Intimal Thickness Is not Associated With Wall Shear Stress Patterns in the Human Right Coronary Artery

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Objective—Low wall shear stress has been implicated in atherogenesis throughout the arterial tree, including the right coronary artery (RCA). The objective of this study was to determine the level of covariation of intimal thickness and wall shear stress in the human RCA.

Methods and Results—Postmortem histological measurements of intimal thickness were compared with wall shear stresses calculated from computational flow modeling in 4 human right coronary arteries. A statistically significant correlation between intimal thickness and wall shear stress was found in only 1 of the 4 arteries studied.

Conclusion—Wall shear stress does not appear to be related to intimal thickness in the 4 RCAs studied. (Arterioscler Thromb Vasc Biol. 2004;24:2408-2413.)

Key Words: hemodynamics • intimal thickening • right coronary artery • wall shear stress • computational modeling

Early atherosclerotic lesions develop preferentially at bifurcations, branch points, and regions of high curvature in the arterial tree.1 This has led to a “geometric risk factor” hypothesis implicating local hemodynamic factors in atherogenesis.2 Studies have generally implicated low, or low and oscillating, wall shear stress (WSS) in atherogenesis.1,3-6

Asakura and Karino1 were the first to report an association between low WSS and intimal thickening in the right coronary artery (RCA). Subsequently, Krans et al7 showed that RCA locations with lower average WSS had higher average wall thickness; however, their study did not explicitly show that low WSS colocalized with high wall thickness, because of the axial averaging technique they used. Giannoglou et al8 found an inverse correlation between wall thickness and WSS in 1 of 3 RCA segments. Their study was limited to a 2-dimensional computational analysis to obtain WSS, which neglects important secondary flow hemodynamic effects that significantly affect WSS patterns.9 Stone et al also found that, on average, regions of low WSS showed an increase in plaque thickness, whereas regions of high WSS showed a decrease in plaque thickness. This study followed plaque progression in vivo in segments of the right and left coronary arteries of 6 patients over a 6-month period.10 Wentzel et al11 found an inverse relationship between WSS and intimal thickening in coronary arteries, but only in vessel segments that showed <10% lumen area reduction.

If low (or low and oscillating) WSS is atherogenic in the RCA, as is frequently claimed in the literature, then we reasoned that there should be an evident colocalization of intimal thickness and low WSS. Most importantly, this correlation should be statistically significant when tested on a point-by-point basis over the entire RCA. To date, no study has looked for such a correlation in a quantitative manner over the entire artery.

The objective of this study was to determine whether a significant correlation between intimal thickness and WSS exists in the RCA. To do so, we compared postmortem histological measurements of intimal thickness (IT) to WSS calculated from computational flow modeling in 4 RCAs.

Methods

Coronary Artery Casting

Four intact human hearts were obtained at autopsy from patients whose primary cause of death was not cardiac-related (Table). Patient medical records indicated that patients 2, 3, and 4 were smokers, and patient 2 had hypertension. No other systemic risk factors for atherosclerosis (diabetes, hyperlipidemia, previous myocardial infarction or angina, obesity, heart valve disease, family history, sedentary lifestyle) were noted in any of the patient records.

The geometry of each RCA was characterized by casting, as previously reported.9 The RCA and surrounding tissue were then carefully dissected from the heart. The cast was removed by an incision along the myocardial surface of the dissected tissue. This allowed the tissue to remain intact for histological analysis.

Morphometric Analysis of RCA Tissue

The tissues and casts were photographed and landmark features (branches) identified. Three-millimeter-long segments of RCA were
collected along the length of the RCAs, embedded in paraffin, sectioned perpendicular to the axis of the artery from the distal end of the 3-mm segment, and stained with a modified Verhoff elastic–trichrome stain. Each resulting cross-section was visualized using a Leica DMRB light microscope with digital imaging (Leica Q500MC image processing software). IT was measured at 8 equally spaced locations about the circumference of each cross-section (Figure 1). The IT was taken as the distance from the lumen surface to the internal elastic lamina, measured perpendicular to the lumen surface.

