Prediction of Coronary Artery Disease Progression in Human from Numerically Determined Endothelial Shear Stress

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Abstract

Using a technique in which intravascular ultrasound images are fused with two planes of angiography, blood flow is measured, and the Navier Stokes equations are solved in 3 dimensions, we have studied the remodeling characteristic of 55 human coronary arteries and the relationship of endothelial shear stress (ESS) to remodeling and plaque progression in 13 human arteries. Results indicate that the remodeling characteristics of 87% of coronaries with minimal luminal narrowing are constant along the length of the artery: 60% percent demonstrate compensatory remodeling; 19% exhibit under-remodeling (consistent with stable CAD) and 21% exhibit excessive remodeling (consistent with unstable syndromes). Serial studies show that plaque progresses almost exclusively in regions of low ESS (<12 dyne/cm^2). This suggests a new paradigm that focuses on segments with low ESS, treating those with excessive remodeling as being at risk for unstable syndromes and those with inadequate remodeling as being at risk for stable CAD.

1. Introduction

Coronary artery disease (CAD) is a diffuse, inflammatory disease, resulting from incorporation of lipoproteins into the wall of the coronary artery. However, the important sequelae of CAD are focal, with evidence gathered over several decades suggesting that the sites of plaque accumulation are determined by patterns of local endothelial shear stress (ESS)[1,2]. Focal progression of CAD is related to both plaque progression and vascular remodeling (outward or inward remodeling of the external elastic membrane [EEM]). Glagov and colleagues[3] observed that, in the aggregate, the response of the EEM to increasing plaque burden is compensatory outward remodeling until plaque occupies approximately 40% of the dilated EEM. However, there is great individual variability in this "Glagov" remodeling. Outward remodeling has been associated with unstable plaque, acute coronary syndromes and myocardial infarction while inward remodeling has been associated with stable CAD[4-7]. Using techniques we have previously described and have subsequently refined[8], we have studied both the remodeling characteristic of human coronary arteries and the relationship of ESS to plaque progression in a subset of those arteries during a follow-up period of approximately 8 months. Our objective is to develop tools to determine which minor lesions will progress and, of those that do progress, which will evolve to stable CAD and which will result in unstable coronary syndromes.

2. Methods

Our methods of intracoronary profiling have been previously described[8-10]. In brief, the 3-D anatomy of the artery was reconstructed from IVUS images and 2 planes of coronary angiography. IVUS (Boston Scientific, Natick, MA) was performed with controlled pullback at 0.5 mm/sec. The ECG was recorded on the IVUS images. The arterial lumen and outer vessel wall were reconstructed from digitized and segmented end-diastolic IVUS frames[9]. The physical 3-D path of the IVUS transducer during pullback was determined using the corresponding biplane angiographic projections. The 3-D reconstructed catheter core served as the stem on which to rebuild the 3-D geometry. The 3-D position of each ECG-gated IVUS frame was determined from the reconstructed trajectory of catheter pullback and pullback speed[11]. The rotation of the frame was determined using computational geometry[9]. Each frame was aligned perpendicular to the catheter core. The boundary points of each frame were connected by spline curves to rebuild the luminal geometry in 3-D space.

The 3-D geometry of the outer vessel wall (area within the EEM) was recreated in a manner similar to that described for the lumen geometry. The 3-D geometry of the plaque (plaque plus media thickness) was taken as the difference between the outer vessel wall and the lumen[13]. Figure 1 illustrates the reconstructed artery.

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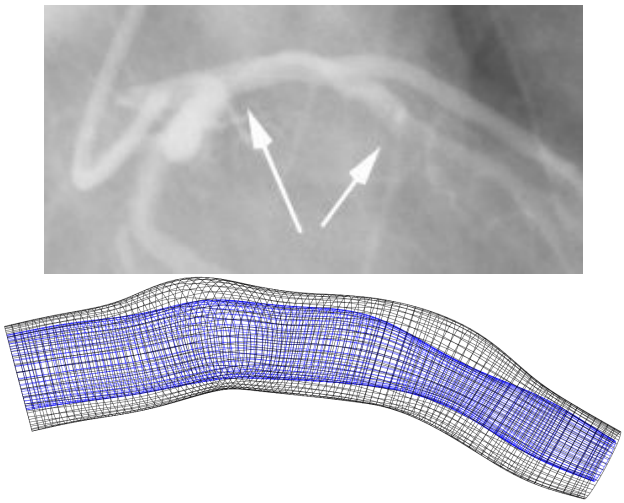

Figure 1: Top: Original angiogram of an arterial segment. Bottom: Corresponding reconstruction, demonstrating lumen, plaque and EEM.

