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Intracoronary vascular profiling of shear stress, lumen, and wall morphology to predict vascular behavior and atherosclerosis progression Part 1: Rationale and methods

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Although atherosclerosis is a pan-coronary disease, most of the important clinical sequelae manifest focally, with individual lesions evolving independently of one another. Over time, some lesions remain quiescent, others evolve into flow-limiting stenoses, and a few become vulnerable and rupture, with the potential to cause an acute coronary syndrome (death, myocardial infarction, unstable angina pectoris). To date, predicting the future course of an individual lesion has been impossible. However, numerous in vivo and in vitro studies argue that the primary factor is local variation in shear stress acting on the endothelial cells that line the vasculature – cells that are uniquely capable of transducing shear forces to the cellular and molecular changes required for initiation and progression of atherosclerosis. Part 1 of this topic, in this issue of Cardiology Rounds, examines the role of coronary endothelium as the modulator of coronary artery disease (CAD) pathogenesis and the role of endothelial shear stress in determining atherogenesis and coronary artery remodeling. The focus will be on the molecular biology underlying the adverse effects of low endothelial shear stress. Part 2 of this examination of intracoronary vascular profiling, to be published in next month's issue of Cardiology Rounds, will describe a unique methodology for determining intracoronary hemodynamics and discerning endothelial shear stress with a spatial resolution of a few hundred microns. Part 2 will also present the results of the first study in humans that relates baseline endothelial shear stress to progression and remodeling at 6 months. A preliminary model for predicting lesion evolution, based on local endothelial shear stress and vascular remodeling characteristics, will also be presented.

The manifestations of atherosclerosis are focal and evolve in an independent manner. The endothelium regulates arterial behavior by responding to its local environment of shear stress. *In vitro* studies indicate that low endothelial shear stress (ESS) upregulates genetic and molecular responses, leading to the initiation and progression of atherosclerosis, promotion of inflammation, and formation of other features characteristic of vulnerable plaque. Physiologic ESS is vasculoprotective and fosters quiescence of the endothelium and vascular wall; however, high ESS promotes platelet aggregation. ESS and vascular wall morphology along the course of human coronary arteries can now be characterized *in vivo*, and may actually delineate the focal areas in which atherosclerosis progression occurs. Rapidly evolving methodologies are able to characterize the arterial wall and the local hemodynamic environmental factors likely responsible for the progression of CAD in humans. These new diagnostic modalities allow visualization of plaque progression; however, future studies are needed to identify the factors responsible for vulnerable plaque formation. Accurate identification of arterial segments at high risk for progression may permit pre-emptive intervention strategies to avoid adverse coronary events.

Atherosclerotic cardiovascular disease is the major cause of morbidity and mortality in the industrialized world. Every year, over 5 million individuals are clinically diagnosed with CAD and



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approximately 1 million myocardial infarctions (MIs) and 500,000 coronary deaths occur in the USA alone. More than 90% of the plaques that rupture and cause death and MI, obstruct the coronary lumen by < 70% and do not limit flow or produce angina pectoris prior to the acute event.¹ Thus, most of the lesions that produce catastrophic events are currently not identified by stress testing prior to plaque rupture. These “vulnerable plaques” are smaller, richer in lipids, and more infiltrated with macrophages than stable fibromuscular lesions. CAD patients, typically, have many coronary obstructions that are in varying degrees of progression for potential future risk. Identifying patients with CAD who are likely to have or develop a vulnerable plaque may permit more intensive or even mechanical interventions before the plaque ruptures. Current angiographic techniques show lumen characteristics, but do not provide information concerning the morphology of the plaque or the critical prognostic information concerning its likelihood of becoming vulnerable and rupturing. Knowledge of intravascular hemodynamics, the profile of ESS, and characteristics of the plaque and arterial wall may be invaluable for predicting the location and rate of atherosclerotic progression, and may help determine specific sites of plaque rupture by identifying lesions evolving towards weakness and instability.² Pre-emptive intervention strategies applied to these high-risk lesions may avert an adverse cardiac outcome.

