Selectend Endothelin-A Versus Combined Endothelin-A/Endothelin-B Receptor Blockade in Rat Chronic Heart Failure

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Background—The relative efficacy of endothelin-A (ET_A) receptor blockade versus combined ET_A-ET_B receptor blockade in chronic heart failure (CHF) is still largely unknown.

Methods and Results—We compared, in a rat model of CHF (coronary ligation), the hemodynamic and structural effects of 1 month of treatment with the ET_A antagonist ABT-627 (5 mg · kg⁻¹ · d⁻¹), the ET_B antagonist A-192621 (30 mg · kg⁻¹ · d⁻¹) or a combination of the 2 drugs. Doses were chosen for their capacity to block the pressor response to ET-1 (for ET_A blockade) or the depressor responses to sarafotoxin S6c or ET-1 (for ET_B blockade). ET_A and combined ET_A-ET_B blockade reduced systolic blood pressure to the same extent, whereas ET_B blockade had no effect. In contrast, only combined ET_A-ET_B blockade significantly reduced heart rate. Both ET_A and combined ET_A-ET_B blockade, but not ET_B blockade alone, increased left ventricular (LV) fractional shortening and wall thickening and reduced LV end-diastolic pressure, as well as LV end-diastolic and end-systolic volumes. However, all treatments (including ET_B blockade) decreased LV collagen accumulation.

Conclusions—The chronic blockade of both ET_A and ET_B receptors improved systemic hemodynamics, as well as LV function and remodeling, to the same extent as ET_A receptor blockade alone. However, only combined ET_A-ET_B receptor blockade decreased heart rate. Whether this differential effect on heart rate affects the long-term outcome after treatment with ET_A or mixed ET_A-ET_B antagonists in CHF remains to be determined. (Circulation. 2000;102:491-493.)

Key Words: endothelin ▪ heart failure ▪ heart rate ▪ remodeling

Mixed endothelin A–endothelin B receptor (ET_A-ET_B) antagonists exert beneficial effects in experimental chronic heart failure (CHF), but selective ET_A antagonists have been shown to be either beneficial or deleterious. However, to date, no study has compared the efficacy of these 2 pharmacological approaches to CHF. Thus, whether simultaneous blockade of ET_A receptors will reinforce or reduce the efficacy of ET_A antagonists in CHF is still unknown. Moreover, the effects of chronic ET_B blockade per se are also unknown. In theory, the blockade of ET_B receptors may have deleterious effects by reducing the ET_B-mediated endothelin-dependent vasodilatation or by decreasing clearance and, thus, increasing plasma levels of ET. We compared the effect of a selective ET_A antagonist, a selective ET_B antagonist, or a combination of the 2 antagonists in rat model of CHF.

Methods
CHF was induced by myocardial infarction, as described previously. Eight days after surgery, the animals were randomized to 1 of the following 5 groups (n=12 per group): sham, CHF untreated, CHF plus ABT-627 (ET_A antagonist; 5 mg · kg⁻¹ · d⁻¹), CHF plus A-192621 (ET_B antagonist; 30 mg · kg⁻¹ · d⁻¹), and CHF plus a combination of ABT-627 and A-192621. All treatments were administered as a food additive for 4 weeks. The dose of ABT-627 was chosen because it blocked the ETA-mediated sustained vasoconstriction to ET-1 without affecting ET_B-mediated transient vasodilatation, whereas that of A192621 was the smallest dose that completely blocked ET-1–induced transient vasodilatation without affecting sustained vasoconstriction. To verify long-term ET receptor blockade, the effects of intravenous bolus injections of ET-1 (1 nmol/kg) and sarafotoxin S6c (0.3 ng/kg) were assessed after 4 weeks of treatment in randomly selected animals from each group.

Systolic blood pressure and heart rate were determined in conscious rats (plethysmography) just before the start of treatment (7 days after ligation) and after 4 weeks of treatment. Transthoracic Doppler echocardiographic studies were performed in anesthetized rats; arterial pressure and left ventricular (LV) systolic and end-diastolic pressures and dP/dt max were measured as described previously. Before euthanization, a blood sample was taken through the carotid artery to determine plasma ET-1 levels (by ELISA).

All values are given as means±SEM. Differences were compared by t test or by ANOVA followed by a Tukey test for multiple comparisons. They were considered significant at P<0.05.
ET-1 antagonist decreased the response to sarafotoxin S6c and the transient depressor effect of ET-1, but it did not affect the sustained pressor response to ET-1. Combined ETα-ETβ treatment reduced the sustained pressor response to ET-1 to the same extent as ETα blockade alone and decreased the response to sarafotoxin S6c and the transient depressor effect of ET-1 to the same extent as ETβ blockade alone (Table 1).

**Systemic Hemodynamics**

After 4 weeks of treatment in CHF rats, ETα blockade and combined ETα-ETβ blockade decreased systolic blood pressure significantly and to the same extent, whereas the ETβ antagonist had no effect (Figure 1). Both the ETα and the ETβ antagonist tended to reduce heart rate. However, a more marked, significant decrease in heart rate was observed after the coadministration of ETα and ETβ antagonists (Figure 1).

**Cardiac Functional Parameters and Remodeling**

Compared with untreated CHF rats, ETα blockade and combined ETα-ETβ blockade (but not ETβ blockade) reduced LV systolic pressure and LV end-diastolic pressure to the same extent, without affecting LV dp/dtmax (Figure 1).

