Does Losartan Benefit Endothelial Dysfunction and Experimental Intact Size in Rats Exposed to Second Hand Smoke?


Background: Second hand smoke (SHS) contributes to endothelial dysfunction. We previously showed that the angiotensin II receptor blocker losartan improved endothelial dysfunction and myocardial ischemia. We sought to determine whether losartan prevents endothelial dysfunction and myocardial ischemia in rats exposed to SHS.

Methods: Sprague-Dawley rats were randomized to receive losartan (40 mg/kg/day) and/or SHS (smoking chamber) in a 2 by 2 design. The source of SHS was sidestream smoke of 4 cigarettes every 15 min, 6 hours a day, 5 days a week. After 6 weeks, the rats were subjected to 17 min of LAD occlusion and 120 min of reperfusion. In fresh aortic rings precontracted with phenylephrine, endothelium-dependent and -independent relaxations were assessed. Vascular endothelial growth factor (VEGF) in the ischemic myocardium was measured by Western blot analysis. Results: SHS impaired endothelial dependent relaxation to aceyloxylicohene and endothelial independent relaxation to nitroglycerin. Losartan reduced the impaired maximal vasorelaxation induced by A23187. Losartan increased effective refractory period (ERP) and VF threshold. SHS increased intact size and VEGF. Losartan decreased intact size, but did not affect the increased intact size caused by SHS. Conclusions: SHS impaired endothelial function and increased intact size and VEGF. Losartan prevented endothelial dysfunction secondary to SHS, but did not affect the increased intact size caused by SHS.

(*P<0.05, **P<0.01 when compared with the control group)

<table>
<thead>
<tr>
<th>Groups</th>
<th>ERP (ms)</th>
<th>VF Threshold (ms)</th>
<th>Maximal relaxation</th>
<th>VEGF (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>27.7±0.6</td>
<td>0.38±0.04</td>
<td>43.2±3.7</td>
<td>46±8</td>
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<tr>
<td>Losartan</td>
<td>30.0±1.2</td>
<td>1.27±0.25</td>
<td>20.3±5.5</td>
<td>-68±10</td>
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</table>
| SHS      | 26.5±1.2 | 0.52±0.10         | 78.2±7.0           | -43±6.9      | 3.1±0.6
| SHS+Losartan | 32.7±1.5 | 1.12±0.13       | 25.5±2.0           | -60±3.2      | 3.5±0.5

Activation of Caspase-3 in the Remodeling Heart After Myocardial Infarction is Prevented by Treatment With Ramiprilate

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Background: Remodeling of the surviving myocardium after regional myocardial infarction can be effectively prevented by ACE inhibition (ACEI). The exact molecular mechanism is not yet clarified. Here we present the results that might contribute to the understanding of the process by which ACEI prevent infarction remodeling.

Methods: Male wistar rats (200 g) were pretreated with ramiprilate (R) (10 µg/kg daily i.p.) for 7 days. Controls were injected with saline (S). After 7 days, regional myocardial infarction was induced by ligation of the LAD. Sham-operated animals served as controls (Co). After 1 day, heart and lung weights were determined. In biopsies from the myocardium remote from the infarction the activation of caspase-3 (by cleavage of its inactive pro-caspase) and the ratio of the regulator proteins bcl-2 and bax were determined by Western blot analysis.

Results: The significant increase of plasma pro-Ang II seen after LAD ligation was reduced by 73% in ACEI-treated animals. Heart and lung weights were unchanged. Activation of caspase-3 after infarction was fully prevented by ACE-inhibition (R): 82±3% of sham, S: 19±5% of sham, p<0.05. The significant shift of the bcl-2/bax quotient after LAD ligation (S: 72±7% of sham) was also prevented by ramiprilate (109±10%).

Conclusion: ACE inhibition is able to block the early biochemical markers of apoptosis in the surviving, remodeling myocardium after infarction. This prevention of early apoptosis is supposed to be an important aspect for the beneficial effect of ACEI after infarction and is a rationale for the begin of treatment early after infarction.