Local nature of CAD

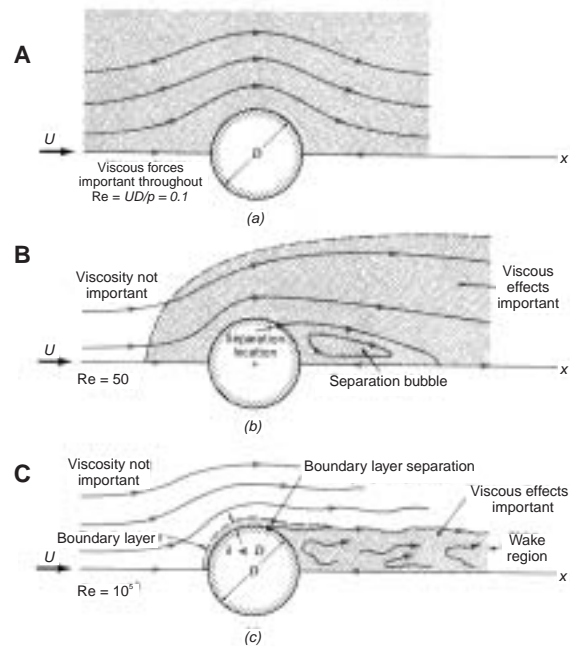
Although atherosclerosis is a systemic disease, its manifestations are focal and eccentric.^{3,4} Within each patient, each coronary obstruction progresses, regresses, or remains quiescent in an independent manner.^{5,6} Since MI and death are very infrequent events in an individual’s life, clearly, not all plaques evolve at a similar rate to become “vulnerable” and rupture. The focal and independent nature of atherosclerosis cannot be due solely to the presence of systemic risk factors such as hyperlipidemia, diabetes mellitus, cigarette smoking, and hypertension. Regional factors that create a unique local environment must be a major determinant of the behavior of atherosclerosis at a focal site in a susceptible individual.

Coronary endothelium as the modulator in the pathogenesis of CAD

The vascular endothelium is in a unique and pivotal position to respond to differences in blood constituents and dynamic forces acting on the vessel wall. Mechanical forces in general, and fluid shear stress in particular, elicit a large number of humoral, metabolic, and structural responses in endothelial cells (Figure 1, 2).⁷⁻¹⁰ The response of a number of sensitive genes to local hemodynamic forces likely leads to the creation of a raised plaque. Once created, alterations in subsequent hemodynamic forces produced by the enlarging plaque may lead to a self-reinforcing cycle of monocyte recruitment, lipid accumulation by macrophages, increased smooth muscle cell proliferation, and increased oxidant activity,^{7,11,12} all characteristics of a vulnerable plaque. The culmination of this process is an eventual plaque rupture that may become clinically evident with lumen obstruction by thrombus even in the absence of a major anatomic blockage.¹²

Figure 1: Patterns of flow and shear stress.

- A.** Laminar flow without flow disturbances; shear stress is positive in all areas.
- B.** Laminar flow, but with low flow and flow reversal just beyond the obstruction. In the area of localized low and reversed flow the shear stress is very low or negative.
- C.** Areas of turbulent flow beyond the obstruction that occur in association with very high flow rates not usually seen in arteries.

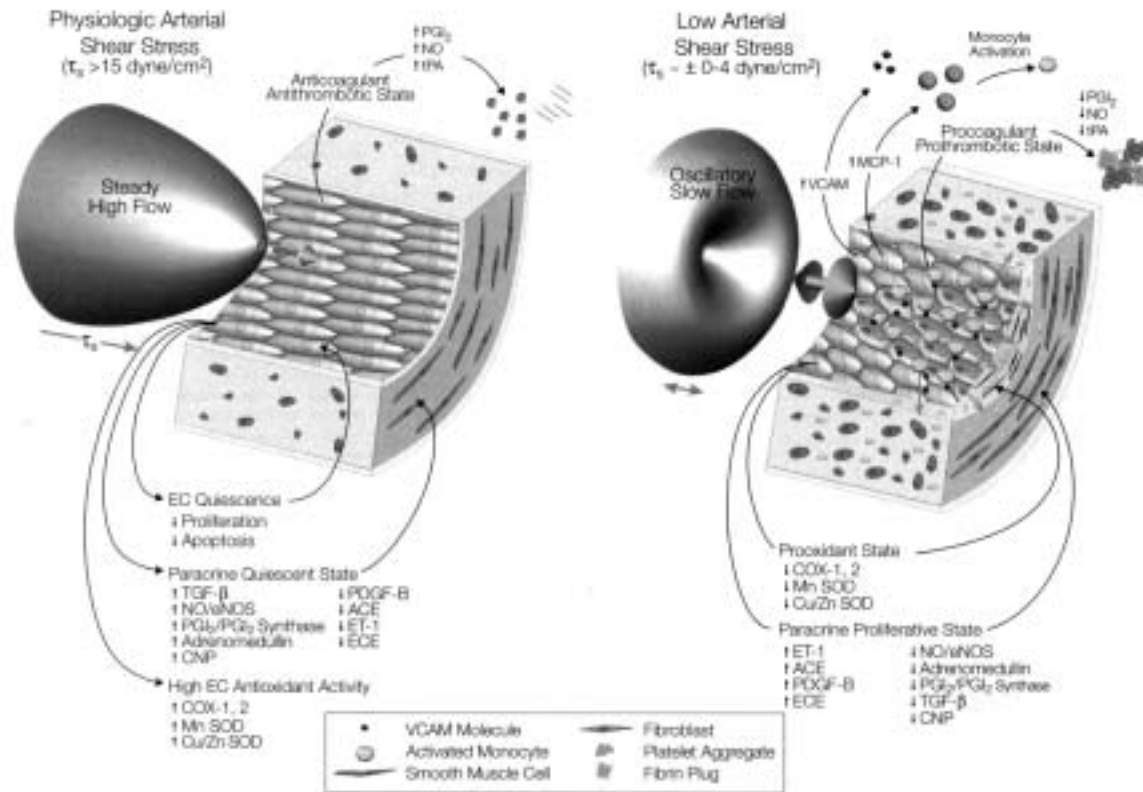


Effects of disturbed flow and low shear stress

Regions of disturbed flow, with low and oscillatory shear stress conditions (< 4 dynes/cm²), are prothrombotic, pro-migratory, pro-apoptotic,^{7,13} and correlate well with the localization of atherosclerotic lesions (Right panel of Figure 2).^{7,13,14} These sites demonstrate increased uptake of lipoproteins, appearance of leukocyte adhesion molecules on the surface of the endothelial cells, and leukocyte transmigration.^{7,13,15} Secretion of chemotactic factors and growth factors causes proliferation of monocytes/macrophages, as well as smooth muscle cells. Smooth muscle cells synthesize a connective tissue matrix composed of elastic fibers, proteins, collagen, and proteoglycans, and the accumulation of lipids and free and esterified cholesterol follows.¹³

The molecular biology underlying the adverse effects of biomechanical stimuli, in particular low ESS, has been an area of intense investigation in recent years.^{10,16} Exposure of human aortic endothelial cells to low shear stress (2 dynes/cm²) is associated with a sustained increase in the activated form of the transcriptional regulator nuclear factor-kappa B (NF- κ B),¹⁷ and this factor is involved in the expression of the genes encoding many proinflammatory functions of the vascular wall and infiltrating leukocytes.¹² Intercellular adhesion molecule (ICAM-1) is readily induced by low levels of shear stress in vitro, while E-selectin and vascular cell adhesion molecule (VCAM-1), may not be as inducible by shear stress.¹⁸ Others have found increased VCAM-1 expression in

Figure 2: Schematic diagram of markedly different endothelial cell responses to physiologic shear stress (~15-70 dynes/cm²) and to low and oscillatory shear stress (< 4 dynes/cm²)



cultured endothelial cells under laminar flow at very low shear stress levels (0.5-1.5 dynes/cm²) that is sufficient to support monocyte adhesion and transmigration across vascular endothelial cells.¹⁹

Effects of physiologic laminar flow and high shear stress

In contrast to the deleterious effects of local flow disturbance and low shear stress, physiologic laminar flow (15 to 70 dynes/cm²) is generally vasculoprotective and associated with antithrombotic, antimigration, and pro-survival effects (left panel of Figure 2).^{7,13} Physiologic flow causes tight alignment and elongation of the endothelial cells limiting cell migration and movement, and the upregulation of gene expression responsible for a variety of important vascular protective molecules.^{7,15,20} However, as the obstruction progresses and further limits blood flow through a narrowed lumen, flow velocity and shear stress may increase excessively (> 70 dynes/cm²) at the neck and decrease abnormally at the outlet, increasing the likelihood of platelet activation and thrombus formation.^{21,22}

Effects of shear stress on vascular remodeling

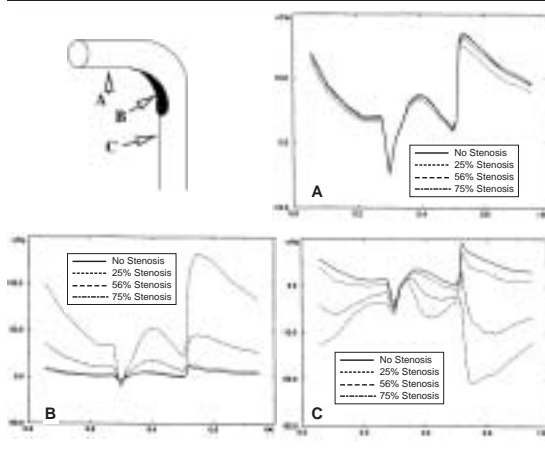
The arterial wall is a dynamic structure that responds to influencing factors in order to preserve and protect its integrity and function.^{23,24} Such remodeling is triggered by local hemodynamic conditions and humoral factors leading to synthesis or activation of factors that influence cell growth, apoptosis, and migration, as well as the composition of the extracellular matrix.^{24,25}

On the basis of autopsy studies of the left main coronary artery, Glagov and colleagues²⁶ proposed that the outer vessel area expanded (“outwardly remodeled”) as atherosclerosis progressed in the arterial wall until the plaque area occupied approximately 40% of the outer vessel area. They hypothesized that once the threshold of expansion was reached, no further outward remodeling would occur and any subsequent progression of the plaque would lead to progressive luminal encroachment. Outward remodeling is related to shear stress-responsive endothelial production of nitric oxide and certain matrix metalloproteinases (MMP-2 and MMP-9),^{23,27} as well as local factors related to the plaque itself²⁸ and to heterogeneities in circumferential wall stress. The clinical significance of this outward remodeling phenomenon is underscored by the recent appreciation that the coronary plaques most likely to be “vulnerable” and rupture are those minor luminal obstructions in an arterial area where outward remodeling has occurred.²⁹⁻³¹ These outward remodeled vessels with minor luminal obstructions are the most likely to be involved in the transition from a stable to an acute coronary syndrome.³²

“Inward remodeling” is due to inadequate remodeling of the artery for the amount of plaque that forms, thereby allowing the developing plaque to encroach on the lumen. Areas of low ESS generally lead to increased arterial wall thickness (plaque development) and outward remodeling but, in some circumstances, the relationship is lost and inward remodeling may occur.³³ Recent intravascular ultrasound (IVUS) studies indicate that 25%-50% of coronary artery segments with minor

Figure 6: An example of computational modeling of phasic coronary blood flow through a circumflex coronary artery. The ESS values are shown on the inner wall of the curvature (vertical axis) throughout one phasic cardiac cycle (horizontal axis; each cycle=0.75 seconds or heart rate of 80 bpm). The shear stresses are enormously different throughout the cardiac cycle along the course of the artery and the differences are dramatically increased as the luminal obstruction increases from 0% to 25% to 56% to 75%. The modeled obstruction is inserted in the middle of the curve of the artery, as illustrated in the figure.

