Endothelin A Receptor Blockade Causes Adverse Left Ventricular Remodeling but Improves Pulmonary Artery Pressure After Infarction in the Rat

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**Background**—Endothelin A (ET A) receptor antagonists have been shown to improve ventricular remodeling and survival in rats when started 10 days after infarction. Whether starting them earlier would have a more or less beneficial effect is uncertain.

**Methods and Results**—Rats surviving an acute myocardial infarction (MI) for 24 hours (n = 403) were assigned to saline or the ET A receptor antagonist LU 127043 or its active enantiomer LU 135252 for 4 weeks. Chronic LU treatment had no effect on survival, with 46% of LU rats and 47% of saline-treated rats with large MI surviving to the end of the study. LU treatment led to scar thinning, further left ventricular (LV) dilatation, an increase in LV end-diastolic pressure, and an increase in wet lung weight (P<0.05). Despite this detrimental effect on LV function, LU led to a significant decrease in RV systolic (50±2 to 44±2 mm Hg, P<0.05 vs saline) and right atrial pressures. LU treatment also prevented the increase in pulmonary ET-1 found in saline-treated rats with large MI but did not modify the increase in cardiac ET-1 in hearts with large MI.

**Conclusions**—The early use of the ET A receptor antagonists LU 127043 or its active enantiomer LU 135252 after infarction in the rat leads to impaired scar healing and LV dilatation and dysfunction. This is accompanied by a decrease in RV systolic and right atrial pressures and a decrease in pulmonary but not cardiac ET-1 levels. It would thus appear that the early use of ET A receptor antagonists after infarction may be detrimental. (Circulation. 1998;98:2323-2330.)

**Key Words:** infarction ■ remodeling ■ hemodynamics ■ endothelin

Endothelin-1 (ET-1) is an endothelin-derived, powerful vasoconstricting substance that also has positive chronotropic and inotropic myocardial effects. Its long-term effects include stimulation of myocardial and vascular smooth muscle hypertrophy, interstitial fibrosis, and myocardial cell injury. In acute myocardial infarction (MI), ET-1 levels increase markedly, and their elevation is associated with MI size and a poor prognosis. In chronic congestive heart failure, systemic and cardiac ET-1 levels increase significantly. In heart failure, the nonspecific endothelin-A and endothelin-B (ET A+ET B) receptor antagonist bosentan and selective ET A receptor antagonists have generally been shown to have beneficial acute and long-term hemodynamic effects, although there have been exceptions.

Most commonly, heart failure occurs as the result of a MI. In large MI, during the first few postinfarction days, there can be stretching of the scar (scar expansion), which leads to ventricular dilatation and further reduction of the pumping ability of the heart. Later, the scar is stabilized but further ventricular dilatation can occur as a result of eccentric hypertrophy of the remaining myocardium. This dilatation of the ventricle has been shown to be closely related to the long-term prognosis of patients after infarction. Results of experimental studies done by one group using the specific ET A receptor antagonist BQ-123 suggest that ET A receptor blockade is beneficial in this situation when started 10 days after infarction. More recently, another group has found that the use of an ET A receptor antagonist could cause excessive ventricular dilatation when started within 24 hours of an MI. Clearly, more work is necessary in the area of ET-receptor antagonism and postinfarction evolution to help clarify the importance of the timing of initiation of ET receptor antagonists.

In this study, we investigated the effects of the specific ET A receptor antagonists LU 127043 and its active enantiomer LU 135252 started within 24 hours of an acute MI in rats and continued for 4 weeks thereafter.
Methods

Animals

Male Wistar rats (Charles River, St Constant, Quebec, Canada), 7 weeks of age and weighing 200 to 250 g, were selected. The use and care of laboratory animals was conducted according to the Canadian Council for Animal Care and were approved by the Animal Care Committee of the Montreal Heart Institute.

MI Operation Procedure

MI was induced by ligating the left anterior coronary artery as described previously. There was a high peri-infarction mortality rate, with 41% dying within 24 hours of the operative procedure.

