1099-20
Reduction of Myocardial Infarct Size by a HMG CoA-Reductase Inhibitor in Normocholesterolemic Rats
Sebastian Wolfkam, Michael Grimm, Marc Heidenbreder, Andreas Donandorfer, Hugo A. Katus, James K. Lied, Gert Richardt, Munich, Germany, Department of Cardiology, Ludwig-Maximilians University, Munich, Munich, Germany.

Background: To investigate whether the 3-hydroxy-3-methylglutaryl CoA reductase inhibitors (HMG-CoA reductase inhibitors) can decrease infarct size in rats.

Methods: Normocholesterolemic rats (n=21) were randomly assigned to 4 different groups: control group (n=5), 0.25% simvastatin group (n=7), 0.5% simvastatin group (n=7), and 1% simvastatin group (n=2). Infarct size was determined by TTC staining of the heart after 2 hours of ischemia and 4 hours of reperfusion. Statistical analysis was performed using one-way ANOVA.

Results: Infarct size was significantly lower in the simvastatin groups compared to the control group (P<0.05). The 0.25% simvastatin group showed the largest reduction in infarct size (P<0.05 vs control). The 0.5% and 1% simvastatin groups showed a moderate reduction in infarct size (P<0.05 vs control).

Conclusion: Simvastatin, at a dose of 0.25%, significantly reduces infarct size in normocholesterolemic rats.

1099-30
Simvastatin Restores Endothelial Nitric Oxide Mediated Vasorelaxation in Large Arteries After Myocardial Infarction
Kathryn Bates, Steven Goodman, Mohamed Gaballa, SAVAHCS, Tuscon, Arizona.

Congestive heart failure (CHF) after myocardial infarction (MI) is associated with diminished endothelial nitric oxide (NO)-mediated vasorelaxation. The 3-hydroxy-3-methylglutaryl CoA reductase inhibitors have been shown to modulate vascular tone, independent of their effect on lipid lowering. We hypothesized that simvastatin restores NO-dependent vasorelaxation after MI, produced by coronary artery ligation, via upregulation of endothelial nitric oxide synthase (eNOS). We found that compared to normal arterial tissue incubated with culture medium only, incubation with 0.1 mM of simvastatin for 24 hours enhanced acetylcholine (ACH)-mediated vasorelaxation (P<0.05) with peak relaxation at 0.1% (60±11%) as compared to 33.7±7.8% (P<0.05). Compared to untreated rats, simvastatin increased eNOS protein content by 200% (82.0±14.4% vs 21.6±7.9%, P<0.05). In endothelial cells in culture, 10 mM and 20 mM of simvastatin increased eNOS levels by 114.7±3.9% and 210.2±17.0% (P<0.05), respectively. In CHF rats treated by oral gavage with simvastatin (20 mg/kg/day) for three weeks, mean arterial pressure (105±5 vs 96±6.5 mmHg) and LV dP/dt (4298±672 vs 4091±1064 mmHg/sec; N=8) were decreased (P<0.05). Treatment of CHF rats with simvastatin reduced LV mass (P<0.05) with peak relaxation at 0.1% (65±11%) as compared to 33.7±7.8% (P<0.05). The ACH-mediated vasorelaxation with a maximal response of 66.8±5.7% and 32.6±6.8%, N=7, respectively. Inhibition of NO generation using 100 mM N(G)-nitro-L-arginine methyl ester (L-NAME) abolished the ACH-induced vasorelaxation in all rats. Our data suggest that simvastatin restores NO-dependent vasorelaxation in large arteries after MI.

1099-31
Inhibitory Effects of the Novel Antagonist of Both Gi- and Gq/11 Proteins on Formation of Coronary Thromboemboli Caused by an Inhibition of Adenosine Receptors During Coronary Hypoperfusion in Dogs
Hiroshi Asamura, Masafumi Kikakaze, Koichi Node, Shoji Sanada, Hisakazu Seki, Takahisa Masanori Akiyaka, Tetsuo Minamino, Michihiko Tada, Masatsugu Hori, Osaka University Graduate School of Medicine, Suita, Japan, National Cardiovascular Center, Suita, Japan.

