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;22:1334-1340.)

Key Words: disturbed coronary flow ■ Reynolds number ■ outcomes ■ angioplasty

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 high 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 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 excluded 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-
arterial ejection fraction before the intervention from planimetry from a left ventriculogram or by Simpson’s rule from echocardiography was classified as reduced if it was <55%. The study was approved by the Human Research Committee of the Brigham and Women’s Hospital.

Cardiac Catheterization
Exciemer 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 5%) within observer 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 = \( \pi \times \text{average radius}^2 \).

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 stenosis, characterized by recirculation eddies exerting low shear stress on vessel wall, A, Inlet to lesion. B, Within throat of lesion. Figure 1. Disturbed laminar flow distal to a stenosis, characterized by recirculation eddies exerting low shear stress on vessel wall.

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 assess the relative risk of an event (hazard ratio and 95% CIs). Patients were censored 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 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 B, or C, illustrating the expected complexity of disease in patients enrolled in a laser angioplasty study (Table 2). Although there was an ≈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 studies.\textsuperscript{21} 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

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Event During Follow-Up (n=41)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>High cholesterol</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Previous PTCA</td>
</tr>
<tr>
<td>Ejection fraction&lt;55%</td>
</tr>
</tbody>
</table>

All values are n (%) except age, which is mean (SD).

<table>
<thead>
<tr>
<th>TABLE 2. Physical Parameters of the Target Lesion in 97 Subjects After Laser-Assisted Coronary Angioplasty and Risk of a Major Adverse Clinical Event During 245 Patient-Years of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Event (n=41)</td>
</tr>
<tr>
<td>AHA Lesion Type</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B\textsubscript{1}</td>
</tr>
<tr>
<td>B\textsubscript{2}</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>

Location

Left anterior descending | 16 (39) | 30 (54) | 1.0 (reference) |
Right coronary | 17 (41) | 19 (34) | 1.7 (0.9, 3.3) |
Left circumflex | 8 (20) | 7 (12) | 1.9 (0.8, 4.4) |

Mean (SD)

Reference segment diameter, mm | 2.47 (0.58) | 2.50 (0.65) | 0.87 (0.51, 1.50) |
Minimal lumen diameter, mm

Pre-procedure | 0.65 (0.40) | 0.56 (0.42) | 1.14 (0.55, 2.36) |
Post-procedure | 1.43 (0.53) | 1.49 (0.63) | 0.83 (0.46, 1.48) |
Acute gain, mm | 0.80 (0.47) | 0.93 (0.67) | 0.80 (0.45, 1.44) |
Percent stenosis

Pre-procedure | 74 (14) | 76 (16) | 1.00 (0.98, 1.02) |
Post-procedure | 43 (12) | 41 (16) | 1.01 (0.99, 1.03) |
Lesion length, mm | 11.4 (6.0) | 10.7 (5.1) | 1.12 (0.59, 2.11) |
Stenosis angle (gradient of residual lesion) | 0.11 (0.06) | 0.12 (0.09) | 0.93 (0.59, 1.46) |
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.

**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.

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 to 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).

**Does the Reynolds Number Provide Incremental Value?**

Because the Reynolds number incorporates flow velocity, it raises the question of whether the calculation of the Reynolds number provides incremental value. Knowledge of high velocity, although also associated with adverse outcomes, fails to provide a mechanistic insight into this relationship. Specifically, velocity alone cannot predict when blood flow becomes disturbed and, hence, when abnormal shear stresses develop. In contrast, there is an extensive body of knowledge relating Reynolds numbers to the occurrence of abnormal flow patterns. In a straight vessel, the flow of a liquid is laminar if the Reynolds number is <2000. Flow becomes turbulent if the Reynolds number exceeds this value, a
condition rarely achieved in healthy arteries. In contrast, mild, hemodynamically insignificant narrowings interact with Reynolds numbers in excess of 100 to 200 to create more subtle changes in blood flow, so-called disturbed laminar flow (Figure 1).17–20 In the present study, we have demonstrated that the Reynolds numbers at the inlet and the throat of a residual lesion frequently exceeded the threshold for the development of disturbed laminar flow and then predicted adverse clinical outcome.

**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,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

### 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></th>
<th>Unadjusted Estimate</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=97)</td>
<td>(n=93)</td>
<td>(n=65)</td>
</tr>
<tr>
<td>Average velocity target vessel ≤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 ≤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 ≤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 ≤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 ≤400</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;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>
</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.

Figure 4. Effect of combinations of high Reynolds numbers and residual stenosis >30% on risk of major adverse clinical event.
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. These mechanisms collectively contribute to vascular cell proliferation, inflammation, remodeling, and thrombosis, events that are important in restenosis and atherogenesis 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 size and highly correlated with Doppler measurements (correlation coefficients \( \approx 0.8 \)). 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) 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 assisting angioplasty, an ablative procedure that creates a lumen relatively free of complex dissection edges, thus

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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