Treatment Interventions

On the day after the operation (approx. 20 hours after operation), surviving animals were randomized into 3 groups as follows: (1) operated rats + 0.9% saline; (2) operated rats + LU 127043 or its active enantiomer LU 135252, with the treatment stopped for 2 days before the hemodynamic measurements; and (3) operated rats + LU 135252 given continuously until the time of euthanasia (Figure 1). LU 135252 and LU 127043 are essentially the same selective ETA receptor antagonist [(+)-(5)-2-(4, 6-dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3, 3-diphenyl-propionic acid] produced by Knoll AG, LU 135252 being the active enantiomer of LU 127043. All rats received twice-daily gavage with 60 mg/kg per day of LU 135252 or vehicle (0.9% saline), except for rats receiving LU 127043 at 100 mg/kg per day in the drinking water. Results with LU 127043 and LU 135252 were similar and thus considered together.

Long-Term Hemodynamic Effects of LU

The hemodynamic studies evaluating the long-term effects of LU were done 4 weeks after infarction. Rats were anesthetized with a gas mixture containing 100% oxygen and halothane reduced from 2% to 0.5% to 0.8% 15 minutes before left and right heart hemodynamic recordings were measured by a microtip pressure transducer catheter (model SPR-407, 2F, Millar Instruments), as previously described. Rats that died after 72 hours but before the hemodynamic study had morphological assessment of MI size but were not used for other measurements except for survival. Those dying between 24 and 72 hours were assumed to have had a large MI.

Passive Pressure-Volume Relation and Ventricular Remodeling

A first group of rats (n=73) was used to assess LV remodeling. First, the passive pressure-volume relation of these hearts was assessed as previously described; the heart was filled with saline to a pressure of 15 mm Hg, sealed, and fixed in formalin. The heart was then cut halfway (middle) between the base and apex, and slices were prepared for histological study as previously described. A large MI was defined as involving ≥45% of LV circumference and a sham or small infarction as involving ≤20%. Hearts with a moderate infarction (20% to 45%) were excluded because there were too few of them for meaningful analyses. The surface of the scar cross section was obtained by planimetry and divided by scar length to obtain an assessment of average scar thickness.

Assessment of Cardiac Hypertrophy

A second group of rats (n=155) was used to assess the degree of cardiac hypertrophy and endothelin and atrial natriuretic peptide (ANP) levels. After the hemodynamic protocol was completed, 6 mL of blood was collected through the right jugular vein. The lungs were removed and perfused with saline to remove any residual blood; the heart was then rapidly excised and divided into right and left atria, right ventricle (RV), left ventricle (LV) (including septum), and the scarred area. Each tissue was then weighed individually. The scarred area surface was determined by planimetry. Rats were divided into sham or small MI or large MI according to whether they had a scar to body weight ratio ≤0.1 mg/g or >0.2 mg/g. This was based on a relation between the scar to body weight ratio and LV end-diastolic pressure.
pressure (LVEDP). Rats with a large MI based on a scar to body weight ratio $>0.2$ mg/g had hemodynamic values similar to those with a large MI based on a $\approx 45\%$ scar circumference (data not shown).

Assessment of Plasma and Tissue Endothelin Levels

The plasma endothelin concentration and the endothelin concentration of the lungs, the RV, the viable portion of the LV, and the scar were determined by previously established methods.**

Prepro-ET-1 mRNA levels in the viable portion of the LV were measured with a ribonuclease protection assay (RPA) kit from Ambion Inc (RPA II). Samples were then electrophoresed on a vertical Novex system for 2 hours at 150 V, transferred on a positively charged nylon membrane where they were cross-linked by high-energy UV radiation. The biotin moiety on the protected probes was revealed through the use of standard streptavidin alkaline phosphatase coupled with CDP-Star (BrightStar BioDetectKit; Ambion Inc). The resulting chemiluminescent reaction was exposed on BioMax Kodak films for 1 to 4 hours. A low-molecular-weight RNA ladder (0.15 to 1.7 kb; Gibco BRL, Burlington, Ontario, Canada) incorporated on every gel enabled us to accurately identify expected bands at 499 and 313 bases for prepro-ET-1 and $\beta$-actin, respectively. The intensity of prepro-ET-1 bands was quantified by densitometry (GS-700, Biorad) and normalized relative to the $\beta$-actin density.