Early Administration of Losartan Induces Unfavorable Evolution of Postinfarct Remodeling in Rabbits

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Background: It is known that the renin-angiotensin system is activated early in myocardial infarction (MI), and likewise that losartan (L) reduces the mortality and fibrosis present after MI. P-V relationship is shown in the figure. Conclusion: The early administration of L favorably modified post MI ventricular remodeling, increasing ventricular dilatation. The fact that L augmented the cavity size in G3 suggests that MI is not the only factor involved in the observed dilation.

Simultaneous Activation of Both Cardiac Angiotensin Formation and Degradation in the Acute Phase of Myocardial Infarction

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Background: Acute myocardial infarction (AMI) is known to be associated with an activation of the plasmatic renin-angiotensin system (RAS), but up to now no direct information is available in humans about the behavior of the cardiac local system. This study was aimed to investigate whether and when an activation of cardiac RAS occurs in the acute phase of AMI.

Methods: After informed consent in 12 male patients (aged 55+8 years) with anterior AMI (rejection fraction 52±4%) who did not underwent revascularization, angiotensin (Ang) I and II concentrations were assessed in arterial (A) and coronary sinus (CS) blood daily during the first 5 days. On the third day the study of cardiac 125I-Ang I kinetics was also performed. No patient was treated with angiotensin converting enzyme inhibitors. The control group was formed by 10 age-matched subjects who performed coronary angiography for atypical chest pain.

Results: In the control group transcardiac Ang I and II gradients were negative (1.9±2.5 pg/ml and -0.9±1.7 pg/ml, respectively). The kinetics study showed that 29.6±4.4 % of 125I-Ang I and 19.2±3.1 % of 125I-Ang II concentrations were recovered in arterial (A) and coronary sinus (CS) blood daily during the first 5 days.

Conclusion: In the acute phase of myocardial infarction the cardiac RAS is activated with Ang II formation by cardiac tissues being higher than coronary sinus blood. This is in agreement with the recent findings that coronary RAS is activated early after AMI.

ACE Inhibitors and Angiotensin II Receptor Antagonists Indistinguishably but Synergistically Increase Coronary Blood Flow and Attenuates the Severity of Contractile and Metabolic Dysfunction in Ischemic Hearts

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ACE inhibitors (ACEI) or angiotensin II receptor antagonists (ARB) mediate coronary vasodilation, suggesting that the combination of these two types of drugs may synergistically mediate coronary vasodilation in the ischemic hearts. To test this idea, we infused 10µg/kg/min of losartan (ACEI) or 10µg/kg/min of R ASS-270 (ARB) in the canine ischemic hearts; the dose of each drug was the minimal dose that exerts the maximal coronary vasodilation. In the open chest preparation, we measured coronary blood flow (CBF) and coronary perfusion pressure (CPP) of the left anterior descending coronary artery.

We decreased CPP (104±8 to 42±2mmHg) so that CBF decreased to one-third of the baseline value (fractional shortening (FS): 26.1±2.0 to 5.4±1.5%; lactate extraction ratio (LER): 28±5 to -45±6%), and we kept CPP constant at low levels. Ten min following the infusion of losartan, CBF increased to 29±2×44±3ml/min/gm tissue as well as FS (10±2±1%), and LER (2±1%), and the cardiac levels of NO (7.8±2.9 to 17.5±3.2 µM) and bradykinin (32±6 to 98±5pg/ml) (the differences in the endo-product levels of NO (nitrate and nitrite) or bradykinin levels between the coronary venous and arterial blood), were assessed. Vascular endothelial growth factor (VEGF) in the ischemic myocardium increased Ang II formation by cardiac tissues. The simultaneous increase in cardiac Ang II formation and degradation make the combination of ACEI and ARB causes an increase in CBF and CPP as well as the improvement in FS and LER. This study showed that the combination of ACEI and ARB causes an increase in CBF and CPP as well as the improvement in FS and LER.


does not affect the increased intact size caused by SHS.

(*)P<0.05, **P<0.01 when compared with the control group