**Model Construction**

Each cast was CT-scanned using an isotropic voxel size of 207 μm, and a finite element model of the artery was constructed using a previously published technique (Figure 2). Branches large enough to be resolved using this technique (diameter >0.8 mm, or ≈4 voxels across the lumen) were also segmented to obtain branch cross-sectional contours. Each artery model had branches that were visible on the Batson cast but too small to segment from the image volume, and thus were omitted in the model reconstruction. It was difficult to segment the branch ostia regions, so these areas were approximated by smooth filleted surfaces. This approach was adequate because this study was focused on the flow in the trunk of the RCA. In other words, branches were included only because of their effect on the local blood flow rate in the RCA trunk. It was therefore important to construct branches with the correct diameter and branching angle, but not to capture the exact geometry of the branches and branch ostia.

These contours were smoothed, imported into a computer-aided design software package (DDN; ICEM-CFD), and used to reconstruct the artery surface. To facilitate flow modeling, a 5-inlet diameter-long straight inlet extension, a 15-outlet diameter-long outlet extension, and 15-branch diameter-long branch extensions were added to the model. The artery geometry was meshed with quadratic tetrahedral elements (Tetra meshing module; ICEM-CFD).

**Computational Fluid Dynamics**

Steady and pulsatile blood flow was simulated by a 3-dimensional Navier-Stokes flow solver using standard techniques. Blood rheology was assumed to be Newtonian and vessel boundaries were considered stationary and rigid. All simulations used flow rates appropriate for resting conditions, giving a Reynolds number (based on inlet diameter) of 233 for steady-flow simulations. For a blood viscosity of 3.5 centiStokes (cStokes), this corresponds to a flow rate of 1.7 mL/s in a 2.7-mm diameter artery. Pulsatile simulations used a physiologically realistic flow waveform with mean Reynolds number of 233 and a Womersley parameter of 1.82.

Measured flow rates entering each branch were not available. Therefore, flow rates in each branch were computed using a third
power law, equivalent to assuming the same average shear stress in each branch as at the inlet of the RCA. If the inlet diameter and flow rate are $D_i$ and $Q_i$, then the flow rate entering a branch of diameter $D_b$ is given by

$$Q_b = Q_i \left( \frac{D_b}{D_i} \right)^3$$

This third power law has been suggested to govern vessel sizing throughout the arterial tree.\(^{15–17}\) For 2 arteries (cases 1 and 2), all simulations were repeated with branch outflow set to zero to assess the influence of branch flows on hemodynamic patterns in the RCA trunk.

**Data Analysis**

The WSS was calculated by postprocessing the velocity data from the flow simulations.\(^{14}\) For unsteady flow simulations, the WSS field was calculated at 100 evenly spaced time points in the flow cycle and the cycle average WSS, cycle maximum WSS, and cycle minimum WSS and oscillatory shear index (as defined by Ku et al\(^{4}\)) were calculated.

To examine the relationship between IT and WSS, the IT measurements from the RCA tissue samples were spatially registered onto the computer representation of the artery. The axial position of each histological section with respect to the computer model was determined using photographs and sketches made during the artery dissection and landmarks such as bends and branch points. The circumferential orientation of each section was determined by matching the location of the scalpel incision on the histological section with the mark left on the artery cast by the same incision. Each histological measurement was thus assigned a coordinate in the 3-dimensional model space. Later, a computer algorithm found the nearest wall node on the finite element model to the location of the histological measurement.

**Statistical Analysis**

Each IT measurement was paired with a calculated WSS value at the wall node closest to the measurement location, and a correlation between WSS and IT was sought. The average nodal spacing of the finite element mesh was 0.05 R, so the assignment of values to the nearest wall node introduced a negligible amount of error into the registration process.

In addition to searching for a correlation between WSS and IT, we wished to examine the circumferential variation in IT and WSS, to see whether WSS patterns could explain eccentric intimal thickening. However, preliminary analysis showed that both IT and WSS depended quite strongly on axial position and hence on local arterial caliber (because arterial caliber decreased with distance from the RCA ostium). To isolate circumferential variations, we therefore analyzed the data a second way. IT values were normalized to the mean IT at each histological cross-section, and WSS values were normalized to the mean WSS at each cross-section. These locally normalized values measured circumferential variations in IT and WSS and were independent of local lumen diameter and axial position.