Assessment of Cardiac Prepro-ANP mRNA and Plasma Angiotensin II Levels

Plasma angiotensin II levels were measured as previously described.*** Cardiac prepro-ANP mRNA was measured as previously described.** The mRNA level of prepro-ANF was normalized to the level of 28S rRNA to correct for potential differences in the amount of RNA loaded and/or transferred.

Immunocytochemical Analysis

A polyclonal antiserum against human ET-1 was obtained from Peninsula Laboratories. The avidin-biotin-peroxidase complex method was used. Negative controls were performed by replacing nonimmune serum for the primary antibody or by omitting steps in the avidin-biotin-peroxidase complex procedure.

Statistical Analysis

All values are expressed as mean±SEM. Results were compared with the use of a 2-tailed Student’s $t$ test for unpaired data and by ANOVA followed by Dunnett’s test when appropriate. Statistical significance was assumed at $P<0.05$. Kaplan-Meier survival curves over the whole follow-up were constructed and the curves compared by the generalized Savage (Mantel-Cox) test.

### Table 1. Hemodynamic Parameters 4 Weeks After Infarction During Therapy

<table>
<thead>
<tr>
<th></th>
<th>HR, bpm</th>
<th>RVSP, mm Hg</th>
<th>RVEDP, mm Hg</th>
<th>RV $dP/dt$, mm Hg/s</th>
<th>LVSP, mm Hg</th>
<th>LVEDP, mm Hg</th>
<th>LV $dP/dt$, mm Hg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sham or small MI</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Saline solution (n=37)</td>
<td>360±6</td>
<td>26±1</td>
<td>2±0</td>
<td>1196±41</td>
<td>106±2</td>
<td>6±0</td>
<td>4649±125</td>
</tr>
<tr>
<td>LU stop 2 days (n=15)</td>
<td>361±10</td>
<td>26±1</td>
<td>2±1</td>
<td>1175±81</td>
<td>108±4</td>
<td>5±1</td>
<td>4658±257</td>
</tr>
<tr>
<td>LU continuous (n=26)</td>
<td>376±7</td>
<td>26±1</td>
<td>2±0</td>
<td>1327±79</td>
<td>106±3</td>
<td>6±1</td>
<td>4398±202</td>
</tr>
<tr>
<td><strong>Large MI</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Saline solution (n=42)</td>
<td>340±0†</td>
<td>50±2†</td>
<td>14±1†</td>
<td>1469±63†</td>
<td>86±2†</td>
<td>27±1†</td>
<td>2959±134†</td>
</tr>
<tr>
<td>LU stop 2 days (n=16)</td>
<td>330±2†</td>
<td>46±3†</td>
<td>13±1†</td>
<td>1336±110</td>
<td>89±2†</td>
<td>32±1†</td>
<td>2561±159†</td>
</tr>
<tr>
<td>LU continuous (n=27)</td>
<td>350±8†</td>
<td>44±2†</td>
<td>12±1†</td>
<td>1246±66</td>
<td>88±3†</td>
<td>29±1†</td>
<td>2952±158†</td>
</tr>
</tbody>
</table>

HR indicates heart rate; RVSP, RV systolic pressure; and LVSP, left ventricular systolic pressure. Values are mean±SEM.

* $P<0.05$ vs sham or small infarction.

† $P<0.05$ vs saline solution.

Figure 2. Comparison between survival of rats with large MI treated with saline and LU.

Results

Effects of ET$_A$ Receptor Antagonists on Survival

The survival of sham-operated or small MI rats, whether saline treated or LU treated, was excellent. Overall mortality rate in rats with large MI was similar in the 2 treatment groups, with $\approx 47\%$ of rats treated with saline surviving and 46% of rats treated with LU surviving the 4-week study (Figure 2).

Long-Term Hemodynamic Effects of LU

No difference in the hemodynamic characteristics of rats with sham operation or small MI were noted between the various treatment groups (Table 1). However, in rats with large MI, RV systolic pressure was significantly decreased in the LU group in which the medication was continued until euthanasia ($P<0.05$) as compared with the saline-treated group (Table 1). This occurred despite a significant increase in LVEDP in the LU stop group as compared with the saline large MI group. A tendency toward an increase in LVEDP was noted in the LU continuous group. The decrease in RV end-diastolic pressure (RVEDP) in the LU continuous group did not reach statistical significance, but the decrease in right atrial (RA) pressure did. The decrease in these variables in the LU stop

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group was directionally similar but not statistically significant.

**Passive Diastolic Pressure-Volume Relation**

Treatment with LU had no effect on the passive diastolic pressure-volume relation of sham or small MI rat hearts. As expected, a large MI caused this relation to be shifted to the right as compared with the sham or small MI groups (Figure 3). The large MI hearts treated with LU had the greatest rightward shift \( P < 0.05 \), indicating greater ventricular dilation despite similar MI size.

**Cardiac Remodeling and Morphological Studies**

The characteristics of cardiac chamber and scar weight as well as scar surface and lung weight are presented in Table 2. In the sham-operated or small MI groups, treatment with LU had no effect on any of these variables. LU-treated hearts had a significant increase in both RA and left atrial (LA) weight to body ratio, and their wet lung weight to body weight ratio was also increased, suggesting greater pulmonary congestion.

In rats that were sham operated or had small infarctions, no difference in any of the measured morphological variables between saline-treated and LU-treated groups were identified (Table 3). As compared with saline-treated rats with large MI, LU-treated rats with large MI had a greater increase in epicardial circumference and greater thinning of the scar, as reflected by a decrease in cross-sectional scar surface to scar length. Infarct size and other variables were no different between the 2 MI groups.

**Endothelin Concentrations**

Plasma ET-1 concentrations were similar in sham-operated or small MI rats regardless of treatment (Table 4). Rats with large MI treated with saline had an elevated plasma ET-1; however, levels were even greater in LU-treated rats with a large MI.

Sham or small MI rats treated with LU had slightly higher pulmonary ET-1 levels than saline-treated sham or small MI rats (Table 4). Rats with large MI treated with saline had the greatest increase in ET-1. LU rats treated with a large MI had no elevation in pulmonary ET-1 levels.

ET-1 and prepro-ET-1 mRNA levels in the viable portion of the LV of sham-operated or small MI hearts were similar regardless of treatment \([0.20 \pm 0.3 \text{ prepro-ET-1/} \beta\text{-actin mRNA (n=6)} \text{ for saline-treated and } 0.23 \pm 0.06 \text{ prepro-ET-1/} \beta\text{-actin mRNA (n=6)}] \) (Table 4 and Figure 4). The increase

![Figure 3. LV pressure-volume relations according to MI size and treatment group.](image)

