Brief Rapid Communication

Selective 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_α) receptor blockade versus combined ET_α-ET_β 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_α antagonist ABT-627 (5 mg · kg^{-1} · d^{-1}), the ET_β 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_α blockade) or the depressor responses to sarafotoxin S6c or ET-1 (for ET_β blockade). ET_α and combined ET_α-ET_β blockade reduced systolic blood pressure to the same extent, whereas ET_β blockade had no effect. In contrast, only combined ET_α-ET_β blockade significantly reduced heart rate. Both ET_α and combined ET_α-ET_β blockade, but not ET_β 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_β blockade) decreased LV collagen accumulation.

Conclusions—The chronic blockade of both ET_α and ET_β receptors improved systemic hemodynamics, as well as LV function and remodeling, to the same extent as ET_α receptor blockade alone. However, only combined ET_α-ET_β receptor blockade decreased heart rate. Whether this differential effect on heart rate affects the long-term outcome after treatment with ET_α or mixed ET_α-ET_β 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_α-ET_β) antagonists exert beneficial effects in experimental chronic heart failure (CHF), but selective ET_α antagonists have been shown to be either beneficial\(^2\)–\(^4\) or deleterious.\(^5\)–\(^6\) However, to date, no study has compared the efficacy of these 2 pharmacological approaches to CHF. Thus, whether simultaneous blockade of ET_α receptors will reinforce or reduce the efficacy of ET_α antagonists in CHF is still unknown. Moreover, the effects of chronic ET_β blockade per se are also unknown. In theory, the blockade of ET_β receptors may have deleterious effects by reducing the ET_β-mediated endothelin-dependent vasodilatation or by increasing clearance and, thus, increasing plasma levels of ET. We compared the effect of a selective ET_α antagonist, a selective ET_β antagonist, or a combination of the 2 antagonists in rat model of CHF.

Methods

CHF was induced by myocardial infarction, as described previously.\(^1\) 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_α antagonist; 5 mg · kg^{-1} · d^{-1}), CHF plus A-192621 (ET_β 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 ETβ-mediated transient vasodilatation,\(^7\) whereas that of A192621 was the smallest dose that completely blocked ET-1–induced transient vasodilatation without affecting sustained vasoconstriction.\(^8\) 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.\(^1\) 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.
Creased the sustained pressor response to ET-1. The ET B antagonist tended to reduce heart rate. However, a more marked, significant decrease in heart rate was observed after the coadministration of the selective ET A and the ET B antagonists (Figure 1). Compared with untreated CHF rats, ET A and combined ET A-ET B blockade (but not ET B blockade) reduced LV collagen density significantly and to the same extent as ETA receptor blockade alone. However, these effects were associated with a significant reduction of heart rate only with simultaneous ET A-ET B receptor blockade. (2) Chronic, selective ET B 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 significantly and to the same extent (Table 2).

Cardiac functional parameters and remodeling

Compared with untreated CHF rats, ET A blockade and combined ETA-ET B blockade decreased systolic blood pressure significantly and to the same extent, whereas the ET B antagonist treatment had no effect (Figure 1). Both the ETA and the ET B antagonist tended to reduce heart rate. However, a more marked, significant decrease in heart rate was observed after the coadministration of ETA and ET B antagonists (Figure 1).

Systemic hemodynamics

After 4 weeks of treatment, the ET A antagonist did not modify the decrease in blood pressure to sarafotoxin S6c or the transient depressor response to ET-1, but it markedly decreased the sustained pressor response to ET-1. The ET B 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 ET A-ET B treatment reduced the sustained pressor response to ET-1 to the same extent as ETA blockade alone and decreased the response to sarafotoxin S6c and the transient depressor effect of ET-1 to the same extent as ET B blockade alone (Table 1).

Results

ET_A-ET_B Receptor Blockade

After 4 weeks of treatment, the ET A antagonist did not modify the decrease in blood pressure to sarafotoxin S6c or the transient depressor response to ET-1, but it markedly decreased the sustained pressor response to ET-1. The ET B 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 ET A-ET B treatment reduced the sustained pressor response to ET-1 to the same extent as ETA blockade alone and decreased the response to sarafotoxin S6c and the transient depressor effect of ET-1 to the same extent as ET B blockade alone (Table 1).

