Coronary Flow Velocity and Disturbed Flow Predict Adverse Clinical Outcome After Coronary Angioplasty

Scott Kinlay, Jasmine Grewal, Deborah Manuelin, James C. Fang, Andrew P. Selwyn, John A. Bittl, Peter Ganz

Objective—Laminar flow becomes disturbed at high velocities, reducing shear stress and augmenting vascular inflammation and proliferation, processes that are pivotal in restenosis and atherogenesis. We hypothesized that disturbed blood flow after coronary angioplasty is associated with adverse long-term clinical outcome.

Methods and Results—The cineangiograms from 97 patients undergoing laser-assisted coronary angioplasty were analyzed. Coronary blood flow velocity, the residual lesion dimensions, and the Reynolds number (an index of disturbed flow) were measured by using a frame-counting technique and quantitative coronary angiography. Cox proportional hazards were used to assess the relative risk of adverse events (target-vessel revascularization, myocardial infarction, or death) over a mean 2.5 years after the index procedure. There were 41 adverse events during 245 patient years of follow-up (17% per year of follow-up). The risk of an adverse event was increased for patients with a high flow velocity (>250 mm/s; relative risk 2.5, 95% CI 1.3 to 4.7) or a high Reynolds number (>200) at the stenosis inlet (relative risk 2.1, 95% CI 1.1 to 4.1) at the end of the procedure. Adjustment for other factors did not alter these results.

Conclusions—High Reynolds numbers, indicating disturbed blood flow after coronary angioplasty, increase the risk of adverse clinical events, potentially through shear-stress–related molecular mechanisms that promote restenosis and atherogenesis. (Arterioscler Thromb Vasc Biol. 2002;22:●●●●.●●.)

Key Words: PLEASE ■ SUPPLY ■ KEY ■ WORDS

The clinical outcome after percutaneous coronary interventions is related to the risk of restenosis, which is related to the postprocedural minimal luminal diameter,1–4 and to disease progression. These events could also be determined by disturbed laminar blood flow at residual stenoses, which creates shear stresses that adversely affect the biology of the arterial wall.5–13 Normal laminar blood flow acts on endothelial cells to generate molecules that promote a vasodilatory, anticoagulant, anti-inflammatory, and growth-inhibitory surface.5–13 Disturbed laminar blood flow is more likely to occur at higher flow velocities and creates sites of abnormally low and high shear stress, and these are sensed by the endothelium. Abnormally low shear stress in particular activates endothelial cell genes and their products to stimulate vascular inflammation, smooth muscle cell proliferation, and a procoagulant surface.5–13 Disturbed laminar blood flow is prone to occur in vascular segments with high Reynolds numbers (calculated as velocity × diameter/ density × viscosity),14 especially at sites of mild luminal narrowing (Figure 1). Percutaneous coronary interventions aim to favorably alter the stenotic stenosis severity but may not restore normal laminar flow. The present study examines the hypothesis that coronary flow velocity and disturbed laminar blood flow at a residual coronary lesion after successful laser-assisted coronary intervention are associated with adverse long-term clinical outcomes. We studied this cohort because this ablative technique creates a lumen that is relatively free of dissections (avoiding complex flow patterns and making cross-sectional estimates more reliable), and the data were collected prospectively with full ascertainment of clinical events.

Methods
We enrolled serial patients participating in a study of excimer laser angioplasty for coronary artery stenoses at the Brigham and Women’s Hospital. Patients were aged ≥18 years, presenting for elective or urgent coronary angioplasty. Enrollment occurred before the widespread use of coronary stents. They were included if they presented with acute myocardial infarction, if the culprit lesion had filling defects, if the left ventricular ejection fraction was <30%, or if the Thrombolysis in Myocardial Infarction (TIMI) frame count could not be obtained for technical reasons. For this analysis, only patients with a successful angioplasty, free of dissections and with TIMI 3 flow (normal flow), were included. Successful angioplasty was defined as an increase in luminal diameter >20% with a <50% residual stenosis.