Background: Platelet glycoprotein (GP) IIb/IIa is a membrane receptor for fibrinogen and von Willebrand factor, which plays an important role in the formation of platelet aggregates resulting in thrombus. We have previously reported that endogenous adenosine inhibits P-selectin-dependent formation of coronary thromboemboli during hypoperfusion in dogs, we examined whether the GP IIb/IIa receptor antagonist, a new antagonist of both Gi- and Gq/11 proteins, can reduce thromboembolism.

Methods: In the hypoperfusion of the presence of 8-Br-cyclic GMP, the GP IIb/IIa receptor antagonist, was infused during coronary hypoperfusion (18.2 ml/100g/min, 20 % of the control), coronary blood flow decreased gradually and approached almost zero (3.4 ml/ 100g/min) 20 min after its administration. Histological examination revealed thromboemboli in the small coronary vessels. During hypoperfusion in the presence of 8-Br-cyclic GMP, the GP IIb/IIa receptor antagonist attenuated the reduction in coronary blood flow (P<0.05, p<0.05), and the formation of thromboemboli, and improved contractile function (fractional shortening, -7.1 to -1.0 %, p<0.05), and metabolic dysfunction (lactate extraction ratio, -70 to -54 %, p<0.05) of the myocardium.

Conclusion: Thus, we conclude that a novel antagonist of both GP IIb/IIa and vitronectin receptors attenuates platelet aggregation and the worsening of the severity of myocardial ischemia caused by the inhibition of adenosine receptors. There appears the distinct difference between the signals of adenosine receptors and GP IIb/IIa or vitronectin receptors in platelet or coronary endothelial cells.

1099-32
Early Microvascular Reflow Status After Infarct Perfusion Determines Outcome of Postinfarction Remodeling Independent of Myocardial Salvage

Background: Prompt opening of the infarct related artery is the treatment of choice for acute myocardial infarction (MI). A beneficial effect on left ventricular (LV) function often results even in patients in which little myocardium is salvage. We hypothesized that this phenomenon is dependent on adequate early microvascular perfusion.

Methods: Five sheep were subjected to 1 hour of ischemia followed by reperfusion (group 1). Six sheep underwent 6 hours of ischemia followed by reperfusion (group 2) and 7 sheep were infarcted without reperfusion (control). The ischemic region in all animals was 23% of the LV mass at the apex. Microvascular reflow was studied using LV long axis real time contrast echocardiography and microsphere injection during ischemia and after coronary reperfusion and at 2, 4, and 8 weeks. Echocardiography was used to assess changes in LV region and regional function throughout the study period. RESULTS: During coronary occlusion all animals demonstrated complete microvascular ischemia. After 30 minutes of coronary reperfusion, group 1 animals demonstrated microvascular reflow of the area at risk while group 2 animals demonstrated complete transmural no-reflow. At 2 weeks, both groups demonstrated complete return of transmural microvascular blood flow that persisted throughout the remainder of study. Control animals never achieved reflow in the infarct region. The area at risk remained akinetic in all groups throughout the study. At week 8 LV end-systolic volume increased by 134% in control animals and by 114% in group 2 but was unchanged in group 1. CONCLUSION: Early microvascular reflow dramatically improves post-infarction LV remodeling independent of myocardial salvage.

1099-47
Impaired Healing in Factor XIII KO Mice After Myocardial Infarction Assessed by Magnetic Resonance Imaging

Background: Clotting factor XIII has been shown to have a role in wound healing. We therefore studied healing after coronary artery ligation in FXIII KO and wild type mice.

