Relationship Between the Dynamic Geometry and Wall Thickness of a Human Coronary Artery

Hui Zhu, Morton H. Friedman

Objective—It is widely recognized that hemodynamic and wall mechanical forces are involved in the initiation and development of atherosclerosis. In the coronary vasculature, these forces are likely mediated by arterial dynamics and geometry. This research examines the hypothesis that coronary artery motion and geometry affect the local predisposition to disease, presumably through their influence on the stresses at and in the artery wall.

Methods and Results—The dynamics of a human right coronary artery and the variation of wall thickness along its length were characterized from biplane cineangiograms and intravascular ultrasound records, respectively. The dynamic geometry parameters were distance along the vessel, cyclic displacement, axial strain, curvature, and torsion. Multiple regression analyses using principal components show that (1) no single dynamic geometry parameter has a dominant influence on wall thickness, (2) linear combinations of such parameters predict wall thickness measures with high confidence ($P<0.001; R$ between 0.17 and 0.44), and (3) both the time-average values of curvature and torsion and their excursion during the cardiac cycle are positively correlated with maximum wall thickness and cross-sectional asymmetry.

Conclusions—The relationships seen here support the hypothesis that dynamic geometry plays a role in the localization of early coronary artery thickening. (Arterioscler Thromb Vasc Biol. 2003;23:●●●●●.)

Key Words: coronary arteries ■ dynamic geometry ■ wall thickness ■ biplane angiography ■ intravascular ultrasound

Although several cardiovascular risk factors, including hypercholesterolemia, hypertension, smoking, and diabetes, have been associated with coronary heart disease (CHD), it is conventional knowledge among investigators in atherosclerosis that these factors can explain no more than half of the variability in the occurrence of atherosclerotic lesions or CHD.3–5 This situation suggests that there are additional risk factors that predispose to arterial disease. Friedman and colleagues6–8 have proposed that variations in arterial geometry, including the dynamic characteristics of the coronary arteries, can contribute to some of the unexplained variation in cardiovascular risk. This idea is based on the abundant and increasing evidence that hemodynamics and vascular wall stresses play an important role in the initiation and development of atherosclerosis.9,10 The fluid dynamic environment at the arterial wall depends on the geometry and motion of the channel through which the flow is passing, and geometries that promote an adverse hemodynamic milieu could constitute additional risk factors for disease. Similarly, the motion of the coronary arteries during the cardiac cycle can lead to cyclic stresses in the wall that may prompt an atherosclerotic response.

Most research seeking associations between coronary artery geometry and vessel pathology has been based on autopsy hearts.11–14 This is in part because of a lack of relevant data for the in vivo situation. Biplane cineangiography and intravascular ultrasound (IVUS) are 2 powerful modalities for assessing this relationship in vivo. Although the former modality makes it possible to accurately reconstruct the time-dependent 3D course of the coronary vessels on the beating heart, the latter provides the necessary in vivo vessel wall morphology. In this study, we demonstrate the use of these diagnostic techniques to evaluate the relationship between the dynamic geometry and morphometry of a human right coronary artery. This work is based on 2 techniques for 3D analysis of human coronary arteries in vivo: 3D reconstruction from biplane angiography and intravascular ultrasound (ANGUS)15 and 3D motion tracking from biplane cineangiograms.16

Methods

Image Acquisition

Images of a right coronary artery (RCA) segment were acquired during routine clinical catheterization using a Siemens biplane angiographic system and a Boston Scientific (CVIS, 2.9F) IVUS system. The acquisition rate of the angiograms was 25 frames per second. A sequence of 29 biplane angiogram pairs, which extended between the end diastoles of 2 consecutive cardiac cycles, was collected. To calibrate the biplane system, a Plexiglas cube of known size with radio-opaque edges was imaged with the same biplane geometry as that used when capturing the artery images. The IVUS images were acquired at end diastole using an ECG-triggered pullback motor with a step size of 0.5 mm. The total number of
frames captured during the pullback was 145, corresponding to a pullback length of \( \frac{1}{7.2} \) cm. Figure 1A shows the first frame pair of the angiographic sequence, at end diastole. The pullback path is indicated with 2 dark lines in each image and covers the mid-RCA.