### Table 2. Morphology Parameters of Heart at Time of Induced Death

<table>
<thead>
<tr>
<th></th>
<th>Scar wt/Body wt, mm/g</th>
<th>Scar wt/Surface, mg/mm²</th>
<th>LV wt/Body wt, mg/g</th>
<th>LA wt/Body wt, mg/g</th>
<th>RV wt/Body wt, mg/g</th>
<th>RA wt/Body wt, mg/g</th>
<th>Lung wt/Body wt, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham or small MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline solution (n=39)</td>
<td>0.03±0.01</td>
<td>1.26±0.20</td>
<td>2.01±0.03</td>
<td>0.10±0.01</td>
<td>0.55±0.01</td>
<td>0.11±0.01</td>
<td>3.95±0.16</td>
</tr>
<tr>
<td>LU (n=27)</td>
<td>0.03±0.01</td>
<td>1.05±0.04</td>
<td>2.07±0.05</td>
<td>0.11±0.01</td>
<td>0.58±0.02</td>
<td>0.12±0.01</td>
<td>3.86±0.01</td>
</tr>
<tr>
<td>Large MI</td>
<td></td>
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</tr>
<tr>
<td>Saline solution (n=49)</td>
<td>0.35±0.02†</td>
<td>0.74±0.04†</td>
<td>1.91±0.05</td>
<td>0.23±0.01†</td>
<td>1.05±0.04†</td>
<td>0.29±0.03†</td>
<td>6.66±0.46†</td>
</tr>
<tr>
<td>LU (n=40)</td>
<td>0.36±0.02†</td>
<td>0.59±0.02†</td>
<td>1.99±0.04</td>
<td>0.29±0.01†</td>
<td>1.14±0.0-4†</td>
<td>0.45±0.04†</td>
<td>8.50±0.37†</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

* \( P < 0.05 \) vs saline solution.

† \( P < 0.05 \) vs sham or small infarction.
in LV ET-1 and prepro-ET-1 mRNA levels in hearts of saline-treated rats with large MI was significant (1.31 ± 0.17 prepro-ET-1/β-actin mRNA, n = 5, P < 0.02) and similar to that of hearts of LU-treated rats with large MI (0.96 ± 0.17 prepro-ET-1/β-actin mRNA, n = 6). RV ET-1 levels were similar to those of the LV in all 4 groups. The highest levels of tissue ET-1 levels were, however, found in the scar of hearts with a large MI regardless of treatment group.

Cardiac Prepro-ANP mRNA and Plasma Angiotensin II
Cardiac prepro-ANP mRNA expression was increased in the RV and LV of both groups with large MI (Figure 5), with the increase in LU-treated hearts being greatest. Plasma angiotensin II decreased in LU continuously treated rats with sham or small MI as compared with the saline group (Figure 5). Plasma angiotensin II was increased similarly in saline and LU 135252 continuously treated rats with large MI but increased even more when LU 135252 was stopped.

Immunocytochemical Analysis
ET-1 immunoreactivity was found to be very low in the myocardium of sham-operated controls (Figure 6). However, ET-1 immunoreactivity was markedly increased in the viable myocardium of failing hearts with large MI. This was true for rats receiving saline or LU.

**Discussion**
This study demonstrates that the early and sustained use of the orally active ETA receptor antagonists LU 127043 and its active enantiomer LU 135252 after infarction in the rat results in detrimental healing of the scar. This in turn leads to excessive ventricular dilatation and LV dysfunction. These changes are accompanied by an increase in cardiac prepro-ANP mRNA levels and, when LU is stopped, an increase in plasma angiotensin II. The early and sustained use of orally active ETA receptor antagonists was, however, associated with beneficial effects on pulmonary pressures and prevented the increase in pulmonary ET-1 levels found with a large MI. Despite this, there was no improvement in RV or LA and RA hypertrophy. The end result was no change in survival. Taken together, these findings suggest that ETA receptor antagonists should not be started early after infarction because they may lead to detrimental ventricular remodeling, which in turn could counter the potential beneficial effects that these drugs may have when used long term in this model of heart failure.10

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**TABLE 3. Morphological Characteristics of Mid-LV Cross Sections**

