results from a planar symmetric graft. Both models exhibited counter-rotating vortices in the distal and proximal outflow segments. However, the asymmetric model had vortices with different sizes. It also had higher radial wall shear stress in the vicinity of the anastomosis. In addition to the axial movement of the stagnation line seen in planar symmetric anastomoses, radial movement was observed in the asymmetric model. The results suggest that differences between magnitudes of shear in symmetric and asymmetric grafts are not large, but that the locations of near-wall flow phenomena can differ substantially. This may be a source of error in studies that correlate **in vivo** intimal hyperplasia with **in vitro** results from symmetric flow models.

6.3P Circulation

T6.136

Human Coronary Artery Endothelial Cell Migration on a 3D, Smooth Muscle Cell-Seeded Collagen Substrate in the Presence of Flow

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In the present study, a system to quantify the migration patterns of human endothelial cells on a 3D model of the blood vessel wall was developed. The 3D model of the blood vessel wall was formed by embedding human smooth muscle cells (HASMC) in a type I collagen matrix. Fluorescently labeled human coronary artery endothelial cells (HCAEC) were seeded onto the collagen substrate and the migration characteristics of the random motility coefficient, the displacement in the direction of fluid flow and the average distance from the initial position were quantified over a 24 hour period while exposing the HCAECs to either 2.5 or 10 dynes/cm^2 shear stress. For comparison, HCAEC migration was also quantified on collagen-coated glass. The data from these experiments showed that HCAEC seeded onto the 3D collagen substrate exhibited a higher random motility coefficient and an increased average distance from the initial position over 24 hours when compared to HCAEC seeded onto collagen-coated glass. Furthermore, increasing the shear stress from 2.5 to 10 dynes/cm^2 appears to have the primary effect of directing HCAEC migration in the direction of the flow, but does not appear to increase the average distance from the initial position.

T6.137

Mechanical Force Modulates Beta-Catenin Intracellular Signaling Activity

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Beta-catenin is a key signal transduction protein in the wnt signaling pathway that controls embryonic body patterning and cancer. Elevated levels of Beta-catenin protein, and resulting signaling activity, have been identified in human colon and breast carcinoma cells. The transformation of a benign tumor to a metastatic state involves cell invasion into the bloodstream or lymphatic system. One of the most significant environmental changes in this progression is exposure to shear stress in the circulation. In the present study the effect of shear stress, on Betacatenin signaling activity in colon and breast carcinoma cells was examined. Cells were exposed to 0-35 dyn/cm2 of shear stress, imposed by laminar flow in a parallel plate flow chamber, for 0, 3, 6, and 12 hours. Betacatenin signaling activity decreased as shear stress was increased from 0, 15, 26, and 35 dyn/cm2. For a given shear stress, Beta-catenin signaling activity decreased as exposure to shear flow increased in time from 0, 3, 6, and 12 hours. Transfection of cells with dominant-negative kinases (IKKs) reversed the shear stress-induced decrease in beta-catenin signaling activity. These results indicate that shear force modulates beta-catenin signaling activity through IKK in a temporal manner.

T6.138

Breaking Correlation between Kinetic Parameters and Kinematics in Indicator Dilution using Moments and Multiple Flows

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The multiple indicator dilution (MID) method involves injection of a reference (measures vascular transit) and test (measures some cellular function) indicators into an organ's artery followed by venous sampling. Indicator kinetics are interpreted using linear partial differential equations and include both dispersive kinematics (capillary & conducting vessel transit time distributions) and kinetics of indicator-tissue interactions (membrane transport, metabolism). However, correlations between MID kinetic parameter estimates and kinematics undermines robust parameter estimation. Recent numerical studies (**Ann. Biomed. Eng.**, 24:33751, 1996) proposed using techniques, such as injections at multiple flows, to break these correlations. Using statistical moment analysis, we provide a mathematical framework that analytically supports the observation that MID data at different organ flows separate the impact of kinetics from kinematics. The analysis also reveals multiple flows, independent of full transit time information, potentially yields significant kinetic parameter information. E.g., using three moments across a fourfold range of PS/flow reveals Sangren-Sheppard MID curves contain sufficient information to obtain PS without full knowledge of transit time distributions. Supported by HL24349, Falk Trust, & Department of Veterans Affairs.

