1005-5 Endothelial Shear Stress Identified In Vivo Within the Stent Is Related to In-Stent Restenosis and Remodeling of Stented Coronary Arteries

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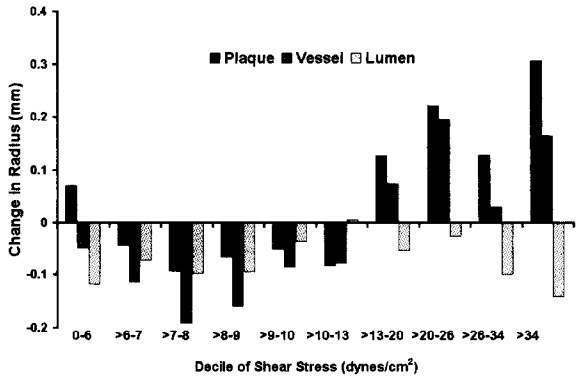
Background: Endothelial shear stress (ESS) is a potent stimulus for regulating endothelial cell activation and the signals for vascular smooth muscle cell proliferation. However, the relationship of ESS to the subsequent development of instent restenosis in-vivo has not been studied previously. The purpose of this study was to relate ESS measured at baseline to instent restenosis. Methods: We studied 3 patients after coronary artery stenting at baseline and 6 months. The 3-D anatomy of the stented segment was determined using intracoronary ultrasound, biplane angiography, and coronary flow measurements. The lumen was reassembled in accurate 3-D space; local ESS was calculated using computational fluid dynamics. Outer vessel dimensions (external elastic lamina [EEL]) and the plaque (difference between EEL and the lumen) were similarly reconstructed. Changes in the artery at 6 mos were assessed by general linear regression accounting for repeated measurements. Results: Increasing ESS was associated with plaque progression and positive remodeling (all p<0.01). Lumen narrowing was least in the middle (physiological) ranges of ESS (9-26 dyne/cm2) and greatest with low and high shear stress. Conclusions: These results show that stented coronary arteries respond to ESS within 6 mos. These changes are important in restenosis and arterial remodeling. This technique could be used to determine whether restenosis can be prevented by interventions that are deployed to yield ESS in the physiological range.



1005-6 A Novel Preparation of Systemic Paclitaxel Reduces In-Stent Restenosis in the Rabbit

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Background: Local delivery of paclitaxel (PXL) from drug-coated stents reduces in-stent restenosis at 28 days in the rabbit. A saline-reconstitutable systemic intravascular preparation of PXL would provide uniform drug delivery at the stent treatment site and allow for repetitive dosing. However currently available PXL is dissolved in toxic excipients such as cremophor and ethanol, which cause hypersensitivity. American BioScience has recently developed an albumin-based nanoparticle (n) formulation of PXL (nPXL), which is free of toxic solvents. Methods: 16 NZW rabbits underwent bilateral iliac artery stenting followed by an infusion of 2.5, 3.5, or 5.0 mg/kg nPXL through a catheter placed proximal to the stents or no treatment (control). Results: At 28 days, nPXL resulted in a dose-dependent reduction in neointima, accompanied by a concomitant increase in PMN on the intimal surface (table). Cellular proliferation was significantly greater in the 5.0 nPXL mg/kg group vs. control (1.5% vs 0.87%, p<0.02). nPXL-treated arteries demonstrated 50-80% endothelialization of the stent surface. Blood leukocyte count remained within normal limits throughout the experiment. Conclusion: A single injection of nPXL inhibits in-stent neointimal growth, similar to stent-based local delivery. Systemic nPXL offers a simplified drug-delivery regimen and allows for repeat dosing which may produce sustained neointimal suppression. Long-term (3 month) studies are ongoing with single and repeat dosing.

PMN = Polymorphonuclear Leukocytes. Values are mean±SEM

	Neointimal Thickness (mm)	Neointimal Area (mm^2)	% Stenosis	Total Surface PMN
Control	0.128±0.01	1.58±0.07	25.9±1.1	10.6±6.0
2.5 mg/kg	0.104±0.01	1.30±0.08*	23.0±1.5	21.3±12
3.5 mg/kg	0.086±0.01*	1.22±0.07*	20.9±1.3*	23.9±11
5.0 mg/kg	0.087±0.01*	1.20±0.06*	20.1±0.89*	36.8±16
* P vs. control	≤ 0.004	≤ 0.02	0.01	NS

1005-7 Pathological and Clinical Outcome of Long-Term Intracoronary Stenting: Is Its Efficacy Permanent?