A structured grid utilizing a body-fitted coordinate system was employed to represent the lumen volume. The lumen was divided into computational control volumes 0.3mm thick, with 40 equal intervals around the circumference, and 16 intervals radially from the center of the reconstructed lumen. Coronary blood flow for the arterial section being studied was calculated directly from the time required for the volume of blood contained within the section to be displaced by radio-opaque material during contrast injection..

Detailed intravascular flow characteristics were obtained by solving the transport equations governing the conservation of mass and momentum. We assumed steady flow, rigid arterial walls, and incompressible and Newtonian blood. The governing equations were integrated over the computational control volumes and the resulting algebraic equations were solved using the PHOENICS computer code. The computations were considered converged when the maximum change in the velocity field between iterations was <0.1%. The shear stress at the luminal surface of the artery was calculated as the product of viscosity (calculated from the measured hematocrit) and the gradient of blood velocity at the wall.

The processes of data acquisition and data analysis are highly reproducible[13]. 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 of repeated coronary blood flow measurements was 3% between measurements, with a maximum of 5%.

Patients were eligible if they underwent percutaneous coronary intervention with a stent and had another coronary artery with a 25-50% luminal obstruction. Exclusion criteria included left ventricular ejection fraction <40%, serum creatinine >1.5mg/dl, 3-vessel coronary disease, or valvular disease[14].

Intracoronary vascular profiling was performed after administration of a parenteral vasodilator. The study was approved by the Human Research Committees of Brigham & Women's Hospital, Northeastern University and the University of Iowa Medical Center. Each patient provided written informed consent.

Studies of the effect of ESS on plaque growth were performed on a subset of the total study. For the ESS portion of the study, only the unstented vessel was used and patients were restudied a mean of 8 months after their baseline study. For remodeling studies, all available vessels were included with the exception of the stented portion of the vessel and 5 mm proximal and distal to the stent.

To determine the effects of ESS on plaque growth, the reconstructed lumen surface of each arterial segment was mapped and divided into approximately 2,560–10,640 independent rectangular patches (average of 5900 patches/arterial segment). Each lumen surface patch had an ESS and a corresponding lumen radius, outer vessel wall radius, and plaque thickness. Adjacent surface patches of similar ESS values were grouped into regions; and these regions were classified into 3 ESS "categories" at baseline: "low ESS" (< 12 dynes/cm^2), "moderate ESS" (12-24 dynes/cm^2), and "higher ESS" (ESS > 24 dynes/cm^2). These categories were selected because our previous pilot study[14] indicated that coronary vascular responses were different across these groups.

Coronary arterial "subsegments of interest" were created from the reconstructed coronary arteries and categorized on the basis of the predominant ESS value in that subsegment. To be considered in the analysis, the subsegment was required to have a surface area region of similar ESS that was $\geq$ 5 mm^2, with a length $\geq$ 3 mm. The region of similar ESS was required to be $\geq$ 30% of the subsegment surface area and the mean ESS in entire subsegment was required to be within the range of values of the respective category. If one region was < 1 mm from a region of similar ESS then the entire region was considered as one region. The margins of the endothelial region were identified, and the subsegment consisted of the portion of the artery from that region. Since there were many areas of different ESS within a coronary artery, each artery may have had several subsegments of interest, each with a similar or different ESS value.

The measurements made at baseline were compared to those made at follow-up, by matching the regions using fiduciary sites based on IVUS-derived, angiographically confirmed standard anatomical landmarks. Each subsegment of interest was considered independently. Outcome variables in the 3 categories of similar baseline ESS values at the follow-up vascular

profiling procedure were compared with values in the same subsegment at baseline. Changes in plaque in the subsegment of interest were categorized as "+" (increased), "-" (decreased), or "0" (no change), where a change was defined as a value at follow-up different from the baseline measurement of by $\geq$ 3 standard deviations of the measurement error.

For remodeling studies, each reconstructed artery was divided into slices at 1.5 mm intervals, perpendicular to the artery centerline[15]. Vessel area at each slice was taken as the cross-sectional area inside the reconstructed EEM; plaque area as the difference between vessel area and lumen area[12]. Because the sizes of these minimally narrowed vessels varied widely, all measurements are reported as relative (i.e., "normalized") to the mean cross-sectional area of the vessel.

The relationships between plaque area and EEM area and between plaque area and lumen area were modeled using linear regression both for the aggregate data set and for each individual segment separately. An artery was considered homogeneous if the relationship between EEM area and plaque area could be fit with a single straight line, with 95% certainty. The slope of the relationship between EEM area and plaque area was defined as the "remodeling index."

3. Results

Thirteen subjects underwent both initial catheterization with intracoronary vascular profiling at baseline and at follow-up, a mean of 8±2 months later. The majority of patients were male, had a history of substantial risk factors for CAD, and had prior manifestations of CAD. All patients were treated with a beta-blocker, a statin, and aspirin. The left anterior descending coronary artery was studied in 2 patients, the circumflex coronary artery in 4 patients, and the right coronary artery in 7 patients.