<table>
<thead>
<tr>
<th>Infarct Size, %</th>
<th>Epicardial Circumference, mm</th>
<th>Epicardial Myocardial Length, mm</th>
<th>Epicardial Scar Length, mm</th>
<th>Cross-Sectional Scar Surface, mm²</th>
<th>Cross-Sectional Scar Surface/Scar Length, mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham or small MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=10)</td>
<td>0</td>
<td>33.69 ± 0.43</td>
<td>34.28 ± 0.70</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LU (n=14)</td>
<td>0.3 ± 0.008</td>
<td>34.91 ± 0.02</td>
<td>34.79 ± 0.01</td>
<td>0.10 ± 0.003</td>
<td>0.08 ± 0.002</td>
</tr>
<tr>
<td>Large MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=25)</td>
<td>50 ± 1†</td>
<td>35.86 ± 0.68</td>
<td>19.28 ± 0.42†</td>
<td>16.87 ± 0.69†</td>
<td>8.42 ± 0.44†</td>
</tr>
<tr>
<td>LU (n=24)</td>
<td>50 ± 1†</td>
<td>37.67 ± 0.49†</td>
<td>19.69 ± 0.69†</td>
<td>17.97 ± 0.57†</td>
<td>7.86 ± 0.33†</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*P < 0.05 vs saline solution.
†P < 0.05 vs sham or small MI.

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**TABLE 4. Plasma and Tissue ET-1**

<table>
<thead>
<tr>
<th>ET-1</th>
<th>Plasma, pg/mL</th>
<th>Pulmonary, pg/mg Protein</th>
<th>LV, fg/mg</th>
<th>RV, fg/mg</th>
<th>Scar, fg/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham to small MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=15)</td>
<td>1.54 ± 0.23</td>
<td>90 ± 2</td>
<td>256 ± 32</td>
<td>280 ± 34</td>
<td>N/A</td>
</tr>
<tr>
<td>LU continuous (n=8)</td>
<td>1.83 ± 0.25</td>
<td>115 ± 4*</td>
<td>260 ± 45</td>
<td>276 ± 27</td>
<td>N/A</td>
</tr>
<tr>
<td>Large MI</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=15)</td>
<td>2.57 ± 0.30*</td>
<td>157 ± 3*</td>
<td>615 ± 74*</td>
<td>626 ± 54*</td>
<td>1826 ± 287†</td>
</tr>
<tr>
<td>LU continuous (n=10)</td>
<td>5.68 ± 1.10†</td>
<td>114 ± 3*†</td>
<td>704 ± 44*</td>
<td>653 ± 26*</td>
<td>1878 ± 297†</td>
</tr>
</tbody>
</table>

N/A indicates not applicable. LV, RV, and scar endothelin are per milligram of wet tissue weight.

*P < 0.05 compared with saline sham to small MI.
†P < 0.05 compared with saline large MI.
‡P < 0.001 compared with viable LV myocardium.
It would nevertheless appear that these agents may be useful in attenuating the pulmonary hypertension associated with LV dysfunction.

One of the major findings of this study is that ET\(_A\) blockade started within 24 hours of an acute MI impairs scar healing and contributes to excessive ventricular dilatation and dysfunction. The early use of an ET\(_A\) receptor antagonist after infarction caused the scar to be thinner, which suggests that collagen deposition was impaired. Considering the known stimulating effect of ET-1 on fibroblasts,\(^3\) the large number of ET\(_A\) receptors on fibroblasts,\(^3\) the increase in circulating and cardiac ET-1 levels, and the marked increase in cardiac prepro-ET-1 mRNA in heart failure,\(^5\) it should come as no surprise that ET\(_A\) receptor antagonists would have this effect. One interesting finding from this study is that the scar had greater ET-1 levels compared with the rest of the myocardium. This finding is compatible with an important role for ET-1 in maintaining scar integrity. Because starting ET\(_A\) receptor antagonists 7 to 10 days after infarction in this model has been found not to affect the scar, to improve LV remodeling and to prolong survival,\(^10\) it would appear that once the scar is healed and stable, ET\(_A\) receptor antagonists no longer have detrimental effects on the scar or ventricular remodeling.

