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Intracoronary vascular profiling of shear stress, lumen, and wall morphology to predict vascular behavior and atherosclerosis progression

Part 2: Clinical implications

By PETER H. STONE, M.D. and CHARLES L. FELDMAN, SC.D.

Although atherosclerosis is a pan-coronary disease, most of its important clinical sequelae are manifest focally and individual lesions evolve independently of one another. Over time, some lesions remain quiescent, some 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, prediction of the future course of an individual lesion has been impossible. Part 1 of *Cardiology Rounds* (published last month) reviewed the role of coronary endothelium as the modulator of coronary artery disease (CAD) pathogenesis and the role of endothelial shear stress in atherogenesis and coronary artery remodeling. Emphasis was placed on the molecular biology underlying the adverse effects of low endothelial shear stress. Part 2 describes a unique methodology for determining intracoronary hemodynamics and discerning endothelial shear stress with a spatial resolution of a few hundred microns. To achieve these results, biplane angiograms are fused with an intravascular ultrasound (IVUS) pullback, flow is measured, and the fundamental equations of fluid flow are numerically solved to yield detailed flow characteristics at each point within the lumen and the shear stress at the lumen boundary. The results of the first study in humans relating baseline endothelial shear stress to progression and remodeling are discussed. The relationship between shear stress measured at baseline to plaque growth and arterial remodeling in the following 6 months is described. Finally, a preliminary model is presented for predicting lesion evolution based on local endothelial shear stress and vascular remodeling characteristics.

The value of identifying the natural history of coronary atherosclerosis and the inadequacy of current techniques

Identification of an early atherosclerotic plaque likely to progress and acquire the characteristics of "vulnerability," predisposing it to rupture and, consequently, precipitate an acute coronary event, would permit more definitive pharmacologic or perhaps mechanical interventions prior to the occurrence of a cardiac event. The potential clinical value of identifying and "eradicating" native plaques destined to become vulnerable beforehand is enormous. At present, percutaneous coronary interventions (PCIs) in the catheterization laboratory are performed only on the "culprit" artery or arteries responsible for ischemia. Minor obstructions, including those that may become vulnerable in the future, do not receive PCIs, since it is not known which of the many minor coexisting obstructions in the coronary circulation will become vulnerable in the future. If endothelial shear stress (ESS) and wall/plaque morphology analyses could be performed rapidly and safely in the catheterization laboratory, then minor obstructions likely to become vulnerable could be identified and treated with stent deployment at the time of the catheterization. The development of drug-eluting stents, associated with



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safe deployment and low risks of restenosis,^{1,2} make the consideration of prophylactic or pre-emptive stent deployment plausible at this time.

Previous methodologies have not been able to identify a plaque area likely to develop lesion progression. Coronary angiography provides only a 2-D view of the arterial lumen, cannot provide sufficient detail concerning lumen dimensions or coronary flow, and offers no information concerning plaque and arterial wall size and composition. IVUS can provide more detail concerning plaque and arterial wall size and composition at a given cross-section, but cannot provide the true 3-D location of the wall.

Methodology to assess local vascular characteristics and predict future vascular behavior

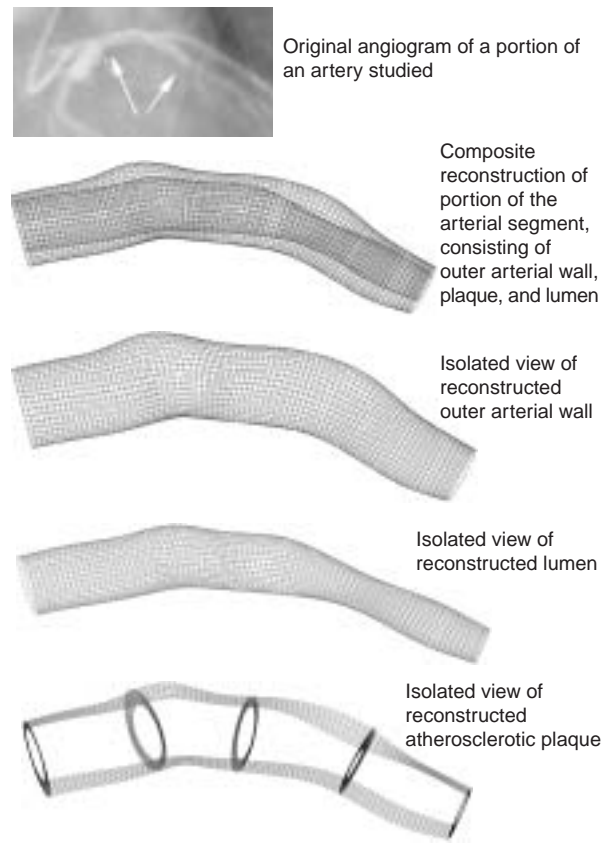
We have developed a unique system using coronary IVUS, biplane coronary angiography, and measurements of coronary blood flow to represent the artery in accurate 3-D space, and to produce detailed characteristics of ESS and arterial wall/plaque morphology.^{3,6} These methods can now identify wall morphology, the presence of plaque, and vascular remodeling, as well as the local hemodynamic environment and ESS that regulate future vascular behavior.

Our methods of intracoronary profiling have been previously described.^{3,6} In brief, the 3-D anatomy of the artery is reconstructed from IVUS images and biplane coronary angiography. IVUS is performed with controlled pullback and the electrocardiogram (ECG) is recorded on the IVUS images. The arterial lumen and outer vessel wall are reconstructed from digitized and segmented end-diastolic IVUS frames. The physical 3-D path of the IVUS transducer during pullback is determined using the corresponding biplane angiographic projections. The 3-D reconstructed catheter core serves as the stem on which to rebuild the 3-D geometry. The 3-D position of each ECG-gated IVUS frame is determined from the reconstructed trajectory of catheter pullback and pullback speed.⁷ The rotation of the frame is determined using computational geometry.⁵ Each frame is aligned perpendicular to the catheter core.

The boundary points of each frame are connected by spline curves to rebuild the luminal geometry in 3-D space. A structured grid utilizing a body-fitted coordinate system is employed to represent the lumen volume. The lumen is divided into computational control volumes comprising 0.3 mm thick slices along the segment, 40 equal intervals around the circumference (lumen interface), and 16 variably spaced intervals in the radial direction from the center of the reconstructed lumen. Coronary blood flow for the arterial section under study is calculated directly from the time required for the previously calculated true 3-D volume of blood contained within the section to be displaced by radio-opaque material during a contrast injection.

The detailed intravascular flow characteristics are obtained by solving the transport equations governing the conservation of mass and momentum.⁴ The shear stress at the

Figure 1: Example of original coronary angiogram and a portion of the 3-D reconstructed artery¹



luminal surface of the artery is calculated as the product of viscosity (calculated from the measured hematocrit) and the gradient of blood velocity at the wall.

The 3-D geometry of the outer vessel wall (area within the external elastic membrane [EEM]) is recreated in a manner similar to that described for the lumen geometry. The 3-D geometry of the plaque (plaque plus media thickness) is taken as the difference between the outer vessel wall and the lumen.⁸ Figure 1 illustrates an example of the coronary angiogram and the 3-D reconstructed coronary artery.

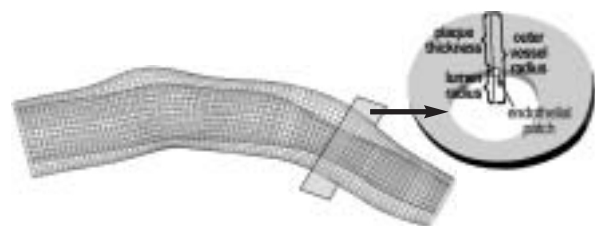
The processes of data acquisition and data analysis are highly reproducible.⁹ The standard deviation of repeated coronary blood flow measurements was 3% between measurements, with a maximum of 5%. The r-values for reproducibility for measurements of lumen radius, outer vessel wall radius, plaque thickness, and ESS were 0.96, 0.96, 0.94, and 0.91, respectively (each $p < 0.0001$). The standard deviation indicated that local lumen radius, EEM radius, and plaque thickness were reproducible within ± 0.1 mm and local ESS values were reproducible approximately within $\pm 25\%$.