T6.139

The Shear Stress-induced c-fos Promoter Activation Is Regulated by Rho GTPases and Intracellular Calcium

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The shear stress resulting from blood flow modulates a variety of cellular processes in vascular endothelial cells (ECs). In this study, we explored the molecular basis of c-fos promoter activation in ECs in response to shear stress, with a special emphasis on the roles of Rho family small GTPases Rho, Cdc42, and Rac. Bovine aortic ECs (BAECs) were co-transfected with plasmids that encode a luciferease reporter gene controlled by c-fos promoter and the dominant-negative mutants of Rho, Cdc42, or Rac. The cells were then sheared at 12 dyn/cm2 or kept as static controls for 3 hours. Shear stress increased the c-fos promoter activity to 3 folds of the static controls. This induction was diminished by negative mutants of Rho, but not by those of Cdc42 or Rac. Pre-treatment of BAECs with genistein (a tyrosine kinase inhibitor), cytochalasin (an actin disrupting drug), or colchicine (a microtubule disrupting drug) did not affect the shear induction of the c-fos promoter activity. In contrast, BAPTA/AM (an intracellular calcium chelator) abolished the shear induction of the c-fos promoter activity. These results indicate that the shear-induced c-fos promoter activation is regulated by Rho and calcium, but is independent of Rac, Cdc42, cytoskeleton, and tyrosine kinase pathways.

T6.140

Effect of Membrane Area Expansion on the Cortical Tension of Human Neutrophils

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A resting human neutrophil behaves, under a steady aspiration pressure, as a Newtonian liquid drop with a surface or cortical tension. Here, we use established micropipette techniques to measure the effect of membrane area expansion on cortical tension. In one set of experiments, neutrophils were suspended in hypotonic solutions and their cortical tension measured. Area expansions of up to ~25% resulted in increased cortical tension, represented by an apparent elastic area expansion modulus of ~40 pN/μm, in good agreement with our earlier work (Needham and Hochmuth, Biophys. J. 61:1664, 1992). In an alternate set of experiments, neutrophils were entirely aspirated into one pipette and their cortical tension measured with a second pipette. Area expansions of up to ~25% resulted in increased cortical tension and an apparent elastic modulus of ~40-60 pN/μm. Thus, the postulated, persistent cortical tension does not appear to be an unique and constant parameter for neutrophils as the membrane area is dilated by either osmotic or mechanical force. Additionally, cells osmotically contracted to varying degrees did not behave as a liquid drop but rather as a viscoelastic solid and exhibited values of ~3.5-8 pN/μm2 for the Young's modulus, E, in an osmolaritydependent fashion. (Supported by NIH Grant HL-23728).

T6.141

The Effect of Vibration on Endothelin-1 Production by Dermal Microvascular Endothelial Cells

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Hand-arm vibration syndrome (HAVS) is a disorder affecting workers using vibrating hand tools such as chainsaws, pneumatic hammers and drills, and grinders. Vascular disorders are most commonly associated with HAVS and manifest as episodes of blanching of the fingers, especially in response to cold. Because of the similarity of symptoms of HAVS and Raynaud's phenomenon, HAVS is also referred to as Raynaud's phenomenon of occupational origin or vibration white finger. The purpose of this study is to develop a cellular model to investigate the effects of vibration on vascular cells. We grew human dermal microvascular endothelial cells on gelatin-coated 35 mm culture dishes and exposed them to a 125 Hz mechanical vibration at an acceleration of 10 m/s2. After 4 hours, supernatants were collected from vibrated cells and from stationary controls. Endothelin-1 (ET-1) protein levels in the supernatant were measured using an enzyme immunoassay. The number of cells in each dish was counted and used to normalize ET-1 concentrations. Preliminary results indicate that ET-1 concentrations were higher for vibrated cells as compared to controls. Our results suggest that vibration-induced alterations in ET-1 production may be involved in the etiology of HAVS.

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