Profiles of Velocity in Coronary Arteries of Dogs Indicate Lower Shear Rate along Inner Arterial Curvature

David R. Bell, Hani N. Sabbah, and Paul D. Stein

Multiple-range, gate-pulsed Doppler velocimetry was used to examine the velocity profile within the lumen of the left circumflex and left anterior descending coronary arteries of 10 anesthetized, open-chest dogs at rest and after administration of propranolol and intracoronary adenosine. The peak diastolic and mean profiles of velocity were skewed away from the inner walls of the vessels \( (p<0.01) \). The extent of skewness was not affected by propranolol or adenosine. The shear rates were significantly lower along the inner wall in comparison to the outer wall under all conditions in both the left circumflex and the left anterior descending coronary arteries \( (p<0.017) \). Irrespective of the levels of flow, therefore, the velocity profiles were skewed away from the inner wall of the coronary arteries. Consequently, the shear rates were lower along the inner walls of the coronary arteries.


Curvature of arteries alters the shear stress at the wall from that which would occur in straight vessels. The magnitude and location of high- and low-shear stress may be important because shear stress may contribute to atherogenesis. Theories that implicate either low-shear stresses or high-shear stresses in the pathogenesis of atherosclerosis have been proposed.\(^1-^5\) Subsequent investigations have shown an influence of shear upon endothelial structure, function, and intimal thickening.\(^6-^22\)

In the coronary vasculature, the large epicardial vessels display a significant curvature as they course over the surface of the heart. In flow through curved tubes, the profile of velocity is skewed away from the inner wall, resulting in lower shear stresses near the inner curvature of the tube.\(^23\) In curved tubes, the effects of increased flow on wall shear are not easily predicted. Increased flow in a curved tube may increase the skewness of the velocity profile, altering the relative magnitude of shear at the inner and outer walls.\(^23\) In addition, high flows can introduce secondary flows in the velocity profile.\(^24\) This factor may tend to reverse the skewness of the velocity profile in a curved tube.\(^25\) Although several investigators have reported the profile of velocity in the coronary arteries of animals,\(^26-^29\) there is no general agreement as to the configuration of the velocity profiles in the coronary arteries.

The shear stress at the wall of arteries caused by the flowing blood is defined as the product of the effective blood viscosity and the shear rate.\(^30,31\) The shear rate at the wall is the velocity gradient at the wall \( (du/dy, \text{ where } u \text{ is velocity in the axial direction and } y \text{ is the distance in the radial direction}) \).\(^30\) To measure shear rate, one must measure axial velocity at various distances from the wall. The configuration of axial velocity across the diameter of the artery is known as the profile of velocity. Alterations of the slope of the velocity profile near the wall indicate changes of the shear rate and, therefore, shear stress at the wall.

A higher prevalence of atherosclerosis along the inner wall of the left anterior descending and the right coronary arteries of patients has been observed.\(^32,33\) This is the surface where velocity is lower and shear rate, presumably, is lower. In view of this observed preferential location of atherosclerosis, it is useful to know the relative differences of shear at the inner and outer curvatures, irrespective of the magnitude of flow. The effects of changes of the magnitude of flow on the shear rate at the walls of the coronary arteries are not known. The purpose of this study, therefore, was to assess the shear rate at the walls of the coronary arteries of dogs at rest and during pharmacological augmentations and reductions of flow.

**Methods**

Ten mongrel dogs weighing 19 to 39 kg of either sex were anesthetized with a bolus intravenous injection of sodium pentobarbital (300 mg), fentanyl (1.2 mg), and droperidol (60 mg) and were maintained with intravenous infusions of pentobarbital (0.9 mg/min), fentanyl (0.007 mg/min), and droperidol (0.36 mg/min). Respiration was maintained with a Harvard pump connected to a cuffed endotracheal tube.

Arterial pressure was measured with a catheter-tip micromanometer (Millar Instruments, Houston, TX) placed within the aortic root and recorded with lead II of the electrocardiogram on an Electronics for Medicine (Honeywell, White Plains, NY) recorder.
In all dogs, a left thoracotomy was performed, and the heart was cradled within the pericardial sac. In all 10 dogs, auffed pulsed-Doppler ultrasonic transducer was placed on the circumflex coronary artery proximal to the second marginal branch. In seven of these dogs, an ultrasonic cuff transducer was also placed on the mid-left anterior descending coronary artery proximal to the second diagonal branch. The ultrasound beam emitted from the crystal was perpendicular to the underlying myocardium. The orientation of the cuff about the artery was alternated randomly so that the ultrasound beam was directed from the inner to the outer wall of the artery in some dogs and from the outer to the inner wall in others. The transducers were connected to a multiple-range, gate-pulsed Doppler velocimeter\(^2\) for the simultaneous measurement of blood velocity at eight equidistant locations across the lumen of the artery. The delay between the signal from each location was 8\(\mu\)sec.\(^2\) This allowed a recording of a virtually simultaneous eight-gate velocity profile across the artery. In the recording of profiles, the span of the Doppler signal adjusted for all measurements as near to both walls as possible. This was accomplished by having a velocity that was nearly zero at gates 1 and 8. This allowed measurement of velocity as near to the wall as technically feasible. Preliminary observations based on polynomial curve fits of the velocity profiles indicated that gates 1 and 8 could be adjusted to within 50 to 200 \(\mu\)m of the inner arterial walls if phasic velocities were recorded and within 10 to 100 \(\mu\)m if mean velocities were recorded.

The distance between gates 1 and 8 (Doppler span) was then noted. The peak diastolic profiles of velocity and mean profiles (time averaged over the entire cardiac cycle) were recorded on a storage oscilloscope (Tektronix, Incorporated, Beaverton, OR) and were photographed. Profiles were examined during control conditions, after an intravenous bolus injection of propranolol (3 mg), and after an intracoronary infusion of adenosine (200 \(\mu\)g/min) through a 26-gauge curved needle inserted in the coronary artery distal to the Doppler transducer.

Individual velocity profiles were reconstructed by fitting the experimental data (eight gates) to a third, fourth, or fifth order polynomial. The degree of the polynomial was selected on the basis of a correlation coefficient of 0.95 or higher. These equations were then used to extrapolate the profiles to zero velocity. The site of zero velocity was considered to be the location of the arterial wall.

The shear rate (du/dx, sec\(^{-1}\)) at the inner and outer wall of the coronary artery was calculated from the fitted curves. The differences between the shear rates at the inner and outer walls of the arteries for each experimental condition were compared using Student's paired \(t\) test with the Bonferroni correction for multiple comparisons. A probability of \(p<0.017\) was considered significant. The effects of experimental conditions on this difference were further tested with Hotelling's multiple \(T^2\) comparison.

For the purpose of providing a statistical means of assessing the effects of flow on the skew of the velocity profile, we first determined the extent of skewness of each velocity profile as follows: The centerline between gates 1 and 8 for each profile was given the value of zero, and the radius in each direction from the centerline was normalized to 100%. The area under each profile was bisected by the median line. The distance between the median line and the centerline \((f)\) was measured and expressed as a percent of the radius. This percent was the measure of skewness. In this example, the profile is skewed 14% toward the outer arterial wall.

\(\text{OW} = \text{direction of the outer arterial wall, } \text{IW} = \text{direction of the inner arterial wall.}\)

**Figure 1.** Method for quantifying skewness of a velocity profile (cm/sec). The area beneath the velocity profile was bisected by the median line. The distance between the median line and the centerline \((f)\) was measured and expressed as a percent of the radius. This percent was the measure of skewness. In this example, the profile is skewed 14% toward the outer arterial wall.

**Table 1. Hemodynamics**

<table>
<thead>
<tr>
<th>Coronary artery</th>
<th>Heart rate</th>
<th>Blood pressure</th>
<th>Doppler span</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(min(^{-1}))</td>
<td>(mm Hg)</td>
<td>(mm)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>Control (n=10)</td>
<td>104±12</td>
<td>118/85±6/4</td>
</tr>
<tr>
<td></td>
<td>Propranolol (n=10)</td>
<td>76±8</td>
<td>107/75±3/3</td>
</tr>
<tr>
<td></td>
<td>Adenosine (n=9)</td>
<td>73±6</td>
<td>106/72±5/4</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>Control (n=7)</td>
<td>101±8</td>
<td>121/87±7/6</td>
</tr>
<tr>
<td></td>
<td>Propranolol (n=7)</td>
<td>67±7</td>
<td>110/76±5/4</td>
</tr>
<tr>
<td></td>
<td>Adenosine (n=7)</td>
<td>73±8</td>
<td>106/73±9/6</td>
</tr>
</tbody>
</table>

The mean heart rate, arterial pressure, and Doppler span for all experimental conditions are listed in Table 1.
Heart rate and arterial pressure were reduced with propranolol and intracoronary adenosine compared to control values. The Doppler span across the arteries (approximate arterial diameter) was not affected by either drug.