Experience predicting vascular outcomes based on vascular profiling

We recently performed the first study in humans relating baseline ESS to subsequent arterial behavior 6 months later.¹⁰

Figure 2: Example of a cross-section of an actual coronary artery reconstruction¹⁰

This illustrates the endothelial patch where ESS is measured and the “icepick” of accompanying lumen radius, plaque thickness, and outer vessel radius.



We performed intravascular flow profiling initially and then repeated the flow profiling 6 months later. Ten patients were enrolled; 9 were male and the mean age was 60.8 years (range 37-83 years). All patients were treated with beta-blockers, statins, and aspirin. The mean fasting lipids were: total cholesterol, 156 mg/dL; low-density lipoprotein (LDL), 95 mg/dL; high-density lipoprotein (HDL), 36 mg/dL; and triglycerides, 150 mg/dL. Mean blood pressure at enrollment was 156/89 mm Hg and, at end of the study, 137/78 mm Hg. One patient refused re-catheterization and one patient developed an acute coronary syndrome requiring urgent repeat coronary stenting prior to the time of follow-up catheterization. A total of 8 patients underwent serial intracoronary profiling and are included. Twelve coronary arteries were serially studied and suitable for analysis: 6 native and 6 stented arteries using bare-metal stents. The native arteries studied in these patients included the left anterior descending in 2 patients, the circumflex in 1, and the right coronary artery in 3. The stented arteries were the left anterior descending artery in 3 patients, the circumflex in 2, and the right coronary artery in 1.

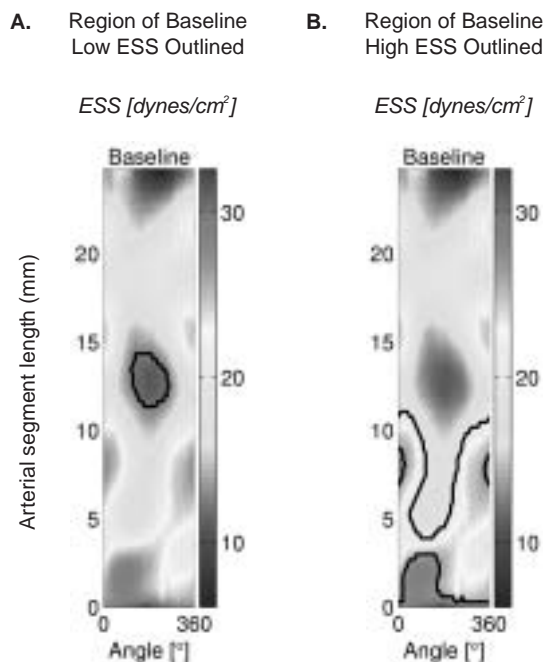
Each arterial segment was mapped and divided on its lumen surface into 2,560-10,640 independent rectangular patches (average of 5900 zones [250 microns x 300 microns]/arterial segment). Each lumen surface patch had an ESS and a corresponding lumen radius, outer vessel wall radius, and plaque thickness (ie, an “icepick” view of the arterial wall; Figure 2). Adjacent surface patches of similar ESS values were grouped into regions and these regions were classified into 6 endothelial “categories,” based on the cumulative percentiles of ESS values. This allowed us to obtain an adequate representation of all values of baseline ESS:

- Category 1: 10th percentile of ESS values (<9.1 dynes/cm²)
- Category 2: 25th percentile of ESS (9.1-12.6 dynes/cm²)
- Category 3: 50th percentile of ESS (12.6-19.1 dynes/cm²)
- Category 4: 75th percentile of ESS (19.1-26.9 dynes/cm²)
- Category 5: 90th percentile of ESS (26.9-38.3 dynes/cm²)
- Category 6: 97th percentile of ESS (38.3-55 dynes/cm²).

