1049-32 Does Losartan Benefit Endothelial Dysfunction and Experimental Infarct Size in Rats Exposed to Second Hand Smoke?

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Background: Second hand smoke (SHS) contributes to endothelial dysfunction. We previously showed that the angiotensin II receptor blocker losartan improved endothelial dysfunction and myocadial ischemia. We sought to determine whether losartan prevents endothelial dysfunction and myocardial ischemia in rats exposed to SHS. Methods: 84 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 sidesream 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 relaxation were assessed.Vascular endothelial growth factor (VEGF) in the ischemic myocardium was measured by Western blot analysis. Results: SHS impaired endothelial dependent relaxation to acetylcholine 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 infarct size and VEGF. Losartan decreased infarct size, but did not affect the increased infarct size caused by SHS. Conclusions: SHS impaired endothelial function and increased infarct size and VEGF. Losartan prevented endothelial dysfunction secondary to SHS, but did not affect the increased infarct size caused by SHS.

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

Groups	ERP(mS)	VF Threshold(mA)	Infarct size(%)	Maximal relaxation(%)	VEGF
Control	27.7±0.8	0.38±0.04	43.2±3.7	-48±8	1.0±0.0
Losartan	30.0±1.2*	1.27±0.25**	30.2±5.5*	-68±10*	1.1±0.2
SHS	26.5±1.2	0.59±0.10	58.7±2.7**	-43±6.9	3.1±0.6**
SHS+Losartan	32.7±1.5*	1.12±0.13**	55.2±2.0*	-60±3.2*	3.5±0.5**

1049-33 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 of this treatment is not yet clarified. It could be shown earlier that as early as 1 day after infarction, biochemical markers of apoptosis such as activation of caspase-3 are detectable in the surviving myocardium, together with early signs of heart failure. If ACEI is operative in preventing remodeling by influencing apoptosis was focus of the present study.

Methods: Male wistar rats (200 g) were pretreated with ramiprilate (Ra, 10 µg/kg daily i.p.) for 7 days. Controls were injected with saline (Sal). 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 and the plasma level of pro-ANP were obtained. In biopsies from the myocardium remote from the infarction the activation of caspase-3 (by cleavage of its inactive procaspase) and the ratio of the regulator proteins bcl-2 and bax were determined by Westernblot analysis.

Results: The significant increase of plasma pro-ANP 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 (Ra: 88±8% of sham, Sal: 195±35 % of sham, p<0,05). The significant shift of the bcl-2/bax quotient after LAD ligation (Sal: 75±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 one important aspect for the beneficial effect of ACEI after infarction and is a rationale for the begin of treatment early after infarction.

1049-34 Early Administration of Losartan Induces Unfavorable Evolution of Postinfarct Remodeling in Rabbits

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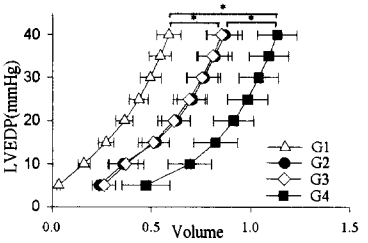
Background: It is known that the renin-angiotensin system is activated early in myocardial infarct (MI), and likewise that losartan (L) reduces the mortality and fibrosis present in the chronic evolution of MI. However, the effects of this drug on ventricular remodeling (VR) remain controversial. Objectives: The aim was to determine if early administration of L to rabbits subjected to MI modifies VR. Methods: 35 rabbits were subjected to ligature of a branch of the left coronary artery. Four experimental groups were formed: G1 (sham;n=9), G2 (MI;n=8), G3 (sham+L;n=9) and G4 (MI+L;n=9). L (12.5 mg/kg/d) was administered during 35 days starting from 3 hours postligature. At the end of the protocol the animals were sacrificed, hearts were isolated and perfused using Langendorff's technique to determine pressure-volume (P-V) curves. Hearts were fixed in formaline, cut from apex to base and stained with Masson's Trichrome. Infarct size (IS) and septum area (SA;mm^2) were measured by means of morphometric analysis. Values are expressed as X±SEM; *P<0.05. Results: IS was G2=27.3±3 and G4=19.5±4.1 (NS). SA was G1=1.6±0.2; G2=1.8±0.4, G3= 1.0±0.2 and G4=1.3±0.4. The inotropic state in the studied group was not modified by L. P-V relationship is shown in the figure. Conclusions: The early administration of L unfavorably modified post MI ventricular remodeling, increasing ventricular dilation. The fact that L augmented the cavity size in G3 suggests that MI is not the only factor involved in the observed dilation.



1049-35 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 RAS. 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 (ejection fraction 52±4%) who did not underwent revascularization, angiotensin (Ang) I and II concentrations were assayed 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 slightly negative (-1.8±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±4.1 % of 125I-Ang II were extracted by cardiac tissues and that 23.7±3.9 % of Ang I was converted to Ang II . The de novo formation by cardiac tissues was 7.8±2.9 pg/ml for Ang I and 2.7±1.3 pg/ml for Ang II. In AMI patients Ang I and Ang II A-CS gradients never differed from controls, but the kinetics study showed a significant increase in the de novo Ang I and Ang II formation by cardiac tissues (p<0.01 vs controls) and a marked increase in degradation of both angiotensins (p<0.01). As a result the Ang I and II concentrations in CS blood did not differ between AMI patients and controls.

Conclusion: In the acute phase of myocardial infarction the cardiac RAS is activated with increased Ang II formation by cardiac tissues. The simultaneous increase in cardiac Ang degradation make the determination of transcardiac gradient unable to study the activity of cardiac RAS in AMI patients.

1049-36 ACE Inhibitors and Angiotensin II Receptor Antagonists Independently 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 temocaprilat (ACEI) or 10µg/kg/min of RNH-6270 (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 dogs, 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): 29±5 to -45±4%), and we kept CPP constant at low levels. Ten min following the infusion of temocaprilat, CBF increased from 29±2 to 44±3ml/100g/min as well as FS (10.2±1.5%), and LER (-21±4%), and the cardiac levels of NO (7.8±1.9 to 17.5±3.2 µM) or 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), which were attenuated by either L-NAME or HOE140. RNH-6270 modestly increased CBF (34±3ml/100g/min), FS and LER, but did not increase the cardiac NO or bradykinin levels (8.8±2.9µM, and 29±3pg/ml, respectively). The infusion of both temocaprilat and RNH-6270 further increased CBF (51±4ml/100g/min), FS (13.9±0.8%) and LER (-12±4%) compared with the condition with either drug alone, which was completely inhibited by HOE140. RNH-6270 augmented the bradykinin-induced coronary vasodilation in the non-ischemic hearts. We conclude that the combination with ACEI and ARB causes more potent coronary vasodilation and mediates more prominent cardioprotection than each drug alone. Furthermore, ARB augments the ACEI- or bradykinin-induced coronary vasodilation. The combination of these drugs may afford better cardioprotection in the clinical settings.