A total of 46 arterial subsegments were identified from the baseline study: 9 subsegments with low ESS, 22 with moderate ESS, and 15 with higher ESS. Since none of the arteries had luminal obstruction > 50%, ESS values ranged primarily from low to high physiologic values**,** with none of the very high values that would be associated with severe luminal narrowing. Mean length of the subsegments was 9.0±6.4 mm. The mean subsegment area was 71±62 mm^2 (range 9-286 mm^2). Mean ESS in the low ESS subsegments was 10.2±1.4 dynes/cm^2; 16.4±2.5 dynes/cm^2 in the moderate ESS subsegments; and 31.1±3.9 dynes/cm^2 in the higher ESS subsegments.

By follow-up, plaque area progressed in 33.3% of low ESS subsegments, 13.6% of moderate ESS subsegments, and none of the higher ESS subsegments (p=0.02) (Figure 2)

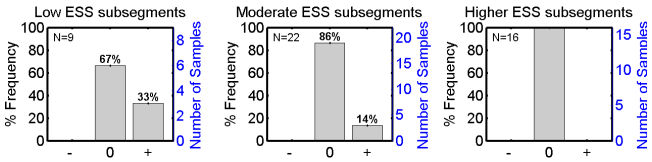

Figure 2: Change in plaque area over subsegments of low, moderate, and elevated ESS categories in 8 ± 2 months.

A total of 1712 reconstructed coronary arterial slices were studied from 55 arterial segments in 40 patients (30 males, 10 females; mean age 64±12 years. Twenty-two native arteries and 33 stented arterial segments were studied: 21 left anterior descending, 15 circumflex, and 19 right coronary arteries. In 15 patients 2 arteries were investigated. Mean segment length was 44.7±31.1 mm, mean number of arterial slices/reconstructed segment was 31.1±14.1, and mean luminal diameter was 3.1±0.7 mm.

In 48 (87%) of the segments the cross-sectional area of the EEM was proportional to plaque area throughout the length of the artery studied. There was marked heterogeneity in the remodeling index among different arteries. The slopes ranged from -0.19 to +2.08. A test of homogeneity using linear regression showed significant variability (p<0.0001) between the individual slopes. Although 60% of arteries exhibited "appropriate" remodeling index (>0.75 and <1.25), 21% of arteries "excessively" remodeled and developed dilatation, while another 19% "inadequately" remodeled or displayed negative remodeling (Figure 3).

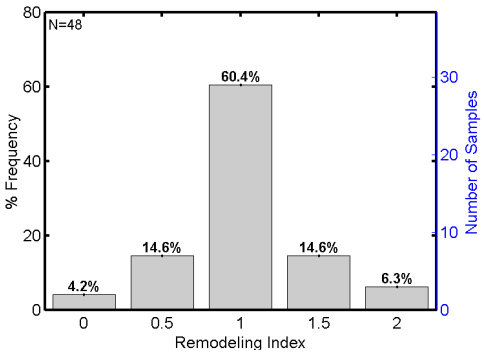

Figure 3: Frequency distribution of "Remodeling Index" (slope of EEM area vs Plaque area)

4. Discussion and conclusions

As a result of decades of observational and in vitro studies, the growth of coronary arterial plaque has long been associated with regions of low ESS. We have confirmed this observation in 13 human coronary arteries observed over 8 months using a new technique that we call vascular profiling. In particular, we have shown that

only rarely does plaque progress in human coronary arteries unless the ESS is < 12 dyne/cm^2.

Furthermore, we have shown that although the Glagov observation of compensatory arterial remodelling in response to increasing plaque burden is valid in the aggregate, there is wide individual variation in arterial remodelling characteristics. We have shown that in approximately 90% of human coronary arteries with minimal luminal narrowing, it is possible to characterize the remodelling characteristics of the artery with a single remodelling index. For approximately 60% of arteries studied, remodelling followed the classic Glagov pattern of compensatory remodelling, while approximately 20% of arteries demonstrated inadequate remodelling and 20% demonstrated excessive remodelling.

Since it is well understood that inadequate remodelling is typically associated with stable, occlusive disease while excessive remodelling is associated with unstable plaque and myocardial infarction, vascular profiling now makes it possible to explore a new paradigm for the diagnosis and treatment of coronary artery lesions with minimal luminal narrowing. Specifically, since plaque primarily progresses in regions of low ESS (<12 dynes/cm^2), these are the only regions that need be considered for additional study. Those regions of low shear stress that appear to remodel appropriately might be considered for "watchful waiting", while those lesions that inadequately or excessively remodel might be targets for interventions.

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