1177-135 **Lipid-Lowering Therapy With Pravastatin Reduces Coronary Plaque Volume: Role of High-Density Lipoprotein Cholesterol Containing Apolipoprotein A-1**

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Background: Atheroprotective high-density lipoprotein cholesterol (HDL-C) and its major structural protein, apolipoprotein A1 (apoA1) may inhibit plaque expansion by mediating reverse cholesterol transport. However, whether statin-induced increased the level of HDL-C affects the volume of coronary atherosclerotic plaque is not fully understood. Therefore we investigated the relationship between HDL-C levels and plaque appearances with statin therapy.
Methods and Results: 50 patients undergoing percutaneous coronary intervention (PCI) were studied with intravascular ultrasound (IVUS) after PCI and at a 6-month follow-up period of treatment with pravastatin. In non-dilated matched coronary segments, volumetric analyses were performed with 3-dimensional (3-D) IVUS system. After 6-months therapy, pravastatin significantly reduced plasma levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C), and oxidized-LDL by 24, 25, and 15%, respectively, and increased HDL-C and apoA1 levels by 10.2 and 9.2% ($p<0.001$ vs. baseline levels for all variables). 3D-IVUS examination revealed that plaque volume was significantly decreased (baseline vs. 6 months: 48.4±30.3 vs. 39.0±26.2mm^3, $p<0.0001$), whereas no significant differences in lumen and vessel volume are observed (64.9±39.7 vs. 69.0±37.1mm^3, $p=0.10$; 113.4±63.7 vs. 108.0±57.4mm^3, $p=0.13$). Furthermore, % changes in plaque volume were inversely correlated with those in plasma levels of HDL-C ($r=-0.54$, $p<0.0001$) and apoA1 ($r=-0.43$, $p<0.05$), but not with those in the levels of total cholesterol ($r=0.23$, $p=0.12$) and LDL-C ($r=0.24$, $p=0.25$), and oxidized-LDL ($r=0.12$, $p=0.35$).
Conclusions: Our results demonstrated that pravastatin-induced increased the levels of HDL-C and apoA1 were associated with a comparable, significant reduction in the amount of plaque volume. We suggest that pravastatin therapy even at a 6-month follow up may enhance the role of HDL-C containing apoA-1 in reverse cholesterol transport.

1177-136 **Statins Inhibit Calcification of Aortic Valve Interstitial Cells**

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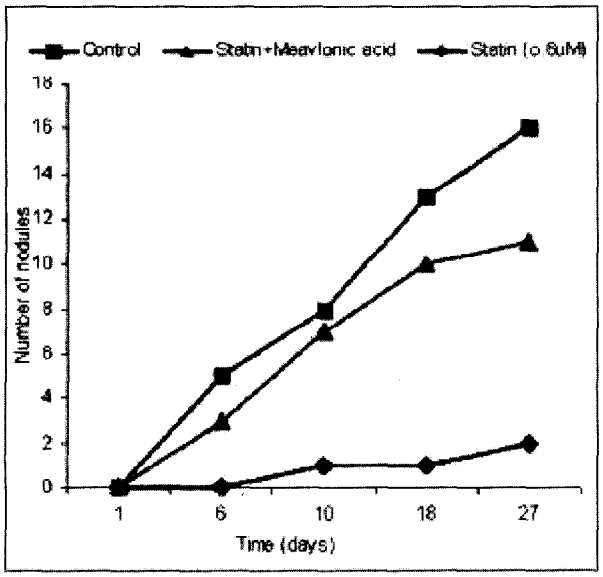
Background: Retrospective clinical data indicate that HMG-CoA reductase inhibitors (statins) limit calcification in atherosclerotic coronary arteries and aortic valves. However the mechanism of action of statins in prevention of calcification is unknown.**Methods:** We evaluated the effects of statins on cardiac valve calcification *in vitro* using a previously validated cell culture model of valve calcification. Porcine aortic valve interstitial cells were incubated in varying concentrations of simvastatin and pravastatin (0.1, 0.3, and 0.6 μM) to determine if these drugs inhibit calcific nodule formation. Mevalonate (1.0 μM), metabolite of HMG-CoA reductase, was given to determine if the mechanism of inhibition involves the cholesterol biosynthetic pathway. Alkaline phosphatase activity, a marker of osteoblastic differentiation, was measured in cell lysates. **Results:** Simvastatin and pravastatin inhibited calcific nodule formation in a dose-dependent manner and there was a partial reversal of effect with mevalonate (Figure). Alkaline phosphatase activity was reduced with statins, also in a dose-dependent manner. **Conclusions:** Statins drugs inhibit valve calcification partially through inhibition of cholesterol biosynthetic pathway and alkaline phosphatase. These data provide further evidence that statins will prove useful therapy for calcific cardiac valve disease.



