocographic measurements, were investigated.

Coronary artery ligation in the rat has provided extensive information about the progression from LV dysfunction to the pathophysiological state of overt heart failure. Seven days after coronary artery ligation, in addition to the ‘classical’ hemodynamic signs of CHF, i.e. a decrease in systolic blood pressure and an increase in heart rate, LV end-diastolic- and end-systolic diameters were significantly increased [3,16,25], and the LV continued to dilate throughout the study. However, it should be stressed that 75\% of this dilation after the healing phase occurred during the first four weeks, after which, the progression of LV dilatation slowed down.

LV dilation was accompanied by a progressive depression of LV fractional shortening and LV posterior wall function, indicating an impaired LV systolic function. As already reported [16,25], LV fractional shortening and LV posterior wall thickening worsened further over time, suggesting a further deterioration of LV function.

Cardiac output and stroke volume were significantly reduced throughout the study in untreated CHF rats. Thus, LV dilation was unable to maintain stroke volume, leading, despite the increase in heart rate, to a reduced cardiac output.

LU dose-dependently reduced arterial blood pressure and heart rate. Similar systemic hemodynamic results have been reported with mixed ET\(_A\)±ET\(_B\) receptor blockers in humans [31] as well as in experimental animal models [16,17]. This is in agreement with the results of Sakai et al. [22] who used the peptide ET\(_A\) antagonist, BQ-123, in the rat model, but does not concord with those obtained in a model of pacing-induced heart failure with the selective ET\(_A\) antagonist PD 156707 [21], which reduced heart rate without any modification of arterial blood pressure. However, this could be due to differences on the model of CHF used in the two studies (i.e. coronary artery ligation in the present study vs. pacing in the previous study), or to differences in the pharmacological profiles of these two antagonists or to the doses administered.

Our experimental design does not allow us to determine whether the reduction of heart rate is the consequence of blockade of the positive chronotrophic properties of ET [32].
or it is related to a reduced sympathetic tone, secondary to the improved hemodynamic conditions. However, whatever the mechanism, the reduction in heart rate might have important consequences. Indeed, due to the non-linearity of the heart rate–diastolic part of the cardiac cycle, a small decrease in heart rate results in a dramatic increase in the diastolic coronary perfusion time [33–35] and improves LV filling [36]. This, together with reduced oxygen requirements induced by the decrease in heart rate [37,38], will improve the oxygen supply–demand ratio, and this might be beneficial, in terms of ‘cardiac reserve’.

The decrease in blood pressure might also contribute, through decreased oxygen demand, to the beneficial effect of the ET antagonist in CHF. However, a sustained dramatic decrease in blood pressure might be deleterious in CHF, through the impaired regional tissue perfusion it induces. However, this is rather unlikely in the present experiments, since the hypotensive effect of the ET antagonist remains limited. Is should also be stressed that this hypotensive effect is less marked than that induced in the same model by ACE inhibitors, which are clearly beneficial in this setting.

As described for the selective ET<sub>a</sub> receptor antagonist PD 156707 [21] or the ET<sub>a</sub>–ET<sub>b</sub> antagonist bosentan [16,17], LU reduced cardiac preload, as illustrated by the reduction of LV end-diastolic pressure as well as central venous pressure, which was determined in anesthetized animals at the end of the treatment period, without causing changes in LV contractility. Although acute administration of the ET<sub>a</sub> antagonist BOQ-123 has been shown to decrease LV contractility in rats with CHF [39], possibly through a prevention of the positive inotropic properties of ET [40], our results suggest that either endogenous ET in vivo does not exert positive inotropic effect and/or that the improvement in the neuro-humoral and hemodynamic status by ET antagonists overrules the possible direct negative inotropic effects due to ET receptor blockade.

In this hemodynamic context, LU limited the increase in left ventricular cavity enlargement. Indeed, as described with the ET<sub>a</sub> antagonist PD 156707, left ventricular end-diastolic, and systolic diameters, obtained at the level of the papillary muscle, were smaller than those observed in time-matched heart failure animals. It must be noted that, in our previous study, the mixed ET<sub>a</sub>–ET<sub>b</sub> antagonist bosentan did not significantly affect LV diameters, although there was a tendency towards a decrease, despite the fact that this drug was markedly effective on LV dilatation when assessed as passive pressure/volume relationship. Although this might represent a true difference between specific and mixed antagonists, this difference must be interpreted with caution. In particular, we do not believe that it is safe to assume that differences obtained between the effects of LU and those of bosentan do represent a definitive proof for differences between ET<sub>a</sub> and mixed ET<sub>a</sub>–ET<sub>b</sub> antagonists. Indeed, LU and bosentan might differ markedly in terms of pharmacokinetics, and the doses used might also not be comparable in terms of the level of blockade of the receptors. Moreover, the two drugs have been evaluated in two different studies, with two different observation periods (ten vs. eight weeks). A definitive proof for different effects of these two types of antagonists would probably require more rigorous comparisons with full dose–response curves, or comparison of the chronic effects of an ET<sub>a</sub> antagonist with those of simultaneous administration of the ET<sub>a</sub> antagonist together with a selective ET<sub>b</sub> antagonist. To the best of our knowledge, this kind of experiment has not been performed.

Fractional shortening and posterior wall thickening were significantly improved by LU. This, together with the hemodynamic effects, as well as the decrease in heart rate and LV dilatation, may induce an improvement of LV filling and an increase in cardiac output without decreasing cardiac contractility. This is confirmed in our study, in which LU increased cardiac output as well as stroke volume and prevented the deterioration of global LV function, without affecting LV dP/dt.

LU did not affect cardiac hypertrophy. This finding is not limited to selective ET<sub>a</sub> receptor blockade, since bosentan similarly does not prevent cardiac hypertrophy [16]. The lack of ET blockade on cardiac hypertrophy could be surprising, since ET has been shown to induce myocyte hypertrophy in vitro [41] and to be implicated in angiotensin II-induced myocyte hypertrophy [42]. Moreover, LU induced major changes in cardiac preload and decreased blood pressure, which have been shown to be implicated in cardiac hypertrophy. Thus, the lack of effect of ET antagonists on cardiac hypertrophy suggests that blockade of ET receptors at the level of the cardiac tissue, at the doses used, is incomplete and/or that other mechanisms are involved in the development of cardiac hypertrophy, such as local neuro-humoral activation, overruling the effects of ET receptor blockade.

Concerning the selectivity the ET<sub>a</sub> blockade, LU 135 252, at dose of 10 and 30 mg kg<sup>−1</sup> day<sup>−1</sup>, significantly reduced the pressor response to ET-1, without affecting the response to sarafotoxin S6c. Thus, our results suggest that, after ten weeks of treatment, blockade of ET receptors by LU 135 252 is probably limited to ET<sub>a</sub> receptors.

Recently, the existence of ET<sub>b</sub> receptors on vascular smooth cells and their vasoconstrictor properties upon stimulation have been demonstrated [43]. However, their physiological role remains controversial. Under normal conditions, the release of vasodilator substances by stimulation of endothelial ET<sub>b</sub> receptors may offset the vasoconstrictor properties of vascular ET<sub>b</sub> receptors. However, in CHF, which is accompanied by a reduced endothelial NO pathway [27], the local vasoconstrictor response to sarafotoxin S6c is enhanced at the level of the brachial artery [43]. The fact that, in our study, ET<sub>b</sub> receptor activation only induced transient vasodilatation without sustained vasoconstriction does not exclude a local,
heterogeneous vasoconstriction, since we did not determine the effect of sarafotoxin S6c at the level of different vascular territories.

In the present study, we found that LU increased the ejection fraction, in contrast with our previous study with bosentan, which did not affect the ejection fraction [16]. However, as mentioned before, this must be interpreted with caution and does not represent a definitive proof that specific ET$_A$ antagonists differ from mixed ET$_A$–ET$_B$ antagonists in terms of cardiac function in heart failure.

In the present study, we have not assessed the effect of treatment with LU 135 252 in the presence of a conventional treatment for heart failure and, especially, in the presence of ACE inhibitors. Clearly, given the numbers of known interactions between the renin angiotensin and the endothelin systems, it would be important to assess whether the effects of ET antagonists do persist or are potentiated in the presence of chronic treatment with ACE inhibitors or AT$_1$ receptor antagonists. Clearly, this hypothesis requires further investigation.

In conclusion, LU 135 252, at doses of 10 and 30 mg kg$^{-1}$ day$^{-1}$, administered chronically for ten weeks in rats with chronic heart failure, dose-dependently decreased arterial blood pressure and heart rate and improved cardiac hemodynamics. Simultaneously, LU 135 252 limited the progression of left ventricular remodeling and the deterioration of left ventricular function. This pharmacological profile gives new perspectives in the treatment of heart failure.

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References