A schematic diagram of the epicardial vessels and a skewed velocity profile are shown in Figure 2. Skewing of actual profiles was observed when the ultrasound beam was oriented in the plane of myocardial curvature (perpendicular to the myocardial surface; Figure 3A). There was no curvature of the circumflex artery in the apex-to-base orientation of the ultrasound beam. When the ultrasound beam was aimed in that direction, we observed no skewing of the velocity profile (Figure 3B).

The profiles of velocity averaged among all of the dogs studied during peak coronary flow are summarized in Figures 4 and 5. Velocity at all points across the diameter increased with adenosine but was little affected by propranolol. The velocity profiles for peak diastolic and mean flow averaged among the dogs were skewed toward the outer wall (Table 2). The magnitude of this skewness was not affected by propranolol or adenosine (not significant by Hotelling's $T^2$ analysis).

Individual profiles of velocity at peak coronary flow used for calculating shear at the wall in the left circumflex and left anterior descending coronary arteries are shown in Figures 6 and 7. Only profiles at rest and after an intracoronary infusion of adenosine are shown. Profiles with propranolol were similar to those obtained at rest. At rest, the peak diastolic profiles were skewed toward the outer wall in the circumflex coronary artery of 8 of 10 dogs. In the left anterior descending coronary artery, the profiles were skewed toward the outer wall in six of seven dogs. All velocity profiles were skewed toward the outer wall after an augmentation of flow by adenosine. The profiles of mean flow were skewed in a similar direction as the profiles of peak diastolic flow.

The peak diastolic shear rates at the inner and outer walls of the arteries during control conditions and with propranolol and adenosine are shown in Figures 8 and 9. Shear rates at mean flow are shown in Figures 10 and 11. Shear rates were greater near the outer wall during all experimental conditions. The difference in shear rate between the inner and outer walls at peak diastolic or
Regarding limitations of the experimental approach, one problem was to know the distance from the arterial walls of the first and last measured velocities (first and last gates). The measuring volume of each gate was no greater than 0.3 mm². The ability to get close to the wall was diminished somewhat because of pulsation of the arterial wall. This was partially overcome by use of mean velocity signals to adjust the gates. In aligning the gates, we advanced both gates as close to the wall as possible without introducing artifacts due to the effects of the walls upon the signal. Based upon extrapolation of third to fifth order polynomial curve fits of the velocity profiles, we calculated that the first and last gates were within 50 to 200 μm of the walls of the arteries when a pulsatile signal was recorded. The distances between the measured velocity gates ranged between 0.33 mm to 0.46 mm based on arterial internal diameters between 2.3 mm and 3.2 mm. In the estimation of shear rate, we based our calculations upon the assumption that the velocity at various distances from the wall followed the third to fourth order polynomial curve fits through the eight measured points.

We do not believe that any artifact was introduced by the application of the cuff. This was confirmed by finding skewing of profiles when the cuff was placed in the plane of curvature; however, skewing was not observed if a cuff was placed normal to the plane of curvature.

Profiles of velocity in the plane of the myocardial curvature have been reported by several investigators using pulsed-Doppler ultrasound, laser Doppler anemometry, and hot film anemometry. There have been inconsistent observations as to the configuration of the velocity profiles in the coronary arteries. Nerem et al. reported skewing of the profiles of velocity away from the inner wall of the left common main coronary artery of horses, which was consistent with our observations. However, resting velocity profiles in the left anterior descending and circumflex coronary arteries of the horse did not show consistent skewing. Later, Altobelli and Nerem showed that the velocity profile in the coronary arteries of excised, fixed, perfused baboon hearts usually was skewed away from the inner curvature of the vessel. Sabbah et al demonstrated in patients that the clearance of radiopaque contrast material in the left anterior descending and right coronary arteries was retarded at the inner wall, suggesting that blood velocity and shear was lower along the inner wall of these vessels. Wells and associates, using pulsed-Doppler ultrasound velocimetry, observed no skewing. Kajiya and associates, using laser Doppler anemometry, showed inconsistent skewing of the velocity profile in the circumflex coronary artery of anesthetized dogs.

There are several possible explanations for the nonuniform observations in previous studies. We observed that the skewness of the velocity profile is more apparent with a higher blood flow. Studies of velocity profiles in the coronary arteries examined only at rest may not show skewness as clearly as if high flow were produced. Also, the technique used in the present study allowed simultaneous measurements of velocity at several points within the arterial lumen, without invading the vessel, and there-
Figure 6. Velocity profiles during peak flow (cm/sec) in the left circumflex coronary artery of individual dogs during control conditions (○) and with adenosine (△). Profiles were reconstructed by fitting the experimental data (velocity at eight equidistant points within the coronary lumen) to a third, fourth, or fifth order polynomial equation and extrapolating the profile to zero velocity. Adenosine was not used in Dogs 7 and 10. OW=outer wall, IW=inner wall.
Figure 7. Velocity profiles during peak flow (cm/sec) in the left anterior descending coronary artery of individual dogs during control conditions (○) and with adenosine (△). The profiles were reconstructed as in Figure 3. OW=outer wall, IW=inner wall.
Figure 8. Shear rate ($du/dx$, sec$^{-1}$) at peak flow at the inner and outer walls of the left circumflex coronary artery during control (n=10), after propranolol (n=10), and after adenosine (n=8). Values represent mean±SEM, *p<0.017 outer vs. inner wall. PROP=propranolol.

Figure 9. Shear rate ($du/dx$, sec$^{-1}$) during peak flow at the inner and outer walls of the left anterior descending coronary artery during control (n=10), propranolol (n=10), and adenosine (n=8). Values represent mean±SEM, *p<0.017 outer vs. inner wall. PROP=propranolol.

Figure 10. Mean shear rate ($du/dx$, sec$^{-1}$) at the inner and outer walls of the left circumflex coronary artery during control (n=10), propranolol (n=10), and adenosine (n=7). Values represent mean±SEM, *p<0.017 outer vs. inner wall. PROP=propranolol.

Figure 11. Mean shear rate ($du/dx$, sec$^{-1}$) at the inner and outer walls of the left anterior descending coronary artery during control (n=10), propranolol (n=10), and adenosine (n=6). Values represent mean±SEM, *p<0.017 outer vs. inner wall. PROP=propranolol.

Part of the difficulty in assessing the relation between shear and atherogenesis arises from a lack of a direct means of measuring the complex flow patterns in regions predisposed to atherosclerosis, particularly near the orifice of branches. Also, there is difficulty in assessing the relation between shear and atherogenesis due to differences of the observed localization of lesions in various animal models. For example, sudanophilic lesions develop distal to the origin of branches of the aorta, an area of high shear, in rabbits and dogs fed atherogenic diets. However, spontaneous atherosclerotic lesions in humans and in pigeons, as well as lesions in hypercholesterolemic pigs, appear in low-shear regions near the ostia of branches. In the hypercholesterolemic minipig, sudanophilic lesions frequently were not at sites of apparent high or low shear. High shear regions of artificial stenoses in animals fed atherogenic diets have been shown to be spared from lipid deposition.

High-shear stresses of 400 to 1000 dynes/cm$^2$ can alter endothelial structure and macromolecular transport, whereas stresses above 1000 dynes/cm$^2$ may result in endothelial denudation. These observations formed the basis for a hypothesis of atherogenesis based on high shear and endothelial damage. We did not observe shear stresses as high as 400 to 1000 dynes/cm$^2$ in the coronary arteries of dogs. Assuming a blood viscosity of 0.04 poise, the maximal calculated shear stress that we observed was approximately 170 dynes/cm$^2$. This level was observed along the outer wall of a circumflex coronary artery of one dog after blood flow increased approximately sixfold with adenosine. Such flow occurs only with maximal vasodilation.

The influence of shear stress on endothelial cells has been examined. Endothelial cells become more elongated and oriented with the direction of flow with increased shear stress. Certain endothelial cell functions, including fluid endocytosis and cytoskeletal assembly, also are sensitive to shear stress. Endothelial prostacyclin production is enhanced by shear stress that is pulsatile. In addition, turbulent shear stress has been found to enhance proliferation of cultured endothelial cells. Endothelial cells develop greater mechanical stiffness, which is related, with the magnitude and duration of exposure, to shear stress. It has been shown that the transport of albumin...
and low density lipoproteins to the arterial wall relates to the magnitude of wall shear stresses. It is not clearly established how low shear may influence atherogenesis. Caro and associates suggested that shear enhances mass transport by means of a steepening effect on the concentration gradient. Subsequently, however, Caro and Nerem showed that cholesterol uptake by arteries is not limited by diffusion boundary layer conditions.

In summary, velocity profiles in the left anterior descending and circumflex coronary arteries of dogs were skewed away from the inner wall. This skewness was apparent during control conditions and was more evident at high flows. Consequently, shear rate was consistently lower along the inner wall of the coronary arteries in comparison to the outer wall.

References


Index Terms: coronary artery • velocity profile • shear rate • dogs
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