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Although coronary stenting effectively reduces clinical cardiac events for as long as 3 years, longer-term efficacy has not yet been established. We reported that angiographic regression of luminal narrowing occurred 6 months to 3 years after Palmaz-Schatz (PS) stenting. However after 4 or more years lesions progressed gradually and late restenosis was observed in 28.7% of 122 lesions PS-stented within the past 10 years; in 11 lesions the stenosis was extremely severe or totally occluded. To have a deeper insight of these phenomena, 31 coronary artery specimens obtained from 27 necropsied patients expiring 1 to 7 years after PS stenting, were examined for histopathological and immunohistochemical studies. Chronic inflammatory cell infiltration, that included T lymphocytes (T cells), macrophages (MPs) and multinucleated giant ce11s was observed around the stent struts in the great majority even in absence of restenosis. Lesions that had regressed within a year after PS stenting, featured spindle-shaped smooth muscle cells (SMCs) along the luminal surface, completely covered by regenerated endothelial cells; the interce11ular spaces contained dense co11agenous tissue, and inflammatory responses were still evident around the struts. In the non-stenotic neointima after more than 3 years post-PS stenting, the SMCs had become atrophic and abundant proliferation of co11agen fibers was evident instead. Immunohistochemically, the presence of a small number of helper/inducer T cells and slight MPs infiltration were evident adjacent to the stent struts. In arteries stented more than 5 years before, prominent infiltration by lipid-laden MPs was observed around the struts which had co11agen-degrading matrix meta11oproteinases immunoreactivity. In 2 of these arteries, the luminal surface of the sites where the PS-stent was located was focally eroded and non-occlusive thrombi consisting of platelets were observed at these portions.
These findings suggest that the metal of PS stent evokes a remarkable foreign body inflammatory reaction. The residual chronic inflammatory cells around the struts may cause new and indolent atherosclerotic changes that induce plaque vulnerability.

1005-8 Small Proximal Vessels Are Not Always Small: An Intravascular Ultrasound Study

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Background: Angiographically small vessels may be large when evaluated by intravascular ultrasound (IVUS).
Methods: Pre-intervention IVUS was performed in 177 angiographically small vessels (<3.0 mm by QCA) in the proximal segment of the major coronary arteries. The lesions were divided into two groups according to the difference in reference vessel size between QCA and IVUS [distal reference minimal vessel diameter (VD)]: 1) VD difference (IVUS - QCA) ≥0.5 mm (n=119) and 2) VD difference <0.5 mm (n=58). IVUS-guided balloon angioplasty or stenting was performed in the lesions.
Results: In multivariate analysis, LAD or RCA lesion (p=0.05) and reference vessel diameter by QCA (p=0.07) were predictors of large difference in reference vessel size.
Conclusion: In angiographically small major proximal vessels, reference vessel size is underestimated in 67% of the lesions. In those vessels, IVUS-guided intervention should be performed to select appropriate (larger) balloon or stent sizes in order to optimize final lumen dimensions.

	Difference <0.5	Difference ≥0.5	p value
Diabetes mellitus (%)	27	36	0.3
LAD (%)	51	66	0.03
Balloon/vessel ratio	1.20±0.18	1.40±0.23	<0.01
QCA			
Lesion length (mm)	12.9±6.2	11.6±7.7	0.3
Reference diam (mm)	2.71±0.27	2.56±0.35	<0.01
Pre-MLD (mm)	0.81±0.40	0.86±0.36	0.4
Final MLD (mm)	2.74±0.50	3.02±0.52	<0.01
IVUS			
Prox. minimal VD (mm)	3.4±0.6	3.9±0.5	<0.01
Dist. minimal VD (mm)	2.9±0.4	3.7±0.6	<0.01
Pre-lumen CSA at lesion (mm^2)	2.2±1.1	2.4±1.2	0.4
Final lumen CSA (mm^2)	5.9±1.4	7.0±1.7	<0.01
Perforation (%)	1.7	0	0.2
1-month MACE (%)	1.7	0	0.2