POSTER SESSION

1178 Mechanisms of Angiogenesis and Cell Therapies

Tuesday, April 01, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1178-137 **Acute Dynamic Exercise Increases Circulating Endothelial Progenitor Cells**

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Introduction: Exercise exerts a pro-angiogenic effect by mechanisms which are not fully understood. Circulating endothelial progenitor cells (EPCs) have been shown to participate in formation of new blood vessels. Since exercise acutely increases circulating lymphocyte number, we investigated whether exercise may act in a pro-angiogenic manner via increases in circulating EPCs.
Methods: Subjects without evidence of coronary artery disease were exercised on a treadmill or bicycle to a mean of 92±2 % of their predicted maximum heart rate. Blood samples were obtained before and immediately after exercise. Whole blood was analyzed for the stem / progenitor cell marker AC133 (n=6) by flow cytometry. EPCs were isolated as previously described by plating the mononuclear cell fraction on a fibronectin-coated plate in EGM-2-MV media (Clonetics) and discarding non-adherent cells (n=9). Adherent EPCs were counted, and conditioned media was collected on a subset of the cell samples (n=5). The conditioned media was assayed for the angiogenic hepatocyte growth factor (HGF), which is not present in EGM-2-MV media. Statistical analysis was performed using a paired t-test comparing pre- and post-exercise values.
Results: Dynamic exercise significantly increased the number of circulating AC133+ cells from 1307±332 cells/ml to 2272±511 cells/ml of blood ($p=0.022$). Exercise also increased the number of adherent EPCs isolated from peripheral blood, by plating and culturing, from 7694±2586 cells/ml of blood to 19656±5716 cells/ml ($p=0.006$). The adherent cells were equipotent in their ability to secrete HGF before and after exercise (44.2±13.3 ng/10^6 cells vs 35.1 ±7.0 ng/10^6 cells, p=not significant).
Conclusions: Exercise can acutely increase the number of circulating cells which express the stem / progenitor cell marker AC133 as well as the EPC cells isolated by plating and culturing. The latter cells also secrete the angiogenic growth factor HGF, which may in turn mediate some of their angiogenic effects. These findings suggest a novel means by which exercise may be cardioprotective. Furthermore, these results may also contribute to our understanding of stem and progenitor cell mobilization.

1178-138 **Intramyocardial Delivery of Bone Marrow-Derived Mesenchymal Stem Cells Improves Myocardial Contractility in a Chronic Ischemic Model**

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Background: Mesemnchymal stem cell (MSC) administration has shown promising results for treatment of LV diysfunction in the acute MI model. We sought to evaluate the safety and efficacy of intramyocardial delivery of allogeneic MSCs in a chronic ischemia model..
Methods: Allogeneic MSCs of dogs were cultured, expanded in vitro. Twelve healthy adult dogs were submitted to ameroid constrictor implant (proximal LAD) with diagonal branch ligation. Surgical intramyocardial injections (IMI) of 100x10^6 MSCs (10 ml) were distributed over 20 sites in the anterior wall in 6 animals(MSC group). The control group (n=6) received saline injections in the same manner. Left coronary angiography was performed immediately before IMI and 30 days after to certify ameroid constriction and assess anatomy. Echo was performed at baseline before ameroid implant and at 30 days (immediately before IMI) and at 30 days after IMI to assess LV ejection fraction (EF).
Results: IMIs were performed without complicationss in all animals. Coronary angiography was unchanged at 30 and 60 days. Serial LVEF in the treatment and control groups are shown in table 1(a vs. b $p=0.6$; c vs.d $p=0.5$; e vs. f $p= 0.02$).
Conclusion: These results suggest that MSC injection did not result in a marked inflammatory response when compared to controls.Improvement in LV function was shown in the MSC group as compared to controls.

Comparison of LVEF in MSC vs. Control group

	Baseline	30 d after ameroid / before IMI	60 d after ameroid / 30 d after IMI
MSCs (n=6)	55 ± 7 (a)	43± 10 (c)	48±7 (e)
Control (n=6)	58 ± 8 (b)	37± 13 (d)	28 ± 14 (f)

1178-139 **Transepicardial Autologous Bone Marrow Transplantation in a Porcine Nonreperfused Myocardial Infarction Model: Angiogenesis or Myogenesis?**

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