All correlations were evaluated using the Spearman rank order correlation. Correlations were considered significant if $P<0.05$ using a 2-tailed test. In addition to correlations based on steady-flow simulations, all analyses were repeated using the cycle average, cycle maximum, and cycle minimum WSS from pulsatile flow simulations. The results were similar to those for steady-flow simulations and are not shown here.

**Results**

**Hemodynamic Environment**

In all 4 RCA models, the combination of complex curvature and changes in arterial caliber created a heterogeneous WSS field (Figure 3). On average, the WSS was lower on the inner wall than the outer wall in regions of strong medial plane curvature; however, the presence of transverse curvature created low and high WSS regions in other areas. The branch ostia regions showed recirculating flow, with low WSS regions upstream of the branch ostia, and high WSS regions downstream of the branch ostia. There were significant differences in the WSS field between models (Figure 3) caused by the differences in arterial geometry. Unsteady flow simulations yielded time-average WSS fields that were similar to the steady-flow WSS fields. The oscillatory shear index was found to be zero everywhere in the models except for small regions around the branch ostia. It is important to note that there was a tendency toward higher WSS values in the distal part of the arteries, and neglecting branch flows exacerbated this tendency.

**Morphometric Analysis and Correlations**

All patients were free of severe coronary artery disease (classified as nonatherosclerotic intimal lesion\(^{19}\)). Approximately 80% of the sections were classified as showing intimal thickening,\(^{19}\) whereas the remaining 20% were classified as showing intimal xanthoma.\(^{19}\) A more detailed classification of plaque morphology and location was not possible in this study because of the fact that macrophages were not specifically stained for. Eccentric intimal thickening was evident in cases 1, 3, and 4. No section showed histological evidence of previous plaque rupture. The mean IT and the number of IT measurements for each artery are given in Table.

Cases 1, 2, and 4 showed inverse correlations between IT and WSS, but only in case 1 was this correlation statistically significant (Table). Further examination of the IT measurements revealed that histological sections from the distal regions of each artery tended to have a lower mean IT than sections from more proximal regions. It was also noted that the WSS tended to increase in the distal regions as a result of the decreased arterial caliber. To quantify this observation, the IT measurements and the WSS values were correlated against axial position (from the ostium). In all 4 cases, IT was inversely correlated with axial position and in cases 1, 2, and 4. This correlation was statistically significant (Table). WSS magni-
tude was positively correlated with axial position in all cases, and this correlation was statistically significant in cases 1, 3, and 4 (Table).

Scatter plots of normalized IT plotted against normalized steady-flow WSS magnitude are shown in Figure 4. The data points are colored by axial position, where data points from the histological cross-section closest to the RCA ostium have a nonparametric axial position of 1, data points from the next cross-section moving distally have a nonparametric axial position of 2, and so on. The coloration of the points shows how points from the distal region of the arteries tend to have lower IT and higher WSS than points from the proximal region.

Because both IT and WSS showed correlations with axial position, locally normalized values of IT and WSS were calculated (see Methods) that were independent of axial position (Figure 5). Cases 1, 2, and 3 showed weak positive correlations between the locally normalized IT and WSS, whereas case 4 showed a statistically significant inverse correlation (Table).

**Branch Flow Sensitivity**

In cases 1 and 2, flow simulations were repeated with branch outflows set to zero to assess the impact of branch outflows. The inclusion of branch flows primarily affected the axial variation in WSS. The correlation between WSS and axial position was stronger in the absence of branch outflows for cases 1 and 2 (Table). The inverse correlation between IT and WSS was also stronger in both cases when branch outflows were ignored (Table). Local flow disturbance at the branch ostia sites did not have an impact on the correlation results in this study. Omission of data points near the branch ostia did not affect the correlations.

**Discussion**

**Dependence of WSS and IT on Axial Position**

In this study of 4 human right coronary arteries, it was surprising that a consistent relationship between IT and WSS was not observed. In those cases in which a correlation was seen between IT and WSS, it was apparently a result of a codependence of IT and WSS on axial position within the artery. In case 1, for instance, a significant inverse correlation was observed between IT and WSS, but when normalized locally, no correlation exists. This indicates that the correlation between IT and WSS is driven by a tendency toward lower IT and higher WSS in the distal region of the artery. Similarly, when branch flows are neglected in case 2, effectively increasing the WSS in the distal regions, a significant inverse correlation is observed between IT and WSS that is not observed when branch flows are included.