The cardiac risk factors and medical history were obtained by patient interview and from medical records. High cholesterol was defined as a total cholesterol >200 mg/dL; hypertension, as high blood pressure requiring medical therapy; smoking, as cigarette smoking of at least 1 cigarette per day; and diabetes, as requiring treatment with diet, insulin, or oral hypoglycemics. The left ventric-
Cardiac Catheterization
Excimer laser angioplasty was performed by using 7F, 8F, 9F, or 10F guiding catheters. All patients received a continuous infusion of intravenous nitroglycerin during the procedure, with bolus doses of intracoronary nitroglycerin (50 to 200 μg) given intermittently and at the end of the procedure. All patients received adjunctive balloon angioplasty after the excimer laser.

Quantitative Coronary Angiography
Electronic digital calipers (Digimatic CD-6P, Mitutoyo Corp, Kawasaki-Shi) were used to measure the diameters of the target-vessel artery by a technique validated in this laboratory. The arterial measurements included the minimal luminal diameter before and after intervention, proximal and distal reference diameters, and proximal mid and distal diameters of the target vessel used to measure the volume of blood flow in the target vessel. These measurements were made by 1 trained observer blinded to the patient outcomes with the use of cine projection that showed the maximum stenosis severity and best displayed the vessel length. Similarly, the length of the lesion at the end of the procedure was measured, and the stenosis angle (gradient of the stenosis) was defined as follows: (reference diameter − minimal lesion diameter)/lesion length at the end of the procedure. The length of the artery was measured by using an electronic digital plan measure (Scale Master II, Calculated Industries Inc).

Blood Flow Parameters and Reynolds Numbers
The average blood flow velocity in the target vessel at the end of the procedure was measured by using a TIMI frame-count method of contrast, with movement along a known length of the target vessel from the final angiogram filmed at 30 frames per second. Blood flow velocity = (30×length/frame count) mm/s. The correlation coefficient (r) and coefficients of variation (CVs) for measuring frame count in 37 randomly chosen angiograms were as follows: r=0.99 (CV 9%) between observers and r=0.99 (CV=9%) between observers.

Blood flow volume was calculated from the average cross-sectional area of the target vessel multiplied by the blood flow velocity and expressed as milliliters per minute. The average cross-sectional area of the target vessel was derived from the proximal, mid, and distal diameters of the target vessel: average cross-sectional area = π(radius²). The velocity of blood at the inlet of the residual lesion was derived from the continuity equation: velocity at stenosis inlet = (average blood velocity × average cross-sectional area)/cross-sectional area at stenosis inlet. The velocity of blood flow within the throat of the residual lesion was calculated in the same way by using the minimal luminal diameter.

In experimental studies, disturbances in laminar blood flow distal to a mild stenosis have been related to high Reynolds numbers at the inlet to the stenosis or within the throat of a stenosis. In the present study, the Reynolds numbers (Reynolds number = velocity × diameter/density/viscosity) at the inlet and within the throat of the lesion were calculated by using the velocity and luminal diameters at these sites, assuming a density of blood of 1.05 g/cm³ and a viscosity of 1/30 poise.

Major Adverse Clinical Outcomes
Major adverse clinical outcomes were obtained by 1 of the investigators (D.M.), who was unaware of the coronary characteristics of the subjects, by telephone interview and from the medical charts of the referring cardiologist up to 6.4 years (mean 2.5 years) after the index procedure for each subject. Major adverse clinical events included death from any cause, myocardial infarction (defined as a clinical history, ECG changes, and elevation of cardiac enzymes [2 times the upper limit of normal]), and target-vessel revascularization by percutaneous coronary intervention or by coronary bypass grafting. Target-vessel revascularization was performed for clinical symptoms of angina with objective evidence of ischemia.

Statistical Analysis
The data were described by means and SDs or medians and interquartile range (25% to 75%) where appropriate. High levels were defined as the upper third of their distributions. Survival curves and Cox proportional hazards models were used to test the relative risk of an event (hazard ratio and 95% CIs). Patients were evaluated after an event or after the follow-up period. There were no patients lost to follow-up. A multivariate model adjusted the risk estimates for age, unstable angina at the index procedure, and the minimal luminal diameter at the end of the index laser angioplasty. A second model also included abnormal ejection fraction (<55%) for the subset of patients who had this measured. Analyses were performed with the use of STATA (Statacorp) software.