- A.** Note that at the entrance of the artery curve, the endothelial shear stress pattern is similar regardless of whether or not there is a downstream obstruction or a progressively more severe obstruction.
- B.** In the middle of the curve the endothelial shear stresses become dramatically increased as the degree of obstruction increases. Endothelial shear stress values are in excess of 100 dynes/cm².
- C.** At the end of the curve the endothelial shear stresses become progressively lower downstream from the obstruction as the obstruction itself becomes progressively more severe. The endothelial shear stress is well below 0 dynes/cm² (ie, recirculating flow and eddy currents) throughout most of the cardiac cycle, and may be as low as -20 dynes/cm².⁴¹



quiescent and do not progress, while others show accelerated progression of atherosclerosis. Furthermore, it is not known if all atherosclerotic segments evolve through the same progression, from fatty streak to cellular plaque, to atheroma and vulnerable plaque and, ultimately, to dense fibrotic and calcified plaque, or if only some atherosclerotic lesions progress in that manner. Blood flow patterns and shear stress on the endothelium are undoubtedly important determinants of regional plaque progression.

Careful scrutiny of the flow and ESS patterns in coronary arteries at different points in the natural history of CAD may be useful in shedding light on the conceptual framework of the mechanisms responsible for atherosclerosis progression, and provide a foundation for methodologies to predict plaque progression. To investigate the hemodynamic consequences of atherosclerosis progression, we modeled intracoronary flow patterns and ESS patterns in a circumflex artery adding arbitrary obstructions of greater severity to the model (Figure 6).⁴¹ We hypothesized that as plaque progressed, downstream hemodynamic environments would amplify atherogenic

stimuli. As a minor obstruction forms on the inner aspect of the curve (25% luminal obstruction), ESS downstream from the minor obstruction becomes substantially lower, which would serve as a more potent atherogenic stimulus. As the obstruction progresses and becomes a 50% luminal obstruction, the ESS downstream becomes much lower still, often characterized by negative ESS (recirculation and reverse flow) that persists for most of the cardiac cycle. This more intense atherogenic stimulus leads, in turn, to progressive plaque enlargement; once the obstruction becomes 75%, the ESS at the downstream side of the obstruction becomes abnormally low and negative throughout the entire cardiac cycle. This model of the “natural history” of plaque progression suggests how different hemodynamic environments created by minor plaque formation lead to the creation of a new hemodynamic environment which, in turn, leads to dramatically different cellular and structural responses.^{7,42} The genetic regulation of phenotypic responses is likely very complicated as well,^{16,42} dependent on the genetic makeup of the host,⁴³ and possibly the specific genetic characteristics of different vascular beds, age, gender, and acquired characteristics.

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Charles L. Feldman, Sc.D. received both his undergraduate and graduate education at the Massachusetts Institute of Technology. He has served on the faculties of Worcester Polytechnic Institute, the University of Massachusetts Medical School and Harvard Medical School where he is currently Lecturer in Medicine and on the staffs of the Massachusetts General Hospital and Brigham and Women's Hospital, where he is currently a Senior Scientist. He has published widely on the use of technology in all aspects of cardiology and has many patents to his credit. Since 1990, he has been working with Dr. Stone to develop instrumentation to measure intracoronary endothelial shear stress and to use that instrumentation to understand the role of shear stress in the genesis, progression and complications of atherosclerotic coronary artery disease.

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