measurements of luminal area, narrowing by neointima (including residual thrombus, hematoma, and fibrmmuscular hyperplasia) and total vessel size (area bounded by external elastic lamina) were performed by investigators blinded to segment identity;

	Time					
	0 hr	1 hr	6 hr	2 wk	3 wk	4 wk
Lumen (mm^2)	3.1 ± 0.4	3.2 ± 0.5	3.2 ± 0.4	3.2 ± 0.5	2.1 ± 0.2	1.9 ± 0.1
% Stenosis	–	22 ± 4	16 ± 4	32 ± 7	53 ± 7	61 ± 4
% Thrombosis	–	22 ± 4	18 ± 4	19 ± 5	16 ± 3	19 ± 2
% Hyperplasia	–	–	–	13 ± 4	37 ± 5	42 ± 4
Vessel Size (mm^2)	4.8 ± 0.4	8.9 ± 0.4	7.4 ± 0.5	7.2 ± 0.4	6.9 ± 0.5	7.0 ± 0.5

Mean luminal area decreased ($p < 0.001$), % stenosis by neointimal thickening increased ($p < 0.001$), and fibromuscular hyperplasia was the predominant contributor to luminal narrowing at 4 wks. Vessel size increased acutely after BA, but did not change significantly thereafter. Thrombosis (residual thrombus and hematoma) is the principal constituent of early narrowing and remains a significant but a smaller component in late narrowing. Thus, increased neointimal thickening by fibromuscular hyperplasia and thrombosis rather than change in arterial size are the predominant mechanisms responsible for late luminal narrowing in this model.

8:45

781-2 Efficient Reduction of Neointimal Hyperplasia in Double Injured Rabbit Carotid Arteries by Cholesterol-Conjugated Antisense *C-myc* Oligonucleotides

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In vitro data suggests that conjugation of antisense oligonucleotides (ODNs) with cholesterol may increase both oligomer transfection level in vascular smooth muscle cells (VSMCs) and inhibition of VSMCs proliferation. The purpose of this study was to evaluate the effect of transfected antisense and sense *c-myc* ODNs either alone or conjugated with cholesterol on neointimal hyperplasia formation in double injured rabbit carotid arteries. A total of 15 New Zealand white rabbit carotid arteries were injured with a 2.5 mm balloon catheter serially inflated for 1 minute to 4 (gentle traction), 6, 8 and 10 atm allowing 45 seconds between inflations. Two weeks later, a second injury was imposed and followed by arterial transfection (30 min) in a 1 cm portion with 80 μM (100 μL of volume) of either *c-myc* antisense alone (ODN-A) or conjugated with cholesterol (ODN-AC), *c-myc* sense (ODN-S) alone or conjugated with cholesterol (ODN-SC), or with 100 μL of NaCl 0.9% as a control. Ratio of intimal/medial area was evaluated on histological sections derived from transfected arteries two weeks following the second injury and transfection. Maximal ratio of intimal/medial area was observed in control group (1.44 ± 0.06), ODN-S group (1.50 ± 0.10, *P* not significant vs. control) and ODN-SC group (1.35 ± 0.08, *P* not significant vs. control). Although ODN-A reduced the ratio of intimal/medial area to 1.08 ± 0.06 ($P < 0.05$ vs. ODN-S and control), ODN-AC was far more effective, the ratio beeing at 0.43 ± 0.06 ($P < 0.05$ vs. ODN-SC and control). Thus, when injured arteries were transfected with ODN-A, neointimal hyperplasia was sequence-specifically reduced by 26.50 ± 1.50%, and by 69.10 ± 1.00% when transfected with ODN-AC ($P < 0.05$ vs. ODN-A). Conclusion: *C-myc* antisense ODNs sequence-specifically reduce neointimal hyperplasia after angioplasty, their effect beeing significantly increased (2.6-fold) by conjugation with cholesterol.

9:00

781-3 Adenoviral Transduction of Endothelial Cell Nitric Oxide Synthase Gene Yielding Functional Enzymatic Activity in Porcine Coronary Arteries