An example of an artery with a region of abnormally low baseline ESS and a region of increased baseline ESS is displayed in Figure 3.

Figure 3: Example of an arterial segment¹⁰

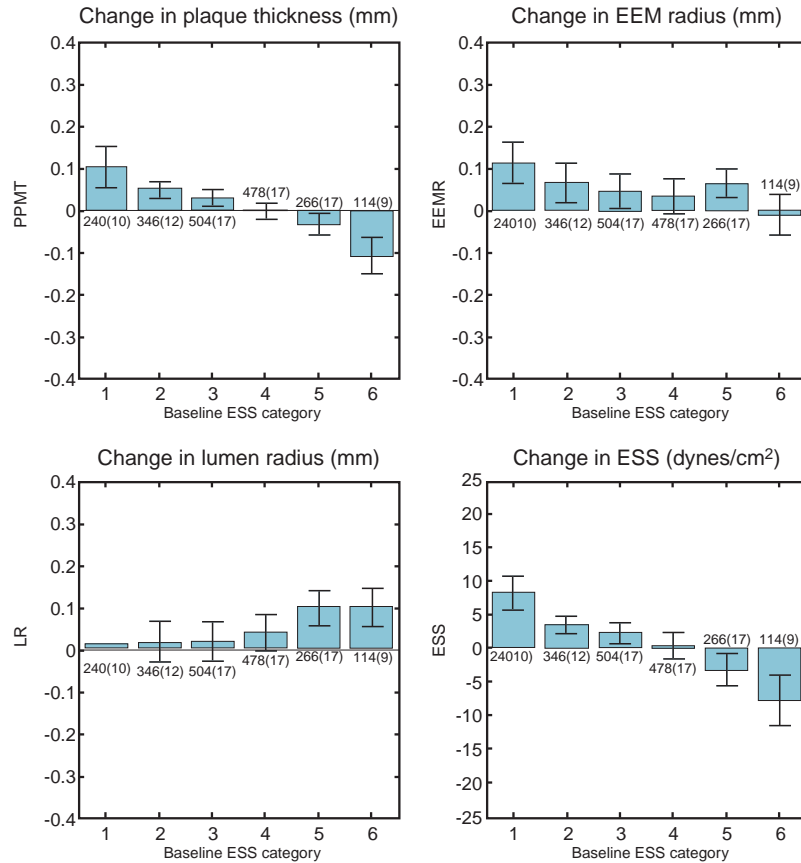
A region of abnormally low baseline ESS (<9.1 dynes/cm²) is outlined in (A), and a region of increased baseline ESS (>27 dynes/cm²) is outlined in (B). Data are presented as a “topographical map,” with the artery opened longitudinally and laid flat as a pathologist would view it. A color-coded scale of absolute values is provided. Adjacent endothelial patches of similar ESS form a region, and the regions are classified on the basis of baseline ESS.



The measurements made at baseline were compared to those made at 6-month follow-up, by matching the regions using IVUS-derived and angiographically-derived anatomical landmarks. The pattern of change in the outcome variables in the 6 categories of similar baseline ESS values were compared against baseline ESS. The changes in these regions were assessed by repeated measures of linear regression, adjusted for within-patient correlation.