**Vessel Wall Thickness**

The vessel wall (intima + media) thickness was calculated from the IVUS images using a semiautomatic contour detection algorithm to extract the inner and outer wall boundaries, signifying the blood-vessel interface and medial-adventitial interface, respectively. The 3D catheter path at end diastole was reconstructed using the first pair of images in the biplane sequence. It served as a backbone for perpendicularly positioning the IVUS images at their corresponding locations along the pullback path. A detailed description of the 3D vessel reconstruction procedure can be found in Slager et al. From each IVUS image, the following 5 measures of the vessel wall thickness were derived: mean thickness (MeT), maximum thickness (MaT), minimum thickness (MiT), MaT/MiT (MmM), and MiT/MaT (MdM). The variable MdM is a nondimensional measure of the cross-sectional asymmetry of the vessel, decreasing from unity as the circumferential variation in wall thickness increases.

To take into account the variation of vessel size along its length, an additional set of scaled thickness variables was generated by dividing each original thickness variable, except MdM, by a nominal value of the vessel radius at the site. The normalizing radius was based on the outer perimeter of the vessel (radius = perimeter/(2\(\pi\)), which varied more smoothly than the luminal perimeter along the length of the artery. The 4 scaled thickness variables were denoted by SMeT (scaled mean thickness), SMaT (scaled maximum thickness), SMiT (scaled minimum thickness), and SMmM (scaled maximum thickness minus minimum thickness).

**Dynamic Geometry Parameters**

The dynamic geometry of the vessel is derived by tracking the segment of interest in 3D using the biplane angiogram sequence. In the first frame of one of the projections, several (8 in the present work) points along the axis of the vessel segment are marked and paired with corresponding points in the other projection using the calibration cube images. Each point pair represents the projections of the same 3D point. The 3D locations of these source points are reconstructed, and they are initially connected by straight lines. This sequence of straight lines constitutes an initial estimate of the 3D vessel segment axis (Figure 1B). Assuming that the 3D vessel axis projects into the intensity valleys (ie, centerlines) in the 2 projection images, the initial estimate is refined by minimizing an energy function that depends on the intensities of the 2 projection images (Figure 1C). After the 3D vessel axis is located in the first pair of frames of the angiography sequence, it is automatically tracked for the rest of the sequence using an algorithm that allows the axis to deform and stretch. For each axial point, pairs of small neighborhood windows in the 2 projections are used to track individual points along the vessel axis from frame to frame (Figure 1D); this permits the...
TABLE 1. Dynamic Geometry Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Explanations/Comments</th>
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<tr>
<td>dst</td>
<td>Axial distance from a point to the most proximal point of the segment</td>
</tr>
<tr>
<td>dsp‡</td>
<td>3D displacement of a material point over a cardiac cycle</td>
</tr>
<tr>
<td>str†</td>
<td>Average relative length change of a segment over a cardiac cycle</td>
</tr>
<tr>
<td>mcur‡</td>
<td>Average r‡ over a cardiac cycle</td>
</tr>
<tr>
<td>pcur‡</td>
<td>Average x‡ over a cardiac cycle</td>
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<td>mtor§</td>
<td>Average r§ over a cardiac cycle</td>
</tr>
<tr>
<td>ptor§</td>
<td>Average f§ over a cardiac cycle</td>
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(1) Displacement is defined as \(|P_{t+\Delta t}-P_t|\) for a given point at the vessel axis, where \(P_{t+\Delta t}\) and \(P_t\) are the positions of the point at times \(t+\Delta t\) and \(t\), respectively; \(\Delta t\) is the time interval between successive cineangiogram frames in a single projection; and \(||\cdot||\) denotes the Euclidean norm.

(2) The strain at a point \(P\) along the vessel is defined here in terms of the length, \(L\), of a short segment of axis centered at \(P\). In particular, the strain at time \(t\) is defined as \(|L(t')-L(t)|/L(t)|\), where \(L(t)\) is the length of a short segment of axis containing a sequence of \(2N\) points centered at \(P\), and \(t\) is the time at which the length of the entire vessel segment is shortest.