Echocardiographic studies (Figure 2) show that ETα blockade increased LV fractional shortening and LV posterior wall thickening, whereas the ETβ antagonist did not affect these parameters. Coadministration of the selective ETα and the selective ETβ antagonist increased both LV fractional shortening and LV posterior wall thickening to the same extent as treatment with the ETα antagonist alone.

The ETα antagonist limited the progressive increase of LV end-diastolic diameter, but the ETβ antagonist did not affect this parameter. Coadministration of the ETα and the ETβ antagonist decreased LV end-diastolic diameter to the same extent as treatment with the ETα antagonist alone (Figure 2).

**Plasma ET-1 Levels**

Compared with sham animals, plasma levels of ET-1 were increased in CHF animals (7±1 and 13±3 fmol/mL, respectively; P<0.05). ETα, ETβ, or combined ETα-ETβ blockade did not affect the levels of ET-1 (13±3, 15±2, and 18±5 fmol/mL, respectively).

**Cardiac Morphology**

Infarct size was not significantly different between the groups (Table 2). Neither treatment affected heart weight or the heart weight to body weight ratio. In contrast, all treatments (ETA, ETB, or combined ETA-ETB blockade) decreased LV collagen density significantly and to the same extent (Table 2).

**Discussion**

The main results of our study, which was performed using a rat model of CHF, are as follows. (1) Chronic, simultaneous blockade of both ETα and ETβ receptors improved systemic and cardiac hemodynamics, as well as LV function and remodeling, to the same extent as ETα receptor blockade alone. However, these effects were associated with a significant reduction of heart rate only with simultaneous ETα-ETβ receptor blockade. (2) Chronic, selective ETβ receptor blockade per se did not affect systemic and cardiac hemodynamics, nor the LV dilation of CHF animals, but it did reduce LV collagen density.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Systolic blood pressure (SBP), heart rate (HR), LV end-diastolic pressure (LVEDP), and LV dp/dtmax, as determined in anesthetized rats with CHF after 4 weeks of no treatment (white bars) or treatment with ABT-627 (up-hatched bars), A192621 (solid bars), or a combination of the 2 drugs (down-hatched bars). *P<0.05 vs untreated CHF.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** LV end-diastolic diameter (LVEDD), LV fractional shortening (FS), and LV posterior wall thickening (PWTh), as determined in anesthetized rats with CHF after 4 weeks of no treatment (white bars) or treatment with ABT-627 (up-hatched bars), A192621 (solid bars), or a combination of the 2 drugs (down-hatched bars). *P<0.05 vs untreated CHF.
Effect of ET_b Receptor Blockade
After 1 month of treatment, the ET_b antagonist did not alter blood pressure, suggesting the absence of ET_b-mediated vaso- motor tone under these conditions. In contrast, short-term admin- istration of ET_a receptor blockers has been shown to induce vasoconstriction in humans and animals. It is possible that ET_b-mediated endothelium vasodilatation might be reduced in CHF secondary to endothelial dysfunction or that the vasodilatory effects of ET_b receptor stimulation differ in acute and chronic situations. Alternatively, CHF might be associated with a downregulation of endothelial ET_b receptors. Although we observed no changes in the systemic response to sarafotoxin S6c, this does not exclude a heterogeneous adaptation of the ET system at the level of different organs.

Despite the lack of hemodynamic effects and functional improvement, chronic ET_b receptor blockade reduced cardiac collagen accumulation. Thus, in contrast to selective ET_a or mixed ET_a-ET_b administration, which provoke a major reduction of cardiac load, other mechanisms, independent of cardiac hemodynamic changes, are involved in ET_b blockade. Indeed, ET activates cardiac fibroblasts though ET_b recep- tors. Moreover, by reducing the ET_b-mediated release of aldosterone, which is implicated in collagen accumulation in CHF, ET_b receptor blockade might indirectly reduce collagen accumulation.

Selective ET_a Versus Combined ET_a-ET_b Receptor Blockade
We observed that the effects of chronic, selective ET_a blockade on systemic and cardiac hemodynamics, as well as on LV dilatation and cardiac collagen accumulation, were quantitatively similar to those induced by combined ET_a-ET_b blockade. These results demonstrate that simultaneous block- ade of ET_b receptors does not adversely affect the outcome of treatment with an ET_a antagonist in experimental CHF.

In the present study, the effects of ET_a or combined ET_a-ET_b blockade were quantitatively similar to those of an angiotensin-converting enzyme (ACE) inhibitor. However, this does not exclude possible synergistic effects of ACE inhibitors and ET antagonists in CHF. Whether ET antagonists can induce beneficial effects after ACE inhibition is still largely unknown and requires further investigation.

Importantly, whereas heart rate was only slightly and nonsignificantly reduced by treatment with the ET_a or the ET_b antagonist, a more marked, significant decrease in heart rate was observed after simultaneous ET_a-ET_b blockade. The more marked reduction in heart rate might have important consequences. Indeed, because of the nonlinearity of the relationship between heart rate and the diastolic part of the cardiac cycle, a small decrease in heart rate results in a dramatic increase in diastolic coronary perfusion time and improves LV filling. This, together with the reduced oxygen requirements, will improve the oxygen supply-demand ratio. However, whether these differences in terms of heart rate reduction affect the long-term outcome of the treatments for CHF cannot be answered from the present study.

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References
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