Cardiac Functional Parameters and Remodeling

Compared with untreated CHF rats, ET A and combined ETA-ET B blockade (but not ET B blockade) reduced LV systolic pressure and LV end-diastolic pressure to the same extent, without affecting LV dp/dt max (Figure 1).

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

The ET A antagonist limited the progressive increase of LV end-diastolic diameter, but the ET B antagonist did not affect this parameter. Coadministration of the ET A and the ET B antagonist decreased LV end-diastolic diameter to the same extent as treatment with the ET A 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). ET A, ET B, or combined ET A-ET B 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, ET B, or combined ETA-ET B 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 ETA and ET B receptors improved systemic and cardiac hemodynamics, as well as LV function and remodeling, to the same extent as ETA receptor blockade alone. However, these effects were associated with a significant reduction of heart rate only with simultaneous ETA-ET B receptor blockade. (2) Chronic, selective ET B 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. Systolic blood pressure (SBP), heart rate (HR), LV end-diastolic pressure (LVEDP), and LV dp/dt max, 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.](image)

![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.](image)

**Table 1. Changes in Blood Pressure Induced by Intravenous Injection of ET-1 and Sarafotoxin S6c**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Control</th>
<th>ET_A-Treated</th>
<th>ET_B-Treated</th>
<th>ET_A+ET_B-Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarafotoxin S6c</td>
<td>−16.5±4.3</td>
<td>−21.2±3.9</td>
<td>−15.6±6.7</td>
<td>−6.9±1.0*</td>
<td>−8.7±1.6*</td>
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<tr>
<td>ET-1</td>
<td>−40.6±3.0</td>
<td>−34.8±3.5</td>
<td>−36.1±4.3</td>
<td>−7.6±3.9*</td>
<td>−14.9±3.6*</td>
</tr>
<tr>
<td>Transient dilatation</td>
<td>21.8±10.0</td>
<td>21.2±2.1</td>
<td>9.7±2.0*</td>
<td>25.8±6.8</td>
<td>10.0±4.2*</td>
</tr>
<tr>
<td>Sustained constriction</td>
<td></td>
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*P<0.05 vs CHF control.
Effect of ET\textsubscript{B} Receptor Blockade

After 1 month of treatment, the ET\textsubscript{A} antagonist did not alter blood pressure, suggesting the absence of ET\textsubscript{B}-mediated vasoconstrictor tone under these conditions. In contrast, short-term administration of ET\textsubscript{A} receptor blockers has been shown to induce vasoconstriction in humans\textsuperscript{9} and animals.\textsuperscript{10} It is possible that ET\textsubscript{B}-mediated endothelium vasodilatation might be reduced in CHF secondary to endothelial dysfunction or that the vasodilatory effects of ET\textsubscript{A} receptor stimulation differ in acute and chronic situations. Alternatively, CHF might be associated with a downregulation of endothelial ET\textsubscript{B} receptors.\textsuperscript{11} 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\textsubscript{B} receptor blockade reduced cardiac collagen accumulation. Thus, in contrast to selective ET\textsubscript{A} or mixed ET\textsubscript{A}-ET\textsubscript{B} administration, which provoke a major reduction of cardiac load, other mechanisms, independent of cardiac hemodynamic changes, are involved in ET\textsubscript{B} blockade. Indeed, ET activates cardiac fibroblasts though ET\textsubscript{B} receptors.\textsuperscript{12} Moreover, by reducing the ET\textsubscript{B}-mediated release of aldosterone,\textsuperscript{13} which is implicated in collagen accumulation in CHF, ET\textsubscript{B} receptor blockade might indirectly reduce collagen accumulation.

Selective ET\textsubscript{A} Versus Combined ET\textsubscript{A}-ET\textsubscript{B} Receptor Blockade

We observed that the effects of chronic, selective ET\textsubscript{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\textsubscript{A}-ET\textsubscript{B} blockade. These results demonstrate that simultaneous blockade of ET\textsubscript{B} receptors does not adversely affect the outcome of treatment with an ET\textsubscript{A} antagonist in experimental CHF.

In the present study, the effects of ET\textsubscript{A} or combined ET\textsubscript{A}-ET\textsubscript{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\textsubscript{A} or the ET\textsubscript{B} antagonist, a more marked, significant decrease in heart rate was observed after simultaneous ET\textsubscript{A}-ET\textsubscript{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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