Results
There were 41 major adverse clinical events among the 97 patients during 245 patient-years of follow-up (incidence was 17% per year of follow-up). During this time, 26 patients had a percutaneous target-vessel revascularization, 8 had coronary artery bypass grafting, 4 had a nonfatal myocardial infarction, 2 had a fatal myocardial infarction, and 1 died of other causes. Approximately half of the events (22 of 41) occurred during the first 6 months of follow-up. There were no detectable relationships between the baseline characteristics and a subsequent clinical event (Table 1).

The clinical events during follow-up were linked to the index lesion by several modalities. Follow-up angiograms were available for 28 (82%) of the 34 patients requiring revascularization by angioplasty or bypass during follow-up. Of these, 26 (93%) had restenosis at the target lesion with >70% narrowing, and 2 (7%) had a new lesion in the target artery. Of another 6 patients who sustained a myocardial infarction during follow-up, 2 had an ECG localizing ST-T changes to the territory of the target vessel. One patient with myocardial infarction had an autopsy showing localized thrombus at the target lesion. Thus, the index lesion could be

Figure 1. Disturbed laminar flow distal to a stenosis, characterized by recirculation eddies exerting low shear stress on vessel wall. A, Inlet to lesion. B, Within throat of lesion.
linked to the adverse clinical outcome in at least 31 (76%) of cases.

Most of the index interventions were on lesions in the left anterior descending artery, and approximately half of the lesions were American Heart Association type B2 or C, illustrating the expected complexity of disease in patients enrolled in a laser angioplasty study (Table 2). Although there was an \( \approx 20\% \) reduction in the risk of a subsequent clinical event for each millimeter increase in the reference diameter and minimal luminal diameter at the end of the procedure, these factors did not reach statistical significance in the present study. Similarly, there was a trend for the residual lesion to be 12\% longer in patients who later had clinical events (Table 2). However, neither lesion length nor stenosis angle at the end of the procedure was significantly related to clinical events.

Table 3 shows the physiological data measured at the final angiogram of the index procedure. The average coronary blood flow volume (in milliliters per minute) was similar to that determined by coronary venous thermodilution methods in earlier stud-

### Table 1. Baseline Characteristics of the 97 Patients After Laser-Assisted Coronary Angioplasty and Risk of a Clinical Event During 245 Patient-Years of Follow-Up

<table>
<thead>
<tr>
<th>Clinical Event During Follow-Up (n=41)</th>
<th>Event-Free During Follow-Up (n=56)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 (12)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Men</td>
<td>32 (78)</td>
<td>41 (73)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>23 (56)</td>
<td>26 (50)</td>
</tr>
<tr>
<td>Smoker</td>
<td>10 (24)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>21 (51)</td>
<td>35 (64)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (22)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (36)</td>
<td>24 (47)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>15 (37)</td>
<td>21 (39)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>19 (46)</td>
<td>20 (36)</td>
</tr>
<tr>
<td>Ejection fraction&lt;55%</td>
<td>7/30 (23)</td>
<td>6/36 (17)</td>
</tr>
</tbody>
</table>

All values are n (%) except age, which is mean (SD).
ies. However, the clinical outcomes were not related to coronary blood flow volume at the end of the index procedure.

In contrast, the average blood flow velocity measured over the artery or at the stenosis inlet was significantly higher in the patients who developed a major adverse clinical event during follow-up. The Reynolds number measured at the inlet or within the throat of the residual lesion was significantly higher among those who later developed an event.

Figure 2 shows the survival curves for cut points at the upper third of the distributions of the blood flow velocities and Reynolds numbers. The clinical events occurred more frequently in the first 6 months of follow-up, which is in keeping with the time frame for restenosis after coronary interventions, and slowed during longer follow-up, which is consistent with the progression of disease.