Methods: Magnetic Resonance Imaging was done 2 days after MI in a T2-Biospec using an ECG-triggered Cine-FASH-sequence: slice thickness 1 mm, echo-time 1.2 ms, resolution 230 x230 x 230 mm. MI-size, left and right ventricular (LV+RV) volumes, cardiac output (CO), wall thickness (WT), and -thickening (SW) and LV mass were determined. To minimize bleeding from the thoracotomy wound, FXIII-free fibrin glue was applied.

Results and Conclusion: All FXIII KO mice died within 3 to 5 days after MI whereas wild type mice, that survived surgery, did not die. Dilatation after MI was not different between groups, but systolic global and regional function was impaired when compared to wildtype. Unchanged RV volumes suggest that hemorrhage from thoracotomy was not
profound. Histology revealed rupture of the infarct area with little inflammatory response to ischemia. These data show that FXIII may have a major role also in healing processes post myocardial infarction.

Conclusion: STRes is related to both TFG and TMPG. As a marker of successful fibrinolysis, STRes appears to integrate both epicardial and myocardial perfusion, and this may help explain its ability to predict clinical outcome.

Background: Complete ST-segment elevation resolution at 90 and 180 minutes after reperfusion therapy identifies patients with a low mortality risk. This study analyzed the extent of 60-minute ST-segment resolution after lythmic therapy from the GUSTO V-RESTART Study.

Methods: This prospective study included 1764 patients with ST-segment elevation MI. A baseline and 60-minute ECG was analyzed by a core lab to categorize 4 groups: complete resolution (>70%), partial resolution (<70%-30%), no resolution (<30%) and worsening ST-segment.

Results: The results are summarized in the table.

<table>
<thead>
<tr>
<th>N patients</th>
<th>Population (%)</th>
<th>30-Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>N (%)</td>
<td>P</td>
</tr>
<tr>
<td>Complete Res</td>
<td>556</td>
<td>500</td>
</tr>
<tr>
<td>Partial Res</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>No Res</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>Worsening ST</td>
<td>33</td>
<td>63</td>
</tr>
</tbody>
</table>

* Mantel-Haenszel p < 0.001

Conclusion: STRes may be a useful marker for the prediction of LV function and LV remodeling in Acute Myocardial Infarction.

Background: It has been reported that a simple angiographic method, the TIMI myocardial perfusion grade (TMPG) could assess viability of myocardium in patients with acute myocardial infarction (AMI) after thrombolytic therapy. This study was designed to evaluate the value of TMP grade itself and correlation with coronary flow reserve (CFR) in the prediction of LV ventricular volume and functional change after percutaneous coronary intervention (PCI) in AMI. Methods: To avoid the effect of epicardial stenosis, we measured CFR and TMP grade after successful elective intervention (residual diameter stenosis <30%, TIMI flow >2) in 83 patients (mean age 55±1 years, 18 female) with AMI within 7 days after symptom onset. To evaluate the area of ischemic injury as a whole, CFR measured at distal segment adjacent to angioplasty site by Doppler wire, TMP grade 0 was defined as no apparent tissue-level perfusion in the distribution of the culprit artery, TMP grade 1 indicates presence of myocardial blush but no clearance from the microvasculature; TMP grade 2 indicates blush clears slowly; and TMP grade 3 indicates that blush begins to clear during washout. Left ventricular end diastolic volume index(LVEDVI), left ventricular systolic volume index(LVESVI), ejection fraction(LVEF), and left ventricular regional wall motion score index(LRVWMSI) were assessed by echocardiography before and after angioplasty (mean 9±2 months). Results: After PCI, angiographic TMP grade correlated well with CFR using Doppler wire (r=0.717, p<0.001). Post-angioplasty TMP grade was significantly correlated to the change of LVEDVI (r=0.452, p<0.001), LVESVI (r=0.435, p<0.001), LVEF (r=0.281, p<0.01) and LRVWMSI (r=0.328, p=0.002). Conclusion: The TMP grade, a simple angiographic method, measured after relief of epicardial stenosis, may be useful as a predictor of LV volume and functional change in myocardial infarction. It might simply replace CFR for assessment of myocardial viability in AMI.