The decrease in IT with increasing axial position agrees with previously reported results.1,20 In our study, cases 1, 3, and 4 showed a statistically significant positive correlation between WSS and axial position (WSS increasing in the distal region). This increase in WSS seems to be caused by our inability to model the many small branches that emanate from the RCA, and which were particularly notable in cases 1, 3, and 4. In other words, “too much” blood flowed in the distal portion of the RCA trunk in our simulations for cases 1, 3 and 4, giving an artifactual elevation of WSS. The results for case 2 were consistent with this conclusion. This case had very few small branches (so that we were better able to account for branch flows) and did not show a significant correlation between WSS and axial position. These results are also consistent with the widely held belief that arteries adjust their local caliber, so as to reach a target value of WSS,15–17 so that a
gradual increase in WSS with axial distance would be unexpected in the RCA. The net implication of all of these data is that it is important to accurately model all branch outflows if global correlations are sought that involve hemodynamic variables in the RCA.

**Relationship Between Locally Normalized IT and WSS**

Fortunately, there is a way that we can analyze the data that ignores this axial dependence. This involved correlating locally normalized IT with locally normalized WSS, which essentially looked for a relationship between circumferential variations in WSS and circumferential variations in IT. When analyzed in this way, only case 4 showed a statistically significant (negative) correlation. These results indicate that the asymmetrical distribution of IT at a given cross-section in the RCA does not correlate with the circumferential WSS distribution at that section. Further, if the magnitude of WSS were responsible for eccentric intimal thickening, one would expect that regions of the RCA with the greatest curvature, and hence largest circumferential WSS differentials, would exhibit pronounced eccentric intimal thickening. Qualitative examination of our samples showed that this was not the case.

These findings are seemingly contradictory to those of other studies that have linked WSS to IT in various arteries. In general, the studies that have found a quantitative correlation between atherosclerotic changes in the vessel wall and WSS have used averaged data. In our specimens exhibited early disease, for which others have shown a relationship between WSS and IT. This difference in findings may be caused by different patient populations (Wentzel et al. used subjects with pre-existing clinically significant coronary artery disease), averaging approaches (Wentzel et al. averaged axially), and modeling methodologies. Tissue shrinkage during histology is another limitation. Although uniform tissue shrinkage would not affect our conclusions, if nonuniform shrinkage of the vessel wall was present, then it could have confounded our results.

This study used rigid, stationary vessel boundaries; however, in vivo the RCA moves and is distensible. A previous study showed that RCA motion influenced the instantaneous WSS field but did not significantly affect the time-average WSS field. Further, the effect of artery motion on instantaneous WSS is small compared with the effect of flow pulsatility. Similarly, a study in the carotid artery bifurcation showed that distensibility does not materially affect the time-averaged WSS. Therefore, we expect that inclusion of vessel motion and wall distensibility would not change our conclusions.

Patient-specific flow waveforms, inlet velocity profiles, and branch flow rates were not available. The flow waveform used for this study is suitable for resting conditions but does not have a reverse-flow component. Our results would not be valid for patients with a strong reverse-flow component in their RCA waveform. Because we do not have detailed information about the velocity profile entering the RCA, the inlet velocity profile was assumed to be fully developed and symmetric. A previous study demonstrated that the effects of inlet flow profile only persisted for the first 9 inlet diameters from the RCA ostium. We therefore repeated all of these correlations,
omitting this inlet region of the artery, and obtained similar results. We conclude that uncertainty about inlet velocity profiles does not affect our conclusions. Finally, we did not have information about branch flow rates. We used the best available estimates of such flow rates (third power law), but if this was shown to be invalid in the coronary vasculature, then our conclusions could change.

Finally, only 4 RCAs were available for this study, and a larger sample would be required to fully investigate how WSS could interact with other local and systemic risk factors to promote intimal thickening.

Summary
We are unable to find a consistent correlation between early intimal thickening and WSS in human RCAs. This result is initially surprising and contradictory to results of other studies. However, this may be caused by the fact that previous studies have looked only at average trends and/or looked only at selected segments of the artery. Our data provide little evidence for a dominant role of WSS magnitude in the localization of intimal thickening in the 4 human RCAs studied.

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References
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