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Recombinant expression of an endothelial cell nitric oxide synthase gene (ecNOS) may have profound effects on vasomotor function, cellular proliferation, and platelet adhesion in diseased coronary arteries. Using a highly efficient replication defective adenoviral vector for ecNOS (AD-NOS), we studied the effects of gene transfer on porcine coronary arteries *ex vivo*. Coronary artery segments were isolated and incubated in AD-NOS or control virus AD-LacZ (6.5×10^9 pfu/ml) for 30 minutes. 48 hours after viral transduction, the arteries were analyzed for recombinant ecNOS expression and function. Histochemical staining with a monoclonal antibody for ecNOS localized recombinant protein production to > 10% of the adventitial cells in the AD-NOS transfected arteries with only endogenous ecNOS expression confirmed in the endothelium of the AD-LacZ arteries. Artery segments (n = 8) were incubated for 2 h in Kreb's buffer containing 1-arginine (10^{-4} M) and calcium ionophore (10^{-6} M) which was analyzed for nitrite concentration with a spectrofluorometrc assay. Total nitrite production was significantly increased in AD-NOS arteries (517 ± 110 nM/ng tissue) compared to AD-LacZ arteries (126 ± 84 nM/ng tissue) $p < 0.05$. Artery rings (n = 8) were suspended for isometric tension recording. At an optimal point of length tension curve, contraction with 20 mM KCL was achieved in the control AD-LacZ arteries but not in the AD-NOS arteries.

Conclusion: These studies demonstrate the adenoviral transduction of a ecNOS gene into coronary arteries yielding recombinant protein production and functional enzymatic activity leading to alteration in vasomotor function.

9:15

781-4 Matrix Metalloproteinase Inhibition Reduces Collagen Synthesis and Content After Arterial Injury

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We have previously shown that collagen synthesis and degradation are significantly increased early after balloon angioplasty (BA). A 72 kDA metalloproteinase (MMP-2) is also induced early following BA. To assess the role of MMPs in mediating collagen turnover, a nonspecific MMP inhibitor, GM6001 (Glycomed Inc, Alameda, CA) was studied in 14 NZW normolipemic rabbits in a double injury model. Rabbits were randomized to receive daily GM6001 (100 mg/kg/day) or placebo. One week after BA #2, ^{14}C-proline (0.11 mCi/kg) was infused 24 hours prior to sacrifice. The BA and contralateral control (no BA) iliac arteries were extracted with 0.5 M acetic acid. The supernatant was passed through a 30 kDa cutoff filter, which separates collagen fragments from intact collagen. Newly synthesized intact collagen and its breakdown products were measured by ^{14}C-hydroxyproline (dpm, mean ± SD) and total vessel wall collagen content (μg) by a colorimetric assay.

		BA	Control	P value
Placebo	Collagen Synthesis	1199 ± 380*	300 ± 154	<0.0002
	Collagen Breakdown	254 ± 146	106 ± 28	<0.02
	Total Collagen	750 ± 143+	354 ± 116	<0.0002
GM6001	Collagen Synthesis	683 ± 278	201 ± 36	<0.003
	Collagen Breakdown	133 ± 51	82 ± 15	ns
	Total Collagen	500 ± 78	322 ± 51	<0.01

*$p < 0.04$ vs GM6001, +$p < 0.004$ vs GM6001

The significant reductions (> 40%) in collagen synthesis and content, and inhibition of collagen breakdown suggest an integral role of MMPs in collagen turnover after BA.

9:30

781-5 Biostimulation of Wound Healing Following Balloon Injury With Red Laser Light in the Atherosclerotic Rabbit

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Restenosis following balloon angioplasty may be attributed to the inability of the vascular endothelium to regenerate and cover the denuded area at the site of arterial injury. We evaluated the impact of very low power red light (632 nm, 1.1 J/cm^2) endothelium regeneration in nonatherosclerotic iliac arteries following balloon angioplasty in 10 New Zealand White rabbits. Vessels were harvested 10 days after treatment and stained with Evans blue dye and fixed for scanning electron microscopy (SEM). Circumferential regeneration of endothelium was increased compared to control (85 ± 5% vs 9 ± 2%, $p < 0.01$). SEM confirmed repopulation of endothelium in the injured area. We next studied the long-term impact of red light on restenosis. Atherosclerotic rabbit abdominal aortas (n = 12/gp) were subjected to: balloon inflation, and balloon inflation plus laser illumination for 3 min. QCA analysis showed that there was no difference in acute gain (0.71 ± 0.06 mm vs 0.61 ± 0.06, $p > 0.05$). However late loss was significantly reduced to 0.14 ± 0.04 mm in the balloon plus laser group compared with 0.91 ± 0.05 mm in the balloon group. Planimetric and histologic analysis of harvested arteries revealed that the laser plus balloon treatment prevented the adverse balloon-induced changes including intimal smooth muscle cell proliferation. We conclude that very low power red light stimulates the wound healing process following balloon angioplasty, increasing the rate and completeness of endothelial regeneration which results in a decrease of late loss and rate of restenosis.