The only study showing prolonged survival with the nonspecific ET receptor antagonist bosentan also started the drug 1 week after infarction.\(^8\) That study, combined with the results of

**Figure 4.** Representative prepro-ET-1 and \(\beta\)-actin bands from viable LV from hearts of saline-treated rats with no MI (control) and large MI. Prepro-ET-1 is much greater in hearts with large MI.

**Figure 5.** Prepro-ANP mRNA expression and plasma angiotensin II levels. Prepro-ANP increased in all large MI groups. *\(P<0.05\) vs sham to small MI.

**Figure 6.** Plasma Angiotensin II levels (pg/ml). Lu 135252 Continuous and Stop increased in all large MI groups. *\(P<0.05\) vs sham to small MI.
Sakai et al. support the possibility that starting endothelin antagonists after the scar is healed is particularly beneficial. Nevertheless, results by Fraccarollo et al. raise the possibility that nonspecific ET receptor blockade may have superior effects on scar healing and thus potentially more favorable effects on postinfarction LV remodeling. They found that starting bosentan 3 hours after infarction had no detrimental effects on LV remodeling 8 days later and improved remodeling slightly by 8 weeks after infarction. Why nonspecific blockade should be better than specific ETA antagonists for scar healing is not obvious because fibroblasts also have ETB receptors. However, because ETB receptors also stimulate nitric oxide release, and nitric oxide has antiproliferative effects, this mechanism remains a possibility.

The dose of bosentan used appears to be important for optimal hemodynamic and remodeling effects and for survival. This raises the possibility that the use of larger doses of LU may have yielded different results than those found in our study. However, the goal of this study was to evaluate the effects of specific ETA receptor antagonists on postinfarction LV remodeling, and larger doses would have reduced the receptor specificity of LU. In pilot studies, we went to great lengths to be certain that the doses of LU used not only blocked the vasoconstrictor effects of ET-1 but also preserved its receptor selectivity. Nevertheless, our therapeutic regimen of LU was active because it led to significant alterations in plasma and pulmonary ET-1 levels, plasma angiotensin II, LV prepro-ANP mRNA levels, LV remodeling, and pulmonary pressures.

ETA blockade decreased pulmonary pressures despite causing an increase in LVEDP in rats with a large MI. Thus the decrease in pulmonary vascular resistance caused by long-term ETA blockade probably is greater than that reflected by the decrease in pulmonary systolic pressures, assuming that cardiac output was similar in both groups. Studies by Sakai et al. suggest that ETA antagonist–induced decreases in pulmonary pressures are largely the result of changes in the pulmonary vasculature itself. They found that a decrease in pulmonary pressures was present even after the ETA receptor antagonist was stopped. That ETA blockade should have particularly impressive effects on pulmonary pressures is compatible with an important pathophysiological role of endothelin in the development of pulmonary hypertension in heart failure.

Despite causing LV dilatation and no change in systemic arterial pressure, ETA blockade was not accompanied by greater LV hypertrophy. This suggests that the known stimulatory effect of ET-1 on myocardial hypertrophy was at least partially suppressed by ETA blockade. However, it would appear that this antihypertrophic effect of ETA blockade was not sufficient to prevent the development of significant RV and RA hypertrophy. This is all the more surprising because RV systolic and RA pressures were decreased and RVEDP also tended to decrease. We are at a loss to explain this finding, except for the possibility that the increase in LVEDP produced by LU treatment activated other systems such as angiotensin II that preferentially stimulated hypertrophy. Reflex stimulation of vasoconstrictor systems would also...
help explain the lack of decrease in systemic arterial pressures that occurred despite the use of a known vasodilatory substance. Another possibility is that the decrease in right-sided pressures was too modest to be translated to a measurable reduction in RV hypertrophy.

In this study, LU was found to suppress angiotensin II plasma levels in sham to small MI rats. Unfortunately, this beneficial effect was lost in rats with large MI and, in LU-treated rats with large MI when LU was stopped, angiotensin II levels were at their highest, a finding compatible with more severe LV dysfunction.

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