After adjustment for other important covariates, the Reynolds numbers and higher blood flow velocities remained significantly related to poorer outcomes over the follow-up period (Table 4). The analysis of tertiles of the Reynolds numbers suggested that there may be a threshold effect (Figure 3). Subgroup analyses demonstrated an interaction between the presence of a residual stenosis (30%) and high Reynolds numbers at the lesion inlet that was particularly likely to lead to an adverse event during follow-up (Figure 4). Postprocedural lesion length and stenosis angle were included in other multivariate models but had no effect on the relationships of Reynolds number to subsequent clinical events.

**TABLE 3. Physiological Measures of the Target Vessel at the End of the Laser-Assisted Coronary Angioplasty and Risk of a Major Adverse Clinical Event During 245 Patient-Years of Follow-Up**

<table>
<thead>
<tr>
<th></th>
<th>Clinical Event (n=41)</th>
<th>Event Free (n=56)</th>
<th>P* Univariate</th>
<th>Multivariate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>90 (85–100)</td>
<td>95 (90–100)</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65 (60–72)</td>
<td>60 (58–70)</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Volume blood flow, mL/min</td>
<td>80 (63–114)</td>
<td>65 (43–104)</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Blood velocity, mm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target vessel average</td>
<td>234 (194–286)</td>
<td>196 (145–246)</td>
<td>0.01</td>
<td>0.006</td>
</tr>
<tr>
<td>Inlet to lesion</td>
<td>264 (156–410)</td>
<td>214 (134–261)</td>
<td>0.012</td>
<td>0.006</td>
</tr>
<tr>
<td>Within throat of lesion</td>
<td>809 (438–1385)</td>
<td>567 (394–932)</td>
<td>0.11</td>
<td>0.12</td>
</tr>
<tr>
<td>Reynolds number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inlet to lesion</td>
<td>236 (139–316)</td>
<td>175 (120–238)</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Within throat of lesion</td>
<td>402 (229–564)</td>
<td>289 (222–423)</td>
<td>0.09</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Values are median (25%–75%).
*From Cox-proportional hazards model.
†Adjusted for reference vessel diameter.

**Discussion**

The novel finding of the present study is that coronary flow velocity and the Reynolds number, a parameter that indicates disturbed coronary blood flow, at the completion of a laser angioplasty procedure are important predictors of subsequent adverse clinical events. Although the conditions for turbulent blood flow rarely occur in coronary arteries (except perhaps in high-grade stenoses >90%), disturbed blood flow can occur, particularly with minor stenoses.

![Figure 2. Survival curves for major adverse clinical event. Survival was reduced with high blood flow velocities (>250 mm/s) and high Reynolds numbers at inlet (>200) or within throat of residual stenosis (>400).](image-url)
The risk of poor outcome related to minimal luminal diameter, lesion length, and the size of the reference segment was similar in magnitude to that in larger interventional trials, but these parameters did not reach significance in the present study, most likely because of the limited sample size. However, the residual stenosis became particularly important when combined with a high Reynolds number (Figure 4).

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![Figure 4](image_url)

**Table 4. Relative Risks of High Blood Flow Velocity and Reynolds Numbers for a Major Adverse Clinical Event During 245 Patient-Years of Follow-Up**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted Estimate (n=97)</th>
<th>Model 1* (n=93)</th>
<th>Model 2† (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average velocity target vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤250 mm/s</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;250 mm/s</td>
<td>2.1 (1.1, 3.8)</td>
<td>2.1 (1.1, 3.9)</td>
<td>2.7 (1.2, 5.8)</td>
</tr>
<tr>
<td>Velocity at lesion inlet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤250 mm/s</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;250 mm/s</td>
<td>2.5 (1.3, 4.7)</td>
<td>2.5 (1.3, 4.6)</td>
<td>2.5 (1.2, 5.5)</td>
</tr>
<tr>
<td>Velocity within throat of lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤250 mm/s</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;250 mm/s</td>
<td>1.5 (0.8, 2.8)</td>
<td>1.5 (0.7, 3.1)</td>
<td>3.8 (1.2, 11.8)</td>
</tr>
<tr>
<td>Reynolds number at lesion inlet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤200</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;200</td>
<td>2.1 (1.1, 4.1)</td>
<td>2.2 (1.1, 4.2)</td>
<td>2.2 (1.0, 4.8)</td>
</tr>
<tr>
<td>Reynolds number within throat of lesion</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≤400</td>
<td>2.0 (1.1, 3.7)</td>
<td>2.0 (1.1, 3.7)</td>
<td>2.7 (1.2, 6.0)</td>
</tr>
<tr>
<td>&gt;400</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are hazard ratio (95% CI).

