Predicting Restenosis
Bigger Is Better but Not Best

David P. Faxon, MD

The ability to accurately predict restenosis after angioplasty continues to be elusive, despite two decades of clinical and angiographic studies. Although these studies have shown that a number of clinical, procedural, and angiographic factors are related to recurrence of the stenosis, the overall predictive value of these factors remains low.1 Angiographic factors have been most extensively studied and variable, such as ostial lesion location, proximal lesion location, left anterior descending artery lesion location, bifurcation lesion, eccentric lesion, and long lesion, and those vessels receiving collaterals have been shown to have a higher rate of restenosis as well. Perhaps one of the most important advances in our understanding of restenosis has been the relationship between the final minimal lumen diameter (MLD), or residual stenosis, and the likelihood of developing restenosis. Often termed “bigger is better,” the inverse relationship between final MLD or percent stenosis and restenosis has been widely studied and well validated.2

The principal of obtaining the largest possible luminal opening during the procedure is now the primary goal of all angioplasty procedures and is the major explanation for why stents reduce restenosis and why their use has become so popular. Even in very large databases, MLD correctly predicted the occurrence of restenosis in only 30% of patients. The price paid for a bigger lumen, however, is more renarrowing, due to unfavorable remodeling and exaggerated intimal hyperplasia. Fortunately, Mother Nature has been kind and, in the clinical setting, only renarrows the artery to roughly half the initial gain in lumen diameter. This allows for less restenosis with larger lumens. A more precise way to look at the restenotic process itself is to evaluate the effect of any treatment on the late loss index, or the ratio of the late loss in lumen diameter to the acute gain. Stenting, for instance, does not affect the late loss index but does significantly reduce restenosis by creating a larger lumen than usually can be obtained by balloon angioplasty or other devices. However, our obsession with luminoology, as Topol and Nissen pointed out, seems misguided.3 Clearly, angiography is a poor method to evaluate final lumen diameter, because postangioplasty lumens are often irregular and hazy, and the correlation between angiographic findings and intravascular ultrasound or pathological findings is poor. Even after stenting, visualization of the lumen through stent struts is difficult, and confidence that the stent is well opposed against the arterial wall cannot be assessed easily by angiography. Studies that have utilized intravascular ultrasound to assess the postangioplasty or stent lesions have shown a poor correlation with angiographic findings. They have also led to the understanding that restenosis is also influenced by the size of the plaque, often termed “less is best,” although this relationship is weak.4 This has led many interventionists to adopt a policy of debulking lesions to further reduce the odds of subsequent restenosis. Although studies have not been convincing that debulking reduces restenosis, this may be due to the lack of significant removal of tissue to affect the restenosis process. Most recently, combined approaches with both debulking and stenting have shown significant promise.

Our obsession with imaging, however, has led us away from appreciating the importance of coronary flow in restenosis. Restoration of normal hemodynamics and normal coronary flow reserve is the goal of angioplasty. Abnormal flow and shear stress have been shown to be important factors in regulating endothelial function and endothelial and smooth muscle cell growth factor expression.5–7 Experimental studies of restenosis have shown that shear stress correlated with intimal thickening.7 Factors such as the degree of pulsatile flow may also be important in this regard. Flow has also been shown to be an important contributor to both favorable and unfavorable remodeling, the dominant factor in clinical restenosis.8 However, the relationship between flow and clinical restenosis has been less well evaluated. In 4 clinical trials, DEBATE (Doppler Endpoints Balloon Angioplasty Trial Europe), DEBATE II, DESTINI (Doppler Endpoint STent INternational Investigation), and RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis), flow measurements were found to be predictive of subsequent events. In the first 3 trials, flow was assessed by the measurement of Doppler flow–velocity reserve, using a Doppler flow–velocity guidewire. Flow reserve was determined by measurement of velocity distal to the stenosis before and after maximal vasodilation with adenosine. In the DEBATE study, when both flow reserve (coronary flