

Additional effects of endothelin receptor blockade and angiotensin converting enzyme inhibition in rats with chronic heart failure

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of tezosentan are similar to those of enalapril. Furthermore, the benefits of tezosentan are apparent in addition to ACE inhibition. Thus, tezosentan could be a useful therapeutic agent in the acute treatment of heart failure.

ABSTRACT

AIM: To evaluate the acute effects of tezosentan, a new dual parenteral endothelin receptor antagonist, on hemodynamics in a rat model of chronic heart failure (CHF), and further investigated if the combination of tezosentan with the angiotensin converting enzyme (ACE) inhibitor, enalapril, had additive hemodynamic effect. **METHODS:** Hemodynamics was measured in rats with CHF, induced by ligation of the left coronary artery. **RESULTS:** At 3 to 5 weeks after myocardial infarction, rats developed CHF. This was evidenced by a marked increase in left ventricular end-diastolic pressure (LVEDP) with mean values of 23 to 26 mmHg, by a 30% to 40% reduction in left ventricular dp/dt_{max} and by a more than 10% decrease in mean arterial pressure (MAP) as compared to sham-operated rats. In CHF rats, acute intravenous administration of either tezosentan ($10 \text{ mg} \cdot \text{kg}^{-1}$) or enalapril ($1 \text{ mg} \cdot \text{kg}^{-1}$) markedly decreased MAP and LVEDP, without affecting heart rate or dp/dt_{max} . Tezosentan had additive effects on MAP and LVEDP when given with enalapril compared with tezosentan ($P < 0.05$) or enalapril ($P < 0.05$) alone. There were no significant changes in heart rate and dp/dt_{max} with the combination treatment compared with tezosentan- or enalapril-treated CHF rats. **CONCLUSION:** Acute intravenous tezosentan improves cardiac hemodynamics and decreases LVEDP and afterload (MAP) without changes in heart rate and cardiac contractility (dp/dt_{max}) in CHF rats. These favorable effects

INTRODUCTION

Chronic heart failure (CHF) is a multiple-etiology, high-prevalence, poor-prognosis cardiovascular disorder. Activation of the renin-angiotensin system (RAS) contributes importantly to the pathophysiology of this disease complex⁽¹⁻³⁾. Inhibition of angiotensin II (A II) formation with angiotensin-converting enzyme (ACE) inhibitors has been shown to have favorable effects on hemodynamics, exercise tolerance, symptoms, and mortality in both animal models and in patients with CHF⁽²⁻⁶⁾. However, despite the efficacy of ACE inhibitors, mortality and morbidity of patients treated with ACE inhibitors is still high^(3,5).

There are both indirect and direct evidence that endothelin (ET) plays a major role in the pathophysiology of CHF^(6,7). Significant elevations of plasma big ET-1 and ET-1 levels are observed in animal models and patients with CHF, and these variables are strongly related to survival in CHF patients⁽⁶⁻¹³⁾. Indeed, it has been demonstrated that the dual ET receptor antagonist bosentan has a beneficial effect on hemodynamics in animal models and in patients with CHF^(8-10,14-17). Also, long-term treatment with ET receptor antagonists greatly improves the survival of rats with CHF^(14,15).

Tezosentan is a new potent dual ET receptor antagonist designed for parenteral use⁽¹⁸⁾. It is currently in advanced development for the treatment of acute heart failure. It is not clear, however, whether tezosentan has favorable effects on cardiac hemodynamics in experimental heart failure. Furthermore, it is unknown whether the benefits of tezosentan therapy can be additive to those of an ACE inhibitor.

Therefore, the goals of this study were to investigate

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the acute effects of tezosentan on systemic and cardiac hemodynamics in a rat model of CHF and to compare these effects with those of an ACE inhibitor. Furthermore, we investigated whether combined tezosentan with the ACE inhibitor enalapril had additive hemodynamic effect in this experimental model of CHF.

MATERIALS AND METHODS

Induction of myocardial infarction (MI)

Studies were performed on male normotensive Wistar rats weighing 200–290 g (supplied by the Experimental Animal Center of Chinese Academy of Sciences, Shanghai, China, Grade II, Certificate No 9904). All rats were housed in climate-controlled conditions with a 12-h light/dark cycle and free access to normal rat chow and drinking water.

Myocardial infarction was produced by a method previously described^[14]. In brief, rats were anesthetized with a mixture of ketamine/rompun ($50 \text{ mg} \cdot \text{kg}^{-1}/5 \text{ mg} \cdot \text{kg}^{-1}$, ip). The trachea was intubated with a small metal cannula (20 G) and mechanically ventilated with room air by use of a small rodent ventilator (Model 7025 Rodent Ventilator, Hugo Sachs Elektronik, Germany) at a rate of 60 cycles per minute and a total volume of 1 mL/100 g body weight. A left thoracotomy was performed, and the heart was exposed. The left coronary artery was ligated approximately 2 mm from its origin with a 6–0 silk suture, between the pulmonary artery outflow tract and left atrium. The sham-operated rats were subjected to the same procedure except that the coronary artery was not ligated. After these maneuvers were performed, the chest was closed in three layers (ribs, muscles, and skin). The air within the thorax was removed, allowing the rats to resume spontaneous respiration. The rats were allowed to recover from anesthesia, and after which they were returned to their cages. The 24-h postoperative mortality rate was about 15 % for the infarction group.

Measurements of hemodynamic parameters

Short-term hemodynamic experiments were conducted in the sham-operated rats and in MI rats at 3 to 5 weeks after surgery. At this time, the MI rats developed established heart failure (see below). For the hemodynamic study, rats were anesthetized with inactin ($100 \text{ mg} \cdot \text{kg}^{-1}$, ip). Body temperature was maintained at $36 \sim 38 \text{ }^\circ\text{C}$ during the experiment, and spontaneous respiration was facilitated by tracheal intubation. The right carotid artery was cannulated with a high-fidelity microtip 2F catheter (SPR-

249, Millar Instruments, USA) that was advanced through aorta into the left ventricle (LV) to record LV pressure, heart rate (HR) and the maximal rate of rise of LV pressure (dp/dt_{\max}). Before implantation, the high-fidelity catheter was calibrated against a mercury manometer. A tygon catheter was placed in the right jugular vein for injection of drugs or vehicle. A polyethylene cannula was placed in the left femoral artery and connected to a pressure transducer (MLT1050 precision BP transducer) for continuous recording of arterial pressure. All tracings were recorded on a computer with a PowerLab system. The data acquisition system consisted of a PowerLab (ML780 PowerLab/8s and ML118 QUAD amplifiers, AD Instruments Ltd, Australia) which was connected to a HP Pavilion 8565C computer with the Chart software (version 3.4, AD Instruments).

Experimental protocols Once the above surgical procedure for hemodynamic measures was completed, an additional 15-min stabilization period ensued before the start of the experiment. Following stabilization, a 10-min baseline measurement was made for mean arterial pressure (MAP), LV systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), HR, and dp/dt_{\max} . The MI rats with LVEDP ≥ 15 mmHg were considered to have CHF and were included in this study. Six MI rats were excluded as results of this selection criterion.

After measurements of baseline hemodynamic parameters, the acute effects of tezosentan, the ACE inhibitor enalapril or the combination of tezosentan and enalapril on these parameters were examined in the MI-induced CHF rats. Specifically, the CHF rats were randomly divided into four groups. Group 1 rats (Veh-CHF, $n=9$) received vehicle (saline $1 \text{ mL} \cdot \text{kg}^{-1}$, iv); Group 2 (Tezo-CHF, $n=10$) received tezosentan ($10 \text{ mg} \cdot \text{kg}^{-1}$, iv); Group 3 (Ena-CHF, $n=9$) received enalapril ($1 \text{ mg} \cdot \text{kg}^{-1}$, iv); Group 4 (EnaTezo-CHF, $n=10$) were administered a combination of the same doses of enalapril and tezosentan. After vehicle or drug administration, the above hemodynamic parameters were recorded for a duration of 1 h.

The acute hemodynamic responses to tezosentan were also assessed in the age-matched normal and sham-operated rats. Since we found that the hemodynamic parameters in both normal and sham-operated rats were similar, we pooled them together (sham rats). Two groups of sham rats were used. One group of sham rats (Veh-sham, $n=11$) received vehicle (saline $1 \text{ mL} \cdot \text{kg}^{-1}$, iv). The other (Tezo-sham, $n=9$) received tezosentan

(10 mg·kg⁻¹, iv).

Cardiac histomorphometry At the completion of the hemodynamic measurements, the rats were killed, and the heart was removed and weighed. The right and left ventricle were dissected and weighed. The left ventricle including the interventricular septum was fixed in 10 % buffered formalin and cut from apex to base in 4 transverse slices, which were processed in a routine manner for histologic study. Sections were stained and projected. The entire length of the endocardial circumference and the segment of the endocardial circumference made by the infarcted segment of each of the four slices of the left ventricle were measured. The entire length of the epicardial circumference and the segment of the epicardial circumference made by the infarcted segment of each of the four slices of the left ventricle were measured. These were then averaged for each of the four slices. The fraction of the ventricle that was infarcted was calculated as the average of the four slices expressed as a percent of the length of circumference.

Statistical analysis All data were presented as $\bar{x} \pm s_x$. Statistical analyses were performed by analysis of variance (ANOVA) using Statistica (StatSoft) and the

Student-Newman-Keuls procedure for multiple comparisons. The null hypothesis was rejected when $P < 0.05$.

RESULTS

Characteristics of MI-induced CHF rats

The baseline values before drug administration for sham and CHF rats from all protocols were shown in Tab 1 and 2. Coronary artery ligation resulted in moderate to severe MI with infarct size of 39 % to 42 % (Tab 1). At 3 to 5 weeks after MI, rats developed CHF, which was characterized by a marked increase in LVEDP with mean values of 23 to 26 mmHg and by a significant decrease ($P < 0.01$) in the maximal rate of rise of dp/dt_{max} (Tab 2). In these CHF rats, MAP was significantly lower as compared to sham rats ($P < 0.05$, Tab 2). The heart weight to body weight ratio and right ventricular weight to body weight ratio were larger in CHF rats than in sham rats (Tab 1).

Acute effects of tezosentan in the anesthetized sham rat Acute intravenous administration of tezosentan (10 mg·kg⁻¹) caused a small but significant decrease in MAP ($P < 0.01$, Fig 1). It had no effect

Tab 1. Baseline body and organ weights and infarct size among experimental groups. $\bar{x} \pm s_x$. ^b $P < 0.05$, ^c $P < 0.01$ vs sham groups.

	BW/g	HW/BW/ mg·g ⁻¹	RVW/BW/ mg·g ⁻¹	LVW/BW/ mg·g ⁻¹	Infarct size/%
Veh-sham (n = 11)	249 ± 8	3.29 ± 0.06	0.580 ± 0.012	2.23 ± 0.05	0
Tezo-sham (n = 9)	249 ± 10	3.22 ± 0.08	0.568 ± 0.013	2.22 ± 0.06	0
Veh-CHF (n = 9)	258 ± 8	3.81 ± 0.15 ^b	0.76 ± 0.07	2.33 ± 0.03	42.3 ± 1.7
Tezo-CHF (n = 10)	261 ± 10	4.02 ± 0.25 ^b	0.84 ± 0.09 ^b	2.30 ± 0.10	40.3 ± 1.6
Ena-CHF (n = 9)	259 ± 9	3.97 ± 0.22 ^b	0.84 ± 0.08 ^b	2.26 ± 0.07	42 ± 3
EnaTezo-CHF (n = 10)	253 ± 6	4.40 ± 0.14 ^c	0.89 ± 0.06 ^b	2.35 ± 0.05	39.0 ± 1.2

BW, body weight; HW/BW, heart weight/body weight; RVW/BW, right ventricular weight/body weight; LVW/BW, Left ventricular weight/body weight.

Tab 2. Baseline hemodynamic parameters among experimental groups. $\bar{x} \pm s_x$. ^b $P < 0.05$, ^c $P < 0.01$ vs sham groups.

	LVSP/mmHg	MAP/mmHg	HR/bpm	$dp/dt_{max}/$ mmHg·s ⁻¹	LVEDP/mmHg
Veh-sham (n = 11)	158 ± 4	116 ± 4	358 ± 15	8949 ± 238	3.7 ± 0.6
Tezo-sham (n = 9)	164 ± 5	118 ± 4	366 ± 13	8895 ± 412	2.7 ± 0.6
Veh-CHF (n = 9)	130 ± 6 ^c	100 ± 3 ^b	321 ± 11	5753 ± 414 ^c	23.1 ± 2.3 ^c
Tezo-CHF (n = 10)	124 ± 6 ^c	102 ± 6 ^b	341 ± 12	5153 ± 334 ^c	24.9 ± 1.9 ^c
Ena-CHF (n = 9)	130 ± 4 ^c	100.0 ± 1.8 ^b	357 ± 7	6155 ± 380 ^c	25 ± 3 ^c
EnaTezo-CHF (n = 10)	126 ± 4 ^c	98 ± 3 ^b	366 ± 11	5466 ± 253 ^c	26.3 ± 1.4 ^c

LVSP, Left ventricular systolic pressure; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; dp/dt_{max} , maximal rate of rise of left ventricular pressure.

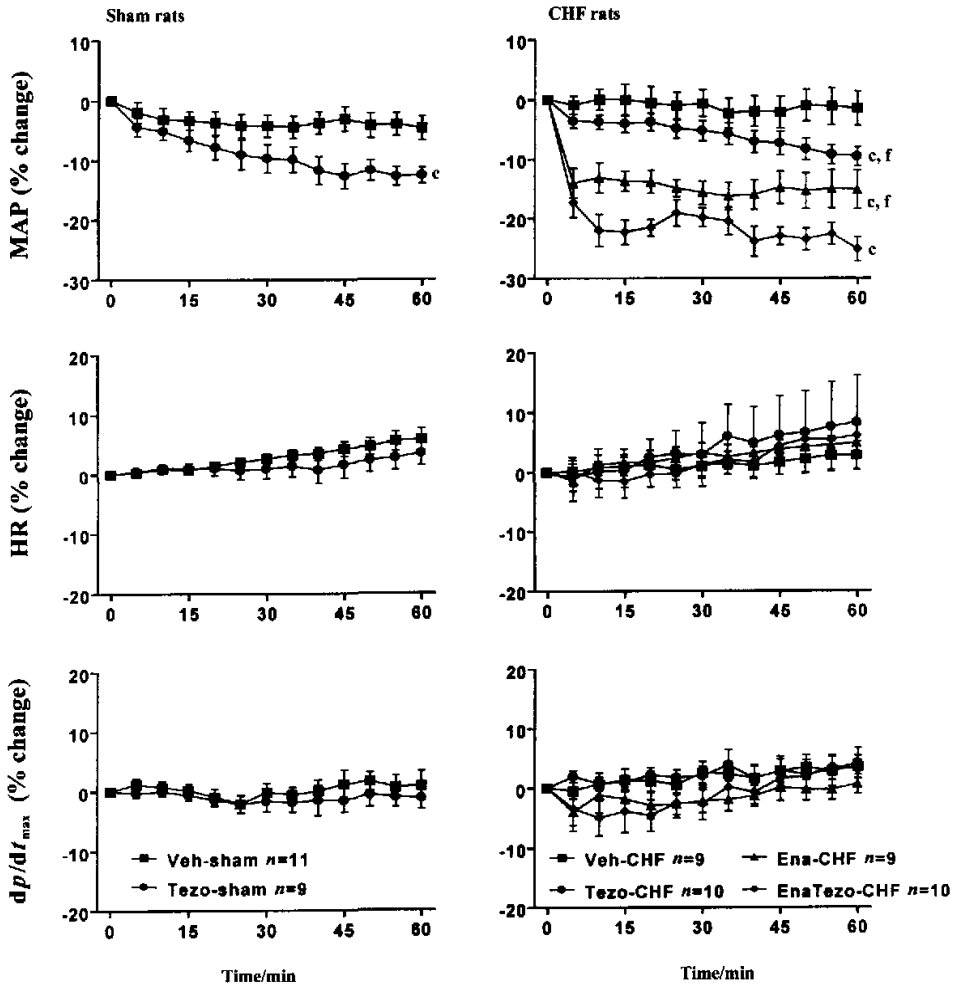


Fig 1. Percent changes in mean arterial pressure (MAP), heart rate (HR) and maximal rate of rise of left ventricular pressure (dp/dt_{max}) in sham and chronic heart failure (CHF) rats. The sham rats received vehicle (Veh-sham) or tezosentan (Tezo-sham). The CHF rats were given an intravenous administration of vehicle (Veh-CHF) or tezosentan (Tezo-CHF) or enalapril (Ena-CHF) or a combination of tezosentan and enalapril (EnaTezo-CHF). $\bar{x} \pm s_x$. * $P < 0.01$ vs vehicle. † $P < 0.01$ vs combination.

on heart rate, dp/dt_{max} , or LVEDP in the anesthetized, sham-operated rats (Fig 1 and 2). Administration of vehicle alone had no effect on any of these hemodynamic parameters (MAP, HR, dp/dt_{max} , and LVEDP) in the sham rats (Fig 1 and 2).

Acute effects of tezosentan, enalapril, or combined tezosentan and enalapril in CHF rats

There were no significant differences at baseline in the hemodynamic parameters in the four groups of CHF rats who were received vehicle, tezosentan, enalapril, or

combined tezosentan and enalapril (Tab 2). There were also no significant differences in infarct size, body weight, heart weight to body weight ratio, and ventricular weights to body weight ratios among the CHF groups (Tab 1).

As seen in Fig 1 and 2, administration of vehicle alone in CHF rats resulted in no significant changes on any of the hemodynamic parameters (MAP, HR, dp/dt_{max} , and LVEDP). Acute intravenous administration of either the ET receptor antagonist tezosentan or the

ACE inhibitor enalapril markedly decreased LVEDP ($P < 0.01$, Fig 2), and significantly reduced MAP ($P < 0.01$) without effect on HR or dp/dt_{max} (Fig 1). The effect of tezosentan on LVEDP was nearly identical to that of enalapril (Fig 2), although its effect on afterload (MAP) was smaller than that of enalapril (Fig 1).

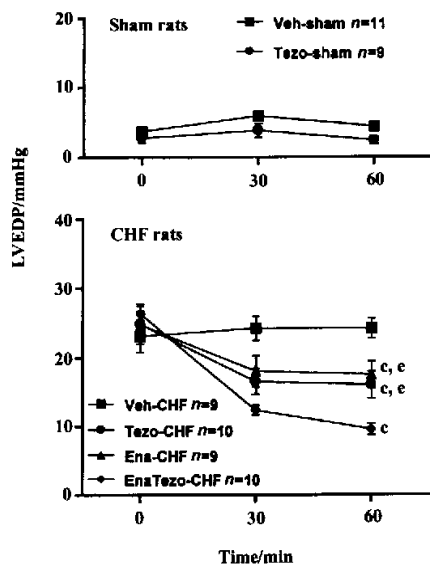


Fig 2. Left ventricular end-diastolic pressure (LVEDP) in sham and CHF rats. LVEDP was measured at baseline, 30-min and 60-min after intravenous administration of vehicle (Veh-sham and Veh-CHF), or tezosentan (Tezo-sham and Tezo-CHF), or enalapril (Ena-CHF), or combination of tezosentan and enalapril (EnaTezo-CHF). $\bar{x} \pm s_x$. $^{\circ}P < 0.01$ vs vehicle. $^{\square}P < 0.05$ vs combination.

The combination of tezosentan and enalapril had an additive effect on MAP when compared with tezosentan or enalapril ($P < 0.01$) alone in the CHF rats (Fig 1). Tezosentan also had an additive effect on LVEDP when given with enalapril as compared with tezosentan ($P = 0.01$) or enalapril ($P < 0.05$) alone in the CHF rats (Fig 2). There were no significant changes in HR and dp/dt_{max} with the combination treatment compared with the tezosentan- or enalapril-treated CHF rats (Fig 1).

DISCUSSION

This study demonstrated that acute intravenous administration of tezosentan, a dual ETA and ETB receptor antagonist, improved cardiac hemodynamics in rats with

CHF. The hemodynamic response to tezosentan was characterized by a marked decrease in LV end-diastolic pressure and a marked afterload reduction as assessed by mean arterial pressure (MAP), without significant changes of heart rate and cardiac contractility (dp/dt_{max}). Despite a smaller effect on afterload (MAP), the beneficial effects of this new ET receptor antagonist tezosentan on LV end-diastolic pressure, an index of cardiac preload, were similar to those of ACE inhibitor enalapril. Furthermore, tezosentan had additive beneficial effects on LV end-diastolic pressure and MAP to the ACE inhibitor in this CHF model.

The rat model of coronary artery ligation is a well-characterized model of CHF that shares many of the features of congestive heart failure in humans. In this study, in which hemodynamic measurements were made at 3 to 5 weeks after left coronary artery ligation, depressed cardiac performance was documented by a marked increase of LV end-diastolic pressure and by marked decreases in MAP and cardiac contractility (dp/dt_{max}). This indicated that CHF occurred in this animal model. This hemodynamic abnormality was associated with increases in heart weight to body weight ratio and right ventricular weight to body weight ratio.

The reported increase in plasma level of ET-1 in animal models and patients with CHF and its strong correlation to mortality in CHF patients^[6-13] have led to speculation that this potent vasoconstrictor plays an important role in the increased peripheral vascular resistance, a hallmark of this disease state. Tezosentan is a new potent dual ET receptor antagonist with a short half-life and high water solubility^[18]. Therefore, we first examined the acute hemodynamic effects of tezosentan in the sham and CHF rats. In the anesthetized, sham-operated rats, tezosentan caused a small but significant decrease in MAP, without affecting heart rate, LV end-diastolic pressure and cardiac contractility. These results are in agreement with earlier report^[19] that ET is involved in the regulation of blood pressure in the anesthetized normal animal, in which some activation of the ET system during anesthesia is inevitable. However, we previously found that ET receptor antagonists had no effects on blood pressure in the conscious chronically catheterized rat^[20], a preparation in which endogenous levels of ET were low. In the CHF rats, acute intravenous administration of tezosentan markedly decreased LV end-diastolic pressure and afterload (MAP), without significant changes of heart rate and cardiac contractility. Previous studies have

demonstrated that ET receptor blockade had a beneficial effect on hemodynamics in animal models and in patients with CHF^[8-10,14-17]. Taken together, these results suggest that activation of endogenous ET system plays a direct and contributory role in the progression of heart failure.

ACE inhibitors have become standard therapy for CHF. In the present study, ACE inhibition with enalapril decreased LV end-diastolic pressure and afterload (MAP), without affecting heart rate and left ventricular maximum dp/dt . These results were in good agreement with previously published reports on the favorable effects of ACE inhibitors in experimental model of CHF^[2,4] and also with the results of large human clinical trials^[21]. In this study, we also compared the acute hemodynamic effects of tezosentan to treatment with an ACE inhibitor enalapril in the CHF rats. The beneficial effects of tezosentan on LV end-diastolic pressure, an index of cardiac preload, were similar to those of enalapril, despite a smaller effect on MAP. These data suggest that the beneficial effect of tezosentan on preload may partly related to a direct cardiac effect, independent of the decrease in MAP.

An important finding of this study was that the effects on LV end-diastolic pressure and afterload (MAP) were significantly greater in CHF rats ($P < 0.01$) treated with combined tezosentan and enalapril compared to those given enalapril alone or tezosentan alone. There were no significant differences in heart rate and cardiac contractility (dp/dt_{max}) with the combination treatment compared with the tezosentan-or enalapril-treated CHF rats. Although Teerlink *et al.*^[10] showed that combined ET receptor blockade and ACE inhibition caused a synergistic reduction in MAP in CHF rats, this was the first study, to the best of our knowledge, to demonstrate that ET receptor blockade had additive beneficial effects on cardiac hemodynamics to ACE inhibition in CHF rats. These data suggest that ET receptor blockade and ACE inhibition can improve cardiac hemodynamics by independent and complementary pathways.

At present, it is not clear whether blockade of both ET_A and ET_B receptors or selective blockade of ET_A receptors is better in CHF, and this issue can not be answered from this study. In theory, specific blockade of ET_A receptors would have the advantage of maintaining ET_B-mediated, endothelium-dependent vasodilation. However, this endothelium-dependent relaxation is minimal, especially in pathological conditions of endothelial

dysfunction. Moreover, ET_B receptors are also present on smooth muscle cells and induce vasoconstriction^[22]. Also, the vasoconstriction induced by an ET_B agonist sarafotoxin S6c is increased in CHF patients, suggesting that vascular smooth muscle (constricting) ET_B receptors are upregulated in human heart failure^[23]. Similar results are also obtained at the level of the coronary circulation in dogs with CHF^[24]. Furthermore, an increased cardiac output seen in bosentan-treated, but not in BQ-123-treated dogs with myocardial infarction suggests that blockade of ET_B receptors alone or blockade of both ET_A and ET_B receptors will be necessary to improve cardiac function^[25]. Therefore, further studies will be necessary to clarify the difference between selective blockade of ET_A receptors and combined blockade of ET_A and ET_B receptors on hemodynamics in experimental heart failure.

In conclusion, the results of the present study indicate that intravenous tezosentan, a new potent ET receptor antagonist, improves systemic and cardiac hemodynamics, and has additive beneficial effects to ACE inhibitor in rats with CHF after myocardial infarction. These observations suggest that tezosentan may be a useful therapeutic agent in the treatment of heart failure.

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阻断内皮素受体和抑制血管紧张素转化酶在慢性心衰大鼠中的相加作用

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关键词 内皮素类; 内皮素受体; tezosentan; 血管紧张素转换酶抑制剂; 心肌梗死; 充血性心力衰竭; 血流动力学; 依那普利

目的: 评价一种新的内皮素受体拮抗剂 tezosentan 对慢性心衰大鼠血流动力学的急性作用, 并进一步研究该药与血管紧张素转化酶(ACE)抑制剂依那普利合用是否有相加作用。 **方法:** 在结扎左侧冠状动脉所致的慢性心衰大鼠中测量血流动力学的指标。 **结果:** 心肌梗死 3-5 周后, 大鼠产生慢性心衰。与假手术大鼠相比, 慢性心衰大鼠左心室舒张末期压(LVEDP)显著升高, 其均值为 23-26 mmHg, 心肌收缩力(左心室 dp/dt_{max})降低 30%-40%, 平均动脉压(MAP)降低大于 10%。在慢性心衰大鼠中, 静脉注射 tezosentan ($10 \text{ mg} \cdot \text{kg}^{-1}$) 或依那普利 ($1 \text{ mg} \cdot \text{kg}^{-1}$) 显著降低其 MAP 和 LVEDP, 并对其心率或 dp/dt_{max} 无影响。与 tezosentan 或依那普利单用组相

比,两者合用对慢性心衰大鼠的 MAP 和 LVEDP 具有相加作用,对其心率或 dp/dt_{max} 无显著性作用.
结论:急性静脉注射 tezosentan 改善慢性心衰大鼠心脏血流动力学,降低其 LVEDP 和后负荷(MAP),其心率和心肌收缩性 (dp/dt_{max}) 并不受影响. Tezosentan 的这些有利作用与依那普利相似. 而且

在抑制 ACE 作用的基础上, Tezosentan 的这些有益作用也是很明显的. 因此, tezosentan 有望成为急性治疗心衰的有效新药.

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