(3) Curvature at a point on a 3D curve is calculated as:

\[
k = \sqrt{(y'z''-y''z')^2+(z'x''-z''x')^2+(x'y''-x''y')^2} / (z''+y''+z'')^{3/2}
\]

(4) Torsion at a point on a 3D curve is calculated as:

\[
\tau = \frac{\text{abs}(x'z''-y'z''-y''z')}{(z''+y''+z'')^{1/2}}
\]

In (3) and (4), ‘’, ‘’, and ‘’ represent first, second, and third order derivatives, respectively.

Results

The statistical analyses indicated above were applied to the morphometric and dynamic geometry variables illustrated in Figures 2 and 3. Figure 2 presents the maximum, mean, and minimum wall thicknesses and the nominal vessel radius along the vessel segment. The other thickness measures were derived from these 4 quantities. Among the dynamic geometry parameters, the mean and pulse curvature and torsion were measured for each excursion during the cardiac cycle. Each of these parameters varied along the length of the segment and was evaluated at each point at which IVUS frames were analyzed, as described below.

Mapping the IVUS Image Sites on the Catheter Path to the Vessel Axis

Because the IVUS catheter path was not the same as the vessel axis, the first pair of biplane angiograms was used to register the IVUS images with the axis. At each IVUS image site, a plane normal to the catheter path was constructed, and its intersection with the vessel axis was found. Interpolation of the vessel axis was performed with cubic splines. All dynamic geometry parameters were then resampled at these new sites using cubic spline interpolation.

Statistical Analysis

Initially, univariate linear regressions were performed between each thickness measure and dynamic geometry parameter. Direct linear regression is inappropriate here, because the IVUS sampling interval was only 0.5 mm and the data at nearby points are not independent. The autocorrelation length of the thickness measures ranged between 1 and 2 mm, depending on the variable in question. To solve this problem, a generalized least-squares approach using an autoregressive model was applied, which allows for autocorrelation in serial data.

In addition, for each of the 9 thickness measures, multivariate linear regressions were performed against all 7 dynamic geometry parameters. In addition to the autocorrelation of the dependent thickness variables noted above, the independent geometric variables exhibited significant correlations with each other, which made it impossible to isolate their individual importance. Principal components analysis was adopted to remedy this problem.

Results

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For the multivariate regressions, principal components decomposition was initially performed on the 7 dynamic geometry parameters to take account of the correlations among them. Principal components analysis treats standardized values of the variables; each geometry parameter $P$ was standardized by subtracting its mean, $<P>$, and dividing by its standard deviation, $SD(P)$. Denoting the standardized variable by $P_{st}$, $P_{st} = (P - <P>) / SD(P)$. Defined in this way, the mean value of $P_{st}$ is zero and its standard deviation is unity. Each principal component is a linear combination of the standardized geometric variables, and the number of components equals the number of such variables. Thus, in the present case, there are 7 principal components.

The multivariate regressions were carried out with the principal components as the independent variables rather than the individual geometric variables, as is appropriate when the independent variables are correlated. Only 2 or 3 of the principal components were sufficient to explain most of the variance in each dependent variable. After the regressions were performed, the definitions of each principal component were used to recover the dependence of the morphometric quantities on the standardized geometric parameters. When the data are analyzed in terms of standardized independent variables and presented in this way, the regression coefficients measure directly the influence of each of these variables on the variation of the dependent quantities.

Figure 2. Vessel radius and wall thickness along the pullback path. From top to bottom, the 4 curves are vessel radius, maximum wall thickness, mean wall thickness, and minimum wall thickness, respectively. Please note that the scales of the ordinate and abscissa are very different; the wall is not as irregular as it might first appear.

Figure 3. Curvature (top) and torsion (bottom) along the vessel segment. Solid curve indicates mean value; solid curve with beads, pulse value.
Table 3 summarizes the results of the multivariate regression analyses. We find a highly significant correlation (P < 0.001) between each thickness measure and linear combinations of the dynamic geometry parameters. The adjusted R values are between 0.17 and 0.44, significantly larger than those for the univariate regressions.