In the native arterial segments, there were 82 regions of similar baseline ESS (mean region size 24 mm², range 1-129 mm²; Figure 4). Regions of low baseline ESS (Categories 1 and 2) showed progression of atherosclerosis, as evidenced by an increase in plaque thickness, as well as enlargement of the EEM radius (outward or positive remodeling). The lumen radius did not change. These *in vivo* observations of outward remodeling as plaques progress provide the first serial studies supporting the predictions made by Glagov and colleagues from autopsy studies.¹¹ Positive remodeling, a feature of vulnerable plaque, is associated with low ESS. Regions of physiologic baseline ESS (Categories 3 and 4) showed little change in any vascular variable. Regions of increased baseline ESS (Categories 5 and 6) showed outward remodeling with an increase in lumen radius and EEM radius, and a consequent decrease in ESS. The atheroma thickness in regions of increased baseline ESS appeared to decrease as the vessel

Figure 4: Artery outcomes in the native arteries as a function of baseline ESS¹⁰ The x axis displays the baseline ESS categorized into 6 categories based on cumulative percentiles of ESS values, as described in the text. Within each category of baseline ESS, the regions of the artery at baseline are presented with those ESS values. Within each ESS category the total area of the respective regions on each bar is displayed, as well as the number of regions in the category in parentheses. The y-axis displays the change in the vascular variable after 6 months. There were significant changes in plaque thickness and ESS ($p < 0.001$) and lumen radius ($p = 0.03$) as a function of baseline ESS. EEM radius appeared to increase most within regions of low baseline ESS, but increased to some degree in most categories of baseline ESS.



ESS = endothelial shear stress; EEMR = external elastic membrane radius; LR = lumen radius; PPMT = plaque thickness

enlarged, most likely representing redistribution of the plaque volume.

In the stented arteries there were 29 regions of similar baseline ESS values (mean region size 24 mm², range 2-96 mm²; Figure 5). Within the stented portions of the arteries there was an increase in intima-medial thickness, a decrease in lumen radius and, consequently, an increase in ESS at virtually all levels of baseline ESS.

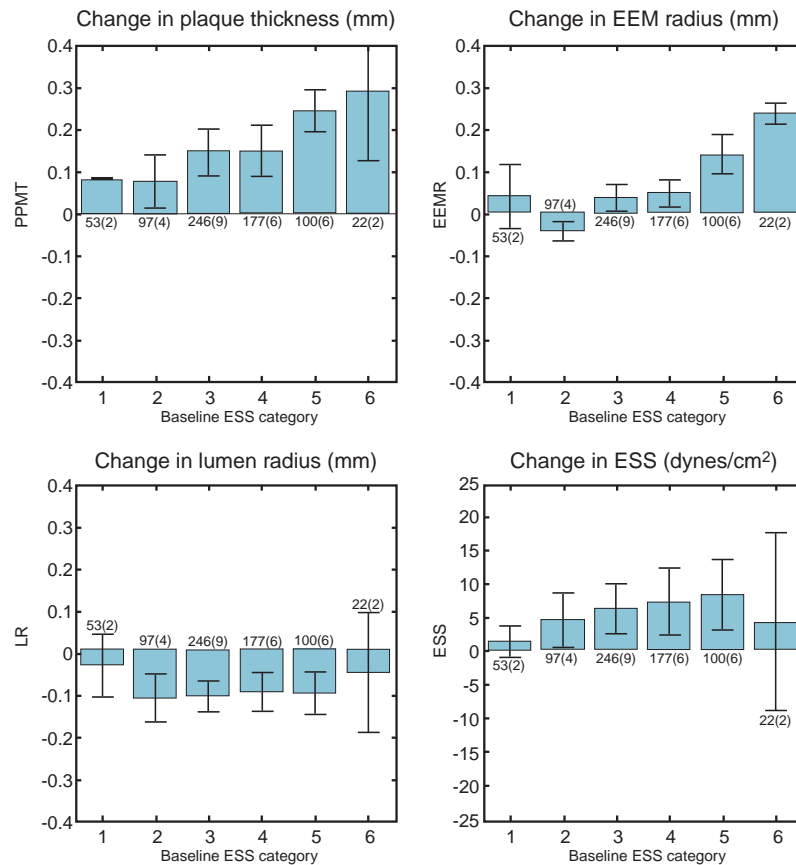
Evidence of in-stent restenosis, using bare-metal stents, appeared to occur to some degree in each category of baseline ESS in our patients (Figure 5), suggesting that ESS may not be critical to the development of in-stent restenosis. In the porcine model of in-stent restenosis, as in humans, neointimal thickness is correlated with local factors relating to vessel injury, such as the anatomic depth to which the stent strut penetrates the vessel wall¹² and the local inflammatory response to the stent struts. The effect of ESS on the process of in-stent restenosis, however, is less clear. In a small 6-month study of patients receiving a Wallstent, neointimal thick-