*Hazard ratio adjusted for age, minimal lumen diameter, and unstable angina at index procedure.
†Hazard ratio adjusted for variables in Model 1 plus abnormal ejection fraction (<55%)

Figure 3. Tertiles of Reynolds numbers (Re) adjusted for average vessel diameter and relative risk of major adverse clinical event over follow-up.
Disturbed Blood Flow and Atherogenesis

The present study does not address the recognized poor outcomes from visibly slow flow after coronary interventions because we excluded subjects with TIMI flow <3. Experimental studies have suggested that within the “normal” range of brisk blood flow, a higher Reynolds number leads to dissociated laminar flow patterns, resulting in local regions of sluggish velocity. It is this principle that accounts for the well-known predilection of atherosclerosis at bifurcations, typically on the low-shear side of the flow divider.22–24 The present study applies these principles to the postangioplasty setting and suggests that disturbed laminar flow at mild stenoses, as predicted from high Reynolds numbers, can also have an impact on clinical events, particularly in the first 6 months after a coronary intervention, when restenosis typically occurs.

Recent studies have provided a molecular link between low shear stress and atherogenesis or restenosis. Low shear stress stimulates genes encoding for growth factors, leukocyte adhesion molecules, cytokines, chemokines, or vasoactive factors that in their promoters contain shear-stress–sensitive regulatory elements.5–11 These mechanisms collectively contribute to vascular cell proliferation, inflammation, remodeling, and thrombosis, events that are important in restenosis and atherogenesis25 and that subsequently lead to clinical events. It is also possible that disturbed flow reflects plaques that are prone to restenosis because of unfavorable postinterventional lesion shape, composition, predisposition to platelet deposition, or vasomotor instability.

Limitations of the Study

We used the TIMI frame count rather than Doppler techniques to measure coronary flow velocity. It is a reproducible and validated method to measure blood flow that is independent of injection rate and catheter size26 and highly correlated with Doppler measurements (correlation coefficients ~0.8).27–29 Any error of our measurements due to the use of this method is likely to bias the study results toward the null hypothesis and to underestimate the significance of the risk from disturbed flow. More complex models would have accounted for pulsatile flow (which varies the length of the region of disturbed flow) and other vessel characteristics. Methods incorporating these features are being developed but currently require data interpolation and smoothing. The present study indicates that even relatively simple approaches can elucidate the importance of blood flow and shear stress on clinical outcomes and encourages the development of more complex modeling techniques. Although some of the clinical end points during follow-up could have been related to other mechanisms or to other lesions, most of the events were localized by angiography or ECG as being directly related to the lesion at which the Reynolds number was measured. Finally, nitroglycerin was used intermittently during the study. However, the direct effect of nitroglycerin to increase coronary blood flow is transient (lasting only seconds)30 and not likely to have affected our results.

We examined patients after successful excimer laser-assisted angioplasty, an ablative procedure that creates a lumen relatively free of complex dissection edges, thus avoiding complex flow patterns and cross-sectional areas that are difficult to assess accurately. Further studies are required to ascertain whether the findings of the present study apply to other types of coronary intervention, including stents.

In conclusion, high Reynolds numbers at the inlet or within the throat of a residual stenosis predict adverse long-term clinical outcome of patients after successful coronary angioplasty. High Reynolds numbers are associated with disturbances of blood flow patterns known to stimulate molecular

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**Figure 4.** Effect of combinations of high Reynolds numbers and residual stenosis >30% on risk of major adverse clinical event.
pathways to promote atherogenesis and restenosis. Our data validate the concept that flow dynamics contribute to restenosis and disease progression and suggest that the restoration of laminar blood flow should become an important goal in the development of new interventional techniques to improve the outcomes after percutaneous coronary interventions.

Acknowledgment
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References


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