### Discussion

The results in this study indicate significant relationships between dynamic geometry and vessel wall thickness. The R values of the univariate regressions indicate that no single geometric factor has a dominant role in determining vessel wall thickness. On the other hand, the probability values of the multivariate regressions are all highly significant, and the correlation coefficients are substantially higher as well. Thus, thickening seems to be influenced by multiple aspects of the dynamic vascular geometry. This is to be expected; the geometric factors are postulated to act through their influence on the fluid dynamic and mechanical stresses experienced by the wall, and it is reasonable that each of these stresses would be influenced by multiple dynamic and geometric parameters. It is noteworthy in this respect that the signs of the regression coefficients in the univariate and multivariate regressions in Tables 2 and 3 are consistent.

According to the signs of the regression coefficients in the multivariate regression results, the dynamic geometry parameters listed in Table 1 can be classified into the following 3 groups: the distance along the vessel axis (dst) and its displacement during the cardiac cycle (dsp); axial strain (str) and mean (mcur) and pulse (pcur) curvature; and mean (mtor) and pulse (ptor) torsion. The parameters in each of these groups play similar roles. The association of distance along the vessel axis and displacement reflects the fact that the cyclic motion of the RCA increases distally; the correlation coefficient between these 2 parameters is 0.94. These 2 parameters have negative effects on all of the unscaled thickness measures, which is not surprising, because the vessel size decreases distally (Figure 2). This is also seen in the univariate regressions. The scaled morphometry variables are expected to be less sensitive to vessel size and hence location along the artery; this would seem to be reflected in the lower R values for the scaled thickness measures, vis-à-vis the corresponding unscaled measures. The similar effects of axial strain and curvature reflect the fact that higher strains are evident where the curvature is large. The clustering of the geometric variables into the 3 groups, the members of which are correlated with each other, precludes identification of the specific variables that most directly influence wall thickness.

The interest in the relation between local curvature and torsion and early signs of vascular pathophysiology is prompted by the observation that atherosclerotic lesions are frequently found in the neighborhood of bends. In this study, both the mean and pulse values of curvature and torsion were positively correlated with the maximum wall

<table>
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<th>TABLE 3. Multivariate Regression Results</th>
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<tr>
<td><strong>Regression Coefficients Against Standardized Geometric Variables</strong></td>
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<tr>
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<td>dst</td>
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NS indicates P < 0.1; bold R^2 designates positive correlation, and plain font designates negative correlation.
thickness (MaT and SMaT). These thickness variables are of particular interest, because wall thickening is an important part of the atherosclerotic process. Vessel asymmetry also increases with all 4 geometric variables, as shown by the negative regression coefficients for MdM (recall that MdM decreases as the wall becomes more asymmetric). The torsion result is consistent with an earlier observation that vessel segments in the neighborhood of angiographically identified atherosclerotic lesions exhibited significantly higher torsion than angiographically normal portions of the same vessels.

Maximum (MaT) and mean (MeT) wall thickness are most strongly influenced by the torsion variables dsp and dst. Both thickness variables are larger where the torsion measures are greater, and both decrease with increases in dsp and dst, as described earlier. SMaT is presumably adjusted for taper, and the 4 variables associated with curvature and torsion are the strongest predictors of this quantity.

However, curvature and torsion have different effects on the minimum wall thickness (MiT and SMiT). Although minimum thickness is negatively correlated with the curvature measures, it increases with the torsion measures. This may be because curvature causes asymmetrical effects on the vessel wall, with respect to both axial wall strain and fluid dynamic shear stress, whereas torsion, acting as twisting, induces relatively uniform effects over the entire circumference. As a consequence, the effect of curvature on asymmetry is greater than that of torsion, because high curvature measures are associated not only with greater maximum thicknesses but also smaller minimum thicknesses. For the same reason, the effect of the curvature measures on mean thickness (MeT and SMiT) is much weaker than that of torsion.

The statistical analysis in this study has considered 2 common problems that are often ignored in linear regressions based on least squares. The first one is lack of independence of the individual measurements. This problem often arises when the data are collected in a time sequence. However, in our case, it came from the dense sampling of thickness data along the vessel segment. This problem can invalidate tests of significance in regression analyses. In multivariate regression analysis, correlation among the independent variables is another common problem. The impact of this problem is very serious if the primary purpose of the regression is to identify important explanatory variables that might play a causal role. The estimated regression coefficients for such correlated variables can be greatly different, even having opposite signs. This problem was solved in our case by principal components analysis.

Acknowledgments
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References
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