ness was inversely related to ESS, suggesting that a hemodynamic mechanism may contribute to neointimal hyperplasia.¹³ Interestingly, we observed that there were increases in both intimal-medial thickness and outer-vessel radius in the stented segments and these increases were more substantial in areas of baseline increased ESS (Figure 4). Nakamura, et al¹⁴ also observed in serial volumetric IVUS analyses that vascular proliferation outside the stent (positive remodeling) was common, and there was a highly significant inverse correlation between change in proliferation outside the stent and the percentage change of neointimal proliferation within the stent.

Clinical implications and future applications

The methodology used in our study, allows serial *in vivo* investigations of the natural history of native coronary disease and stented coronary artery segments for the first time in man. Our studies underscore the rapidly changing behaviors of different areas within a coronary artery in response to different environments.

Figure 5: Artery outcomes after 6 months in the stented portions of the stented arteries as a function of baseline ESS¹⁰ Structure of figure as in Figure 3. Intima-medial thickness increased, lumen radius decreased, and ESS increased in each category of baseline ESS. The magnitude of changes in lumen radius ($p=0.02$), ESS ($p=0.003$), and EEM ($p=0.003$) was associated with the category of baseline ESS.



ESS = endothelial shear stress; EEMR = external elastic membrane radius; LR = lumen radius; PPMT = plaque thickness

Detailed ESS evaluations may give further insight into understanding the initial development and progression of atherosclerosis, the subsequent vascular responses to the abnormal environment created by atherosclerosis, and the vascular responses to stent implantation.

The immediate application of this methodology may be to identify minor, but high-risk luminal obstructions that are evolving towards more severe obstructions or vulnerable plaque. Preliminary studies from our laboratory suggest that an *in vivo* assessment of the percentage volume of the artery occupied by plaque, as well as the local remodeling characteristics of that artery, can predict whether atherosclerosis progression will be associated with outward remodeling and development of vulnerable plaque, or with inward remodeling and development of luminal encroachment. More animal studies are necessary to determine how different levels of ESS and wall characteristics trigger the initiation of the inflammatory process in plaque vulnerability, and the adaptive processes of vascular remodeling. Use of adjunctive diagnostic techniques such as thermography,¹⁵ spectroscopy,¹⁶ or optical coherence tomography techniques¹⁷ may further aid the identification of areas likely to become inflamed or vulnerable in the future. Ultimately, it may even be

possible to employ more noninvasive techniques to identify vascular areas of high-risk. With improvements in data acquisition and analysis, more definitive clinical trials will permit the evaluation of a strategy to identify high-risk, minor obstructions for selective pre-emptive therapies (eg, stenting with drug-eluting stents). If a stenting strategy were successful, hundreds of thousands of myocardial infarctions and possible deaths could be avoided each year. The public health benefits from such pre-emptive strategies may be enormous.

Rapidly evolving technologies to characterize arterial disease *in vivo* promise extremely exciting opportunities for the future. These technologies will enable investigators to learn more about the determinants of vascular behavior and create opportunities for future therapeutic intervention.

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Section for *Current Opinion in Cardiology, Current Treatment Options in Cardiovascular Medicine, and Annals of Non-invasive Electrocardiology*. He is past President of the Boston Chapter of the American Heart Association. He has been developing instrumentation with Dr. Charles Feldman to identify local factors *in vivo* responsible for the progression of coronary disease in man and to predict where coronary disease will develop and progress.




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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