Flow recirculation zone length and shear rate are differentially affected by stenosis severity in human coronary arteries

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Javadzadegan A, Yong AS, Chang M, Ng AC, Yiannikas J, Ng MK, Behnia M, Kritharides L. Flow recirculation zone length and shear rate are differentially affected by stenosis severity in human coronary arteries. Am J Physiol Heart Circ Physiol 304: H559–H566, 2013. First published December 15, 2012; doi:10.1152/ajpheart.00428.2012.—Flow recirculation zones and shear rate are associated with distinct pathogenic biological pathways relevant to thrombosis and atherogenesis. The interaction between stenosis severity and lesion eccentricity in determining the length of flow recirculation zones and peak shear rate in human coronary arteries in vivo is unclear. Computational fluid dynamic simulations were performed under resting and hyperemic conditions on computer-generated models and three-dimensional (3-D) reconstructions of coronary arteriograms of 25 patients. Boundary conditions for 3-D reconstructions simulations were obtained by direct measurements using a pressure-temperature sensor guidewire. In the computer-generated models, stenosis severity and lesion eccentricity were strongly associated with recirculation zone length and maximum shear rate. In the 3-D reconstructions, eccentricity increased recirculation zone length and shear rate when lesions of the same stenosis severity were compared. However, across the whole population of coronary lesions, eccentricity did not correlate with recirculation zone length or shear rate (P = not significant for both), whereas stenosis severity correlated strongly with both parameters (r = 0.97, P < 0.001, and r = 0.96, P < 0.001, respectively). Nonlinear regression analyses demonstrated that the relationship between stenosis severity and peak shear was exponential, whereas the relationship between stenosis severity and recirculation zone length was sigmoidal, with an apparent threshold effect, demonstrating a steep increase in recirculation zone length between 40% and 60% diameter stenosis. Increasing stenosis severity and lesion eccentricity can both increase flow recirculation and shear rate in human coronary arteries. Flow recirculation is much more sensitive to mild changes in the severity of intermediate stenoses than is peak shear.

LOCAL PHYSIOLOGICAL PERTURBANCES within coronary arteries resulting from atherosclerosis are known to be associated with detrimental pathogenic processes (2). Recirculation zones within blood vessels cause increased stasis and are associated with endothelial dysfunction, atheroma formation, and thrombosis (18, 20). High shear rate causes platelet and leukocyte activation, which initiate distinct proinflammatory and prothrombotic states (2, 34).

Coronary lesion severity is often graded by the amount of lumen encroachment or stenosis it causes, and most clinical decisions are made based on lesion stenosis severity (23). However, other lesion characteristics, such as eccentricity (11, 32), are determinants of both shear rate and the extent of flow recirculation in vitro (35) and in computational fluid dynamic (CFD) analysis of carotid arteries (16, 25, 27). However, coronary and carotid arteries differ in many important respects, including their diameter, flow patterns, and tortuosity, and each of these could modulate flow recirculation and shear stress. To our knowledge, no studies have systematically evaluated the determinants or predictors of flow recirculation and shear stress in realistic geometries of diseased human coronary arteries.

The aim of this study was to examine the determinants and predictors of flow recirculation zones and shear rate in human coronary arteries, with a particular emphasis on the roles of stenosis severity and lesion eccentricity. CFD analyses of computer-generated coronary artery models and three-dimensional (3-D) reconstructions of diseased human coronary arteries were used to investigate these relationships.

MATERIALS AND METHODS

Computer-Generated Models

Computer-generated models of coronary arteries were created using SolidWorks (Dassault Systems, Concord, MA). The basic coronary artery template was created based on average values obtained from coronary angiograms from the Department of Cardiology of Concord Repatriation General Hospital. The diameter of the arteries was set at 3 mm. Total length of the arteries was set at 8.1 cm with inlet length set at 12 mm, outlet length set at 63 mm, and lesion length set at 6 mm. These lengths were chosen to allow for the full development of fluid flow for accurate CFD simulation and also to prevent inaccuracies that occur due to proximity with the boundary condition set. Models with 30%, 50%, and 80% diameter stenosis were produced. For each level of diameter stenosis, separate models with varying eccentricity were created. Eccentricity was quantified by the eccentricity index (EI), as previously described (11), with EI ranging from 0 to 1, where an EI of 0 represents no eccentricity and 1 represents a lesion with the highest eccentricity.

Patient Cohort

Consecutive patients who presented to the cardiac catheterization laboratory for elective fractional flow reserve-guided coronary intervention of a single target lesion in the proximal or mid left anterior descending coronary artery at our institution were recruited. All patients underwent coronary angiography and physiological measurements within their coronary arteries. Written informed consent was obtained for all patients, and the study was approved by the Human Ethics Committee of Concord Hospital.

3-D Reconstructions of Patients’ Arteries and EI

3-D arterial reconstructions of 25 patients with stenosis in the left anterior descending coronary artery were obtained using 3-D quanti-
tative coronary angiography as previously described (33). In brief, angiographic cine images were acquired at 15 frames/s, consistent with the standard coronary angiography protocol in our institution (Axiom Artis, Siemens, Forchheim, Germany). Vessels were reconstructed offline using 3-D reconstruction software on a Leonardo workstation (IC3D, Siemens), which was derived from the Cardio-op B system (Paieon Medical, Rosh Ha’ayin, Israel). The contrast-filled nontapered part of the guiding catheter was used to calibrate pixel size. The two best orthogonal angiographic views of vessel in the end-diastolic frame were used for the reconstructions. EI was quantified for each lesion as previously described (11).

Physiological Measurements

To validate our CFD results, provide an estimate of flow for individual patients during rest and hyperemia, and subsequently investigate the relationship between coronary physiology measurements and recirculation and peak shear, physiological measurements were performed in all patients before coronary intervention, as previously described (14, 33). In brief, a 6-F angioplasty guiding catheter without side holes was first used to engage the left main coronary artery. A pressure-temperature sensor guidewire (0.036 cm in diameter, Certus Pressure Wire, St. Jude, St. Paul, MN) was used for physiology measurements. The pressure measurement from the wire was first equalized with that of the guiding catheter. The lesion was crossed, and the pressure sensor was positioned two-thirds of the way down the artery, at least 3 cm beyond the lesion. Intracoronary nitroglycerin was administered (100–200 μg). To derive mean transit time at rest (TmnR), thermodilution curves were obtained by three injections of 3 ml of room temperature saline down the coronary artery. Hyperemia was induced using an infusion of adenosine (140 μs g ⁻ min ⁼) via the femoral vein, and mean transit time during hyperemia (TmnH) was recorded. Proximal arterial pressure (Pa) and distal arterial pressure (Pd) were recorded both at rest and during hyperemia. As previously described, coronary flow reserve (CFR) was calculated as follows: CFR = TmnH/TmnR (33).

CFD Analysis

CFD analysis was performed using a slightly modified method from one that we have previously published (34). In brief, computer-generated models were imported into mesh generation software (ANSYS CFX 12.1, Canonsburg). The surfaces of the models were triangulated with a node distance between 0.01 and 0.02 mm. A boundary layer mesh consisting of four rows, with a growth factor of 1.2, was generated in accordance with current standards (12, 17).

Flow for the simulation was assumed to be 3-D, laminar, and steady. The walls were considered rigid, and a zero-velocity, no-slip boundary condition was adopted at the walls. Blood was modelled as an incompressible Newtonian fluid with a dynamic viscosity of 0.0035 Pa·s and a density of 1,050 kg/m³. Fluid motion equations were solved using finite volume-based software (ANSYS CFX 12.1, Canonsburg).

Because flow within the coronary arteries is subject to variation, boundary conditions for the CFD simulations were set to simulate both resting and hyperemic conditions. For computer-generated models, the inlet boundary was set as a static pressure of 100 mmHg and a mass flow rate of 0.9 g/s (representing resting conditions), and 2.7 g/s (representing hyperemic conditions) was imposed at outlet boundaries. For the simulations involving 3-D reconstructions, inlet and outlet boundary conditions were set to the individually measured Pa and Pd both at rest and during hyperemia. Pa was higher than Pd for the entire cardiac cycle in all patients, indicating antegrade flow at all times.

Validation of CFD Analysis

The numeric solution was validated with previously described experimental data (1). The previously published geometry was reproduced and simulated using our CFD method. There was good agreement between our numerical calculations and the experimental data. The physiological calculations by CFD analysis were validated indirectly by comparing the CFR derived from CFD with the actual measured CFR. This showed good correlation and agreement (mean ± SD of bias was 0.15 ± 0.25 by Bland-Altman analysis).

Statistical Analysis

Results are expressed as means ± SD unless otherwise stated. Spearman’s correlation was performed to investigate relationships between continuous parameters that did not follow a normal distribution. Bland-Altman plots were used to compare CFR measured by thermodilution with CFD-derived CFR. Linear and nonlinear regression analyses with F-tests were used to obtain curves of best fit. Statistical analyses were performed using Graphpad Prism (version 5.01, Graphpad Software, La Jolla, CA) and SPSS (version 15, SPSS, Chicago, IL). Two-sided P values of <0.05 were considered significant.

RESULTS

Effect of Eccentricity and Stenosis Severity on Flow Recirculation and Shear Rate

Computer-generated models. Figure 1 shows the qualitative changes in recirculation zone in relation to lesion eccentricity for 30% stenosis (A) and 80% stenosis (B) for resting flow. Deceleration and reversal of flow were observed downstream of the stenosis with the presence of recirculation zones, typically downstream of the location of peak shear rate. Velocities in the region of the recirculation zones were low. Concentric lesions resulted in recirculation zones of shorter length than did eccentric lesions. Eccentric lesions resulted in eccentric recirculation zones located on one side of the vessel, whereas concentric lesions resulted in concentric recirculation zones following the circumference of the vessel.

The quantitative relationship among recirculation zone length, maximum shear rate, stenosis severity, and lesion eccentricity in computer-generated models revealed that an increase in stenosis severity from 30% to 80% resulted in an increase in the length of the recirculation zone and maximum shear rate. For any given stenosis severity, a mild increase in EI (e.g., from 0 to 0.33) led to an increase in the length of the recirculation zone and shear rate, but the effect was less dramatic than the effect of stenosis severity. At rest, the maximum shear rate for eccentric models (EI = 0.33) with 30%, 50%, and 80% diameter stenosis were ~41%, 30%, and 14% higher than the maximum shear rate for the concentric models (EI = 0) with the same diameter stenosis. On the basis of these experiments, we applied our models to 3-D reconstructions of coronary arteriograms.

3-D reconstructions of coronary arteriograms. The baseline demographic, angiographic, and physiological characteristics of the patients included in this study are shown in Table 1. The coronary angiogram, 3-D reconstruction, and CFD analysis of a representative patient are shown in Fig. 2.

We investigated the effect of stenosis severity on recirculation zone length in four patients who had approximately similar EIs (varying between 0.5 and 0.75) and the effect of eccentricity in four patients with similar vessel size, length, and stenosis severity using flow streamline patterns shown in Fig. 3. Recirculation zone length in human coronaries was highly dependent on stenosis severity and, in addition, increased with increasing EI when stenoses of similar severity were compared. Similar results were obtained for three groups of four patients (total of 12 patients).
who had similar stenosis severity or similar eccentricity within the groups (data not shown).

As these data supported an independent role for both stenosis severity and eccentricity in affecting flow in human coronaries, we next investigated their relationship to recirculation zones and maximum shear rate in our whole population of patients with left anterior descending coronary artery disease (1 lesion/patient; Figs. 4 and 5). The length of the recirculation zone correlated extremely closely with the percent diameter stenosis for both resting \( (r = 0.96, P < 0.0001; \text{Fig. 4A}) \) and hyperemic \( (r = 0.97, P < 0.0001; \text{Fig. 4B}) \) flow. Maximum shear rate also correlated very closely with stenosis severity for both resting \( (r = 0.97, P < 0.0001; \text{Fig. 4C}) \) and hyperemic \( (r = 0.95, P < 0.0001; \text{Fig. 4D}) \) flow. In contrast, neither recirculation zone length \( \text{[resting flow: } r = 0.13, P = 0.55 \text{ (Fig. 5A) and hyperemic: } r = 0.10, P = 0.62 \text{ (Fig. 5B)]} \) nor maximum shear rate \( \text{[resting flow: } r = 0.07, P = 0.75 \text{ (Fig. 5C) and hyperemic flow: } r = 0.03, P = 0.89 \text{ (Fig. 5D)]} \) correlated with eccentricity.

The mathematical relationships between stenosis percentage and the maximum shear rate or length of the recirculation zone were investigated using nonlinear regression (Fig. 4). Recirculation zone length demonstrated a threshold effect with a steep increase at stenoses above 40% and followed a sigmoid curve under resting \( (r = 0.96, P < 0.0001; \text{Fig. 4A}) \) and hyperemic \( (r = 0.97, P < 0.0001; \text{Fig. 4B}) \) flow. Maximum shear rate increased in a monoexponential manner with stenosis severity under resting \( (r = 0.97, P < 0.0001; \text{Fig. 4C}) \) and hyperemic \( (r = 0.95, P < 0.0001; \text{Fig. 4D}) \) conditions. As stenosis severity increased from 40% to 50%, recirculation zone length increased from 0.88 to 3.72 mm (an increase of 320%), whereas peak shear

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**Table 1. Baseline clinical and angiographic characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>Sex, number (%)</td>
<td>Male 21 (84.0) Female 4 (16.0)</td>
</tr>
<tr>
<td>Proximal left anterior descending coronary artery lesion, number (%)</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>Lesion diameter stenosis, %</td>
<td>52.9 ± 16.1</td>
</tr>
<tr>
<td>Eccentricity index</td>
<td>0.45 ± 0.27</td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>9.0 ± 9.0</td>
</tr>
<tr>
<td>Resting proximal pressure, mmHg</td>
<td>93 ± 14</td>
</tr>
<tr>
<td>Resting distal pressure, mmHg</td>
<td>69 ± 19</td>
</tr>
<tr>
<td>Hyperemic proximal pressure, mmHg</td>
<td>86 ± 16</td>
</tr>
<tr>
<td>Hyperemic distal pressure, mmHg</td>
<td>51 ± 19</td>
</tr>
<tr>
<td>Fractional flow reserve</td>
<td>0.59 ± 0.20</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>2.0 ± 1.0</td>
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</tbody>
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Values are means ± SD. The eccentricity index did not correlate with percent diameter stenosis \( (r = 0.11, P = 0.60) \).
increased from 21,077 to 26,487 s⁻¹ (an increase of 26%). Thus, recirculation was observed to be much more sensitive to mild changes in the severity of intermediate stenoses than was peak shear. Similar results were found in the computer-generated ideal model (data not shown).

DISCUSSION

These data demonstrate that increased in situ shear rate and flow recirculation are observed to coexist in diseased human coronary arteries, involving a complex relationship between stenosis severity and lesion eccentricity. Stenosis severity is clearly associated with recirculation zone length and maximum in situ shear rate regardless of variations in eccentricity. In contrast, eccentricity has a weaker effect than stenosis severity. Most importantly, in human coronary arteries, the extent of flow recirculation is extremely sensitive to mild increases in the severity of moderate coronary stenoses.

Intracoronary Recirculation and Shear Rate

Atherosclerotic plaques within coronary arteries cause luminal narrowing, which compromises distal blood flow, leading to myocardial ischemia (30). Coronary lesions also cause localized physiological disturbances, such as flow recirculation and shear rate, which can result in detrimental biological and clinical sequelae (2).

Stenosis within the coronary arteries can lead to the development of blood flow recirculation zones that result in areas of low velocity and shear rate. These recirculation zones where low shear stress occurs (21) have been associated with areas of atherogenesis and vessel remodelling within the coronary (26) and carotid (36) arteries. In addition, recirculation zones provide a favorable environment for stasis-related thrombosis as well as platelet activation and aggregation (5). Severe coronary stenosis also causes high shear rate levels, and a high shear rate results in platelet and leukocyte activation, which promotes a proinflammatory and thrombotic state (13, 34).

Effect of Lesion Eccentricity on Flow Recirculation and Shear Rate

The significance of coronary lesions is often judged by their stenosis severity (23, 28). However, coronary lesions also vary in other characteristics such as their eccentricity, and in a study (32) using intravascular ultrasound, 81% of diseased coronary arteries had lesions that were classified as eccentric. Moreover, plaque eccentricity in carotid lesions is associated with increased risk of cerebrovascular events (15), and coronary lesion eccentricity is associated with plaque disruption and acute coronary syndromes (31). Previous studies (3, 16, 25, 27, 35) investigating the effect of eccentricity on physiological parameters have used in vitro models or models derived from the reconstruction of carotid arteries. In vitro models have the disadvantage of not incorporating realistic geometrical properties. Simulations based on carotid arteries may not be applicable to the coronaries as carotid arteries are of larger diameter, a fact that will affect both shear rate and flow recirculation. Our data in human coronary arteries indicate that when two arteries with similar stenosis severity are compared, the lesion with greater eccentricity will result in an increased recirculation zone and shear rate. Recirculation and shear were increased by small degrees of eccentricity and only marginally increased further with severe eccentricity. As stasis and shear can promote thrombosis and platelet activation, respectively, eccentricity could exert significant effects on thrombotic risk. However, as our results suggest that stenosis severity is more important than...
eccentricity in determining flow disturbance in human coronaries, further studies are required to investigate whether there are specific circumstances under which eccentricity relates to clinical outcome.

Effect of Stenosis Severity on Flow Recirculation and Shear Rate

As demonstrated, there were strong associations between stenosis severity and recirculation zone length and between stenosis severity and peak shear rate. However, an important and novel finding in our evaluation of human coronary lesions was the apparent sigmoidal relationship between stenosis severity and the length of flow recirculation zones, which was not apparent in relation to peak shear rate. As stenosis severity increased from 40% to 50%, there was a several fold increase in the length of flow recirculation zones, whereas there was a relatively modest increase in shear rate. Perturbations in shear and recirculation predispose toward thrombosis (4, 8, 13, 19, 33), which plays a crucial role in occlusive plaque ruptures (9, 10). Many coronary occlusions involve stenoses that were previously known to be only moderately severe (6). Flow recirculation may therefore provide a novel pathological mechanism by which moderately severe coronary stenoses may progress to complete thrombotic occlusion.

Study Limitations

This study has some limitations. Our model of CFD assumes steady, laminar flow with Newtonian fluid properties and nonde-
formable end-diastolic vessel wall geometry. While stenotic vessels are stiff, stenoses do have some compliance, and eccentricity could affect vessel compliance. However, previous studies (7, 29) have shown that these assumptions are acceptable for simulations involving human coronary arteries. Lesion length and asymmetry may affect the flow parameters measured. This study controlled for these only in the computer-generated models, which all had identically shaped lesions. Lesion length has previously been shown to have minimal effect on the flow parameters measured (24). Other vessel characteristics, such as curvature, bifurcations, and vessel size, will also likely affect the flow parameters measured and were not addressed in this study. This study attempted to control for these confounding effects by first using highly controlled computer-generated models as well as models only involving relatively straight left anterior descending coronary arteries with minimal variations in size. Because the study was restricted to only left anterior descending coronary arteries, the absolute values derived cannot be generalized to the other epicardial coronary arteries. However, we believe that the general concepts will still be applicable to the other epicardial arteries. In addition, because the left anterior descending coronary artery is a prognostically important vessel, our findings are of clinical importance. The use of intravascular ultrasound could have resulted in improved accuracy in the evaluation of eccentricity and was not
used in this study. However, 3-D coronary angiography measurements correlate well with intravascular ultrasound (22). Moreover, 3-D angiography to assess eccentricity may be more clinically applicable as it does not require additional patient instrumentation and can be easily performed online as well as retrospectively using existing angiographic images. Finally, vessel geometries were obtained for simulation using two monoplane coronary angiography acquisitions. The use of biplane acquisition and intracoronary imaging could improve the accuracy of the vessel geometries. However, 3-D reconstruction measurements have previously been shown to correlate very well with measurements obtained by fusion of 3-D reconstructions and intravascular ultrasound (22). Moreover, we validated our CFD methods by showing good agreement between the CFD obtained by CFD of the 3-D reconstructions and the CFD measured using a pressure-temperature sensor wire.

Conclusions

Flow recirculation and shear rate both increase with the severity of stenosis in human coronary arteries. The extent of flow recirculation is much more sensitive to mild changes in the severity of intermediate stenoses than is peak shear and may be relevant to the pathogenesis of arterial thrombosis in moderately severe coronary stenoses in vivo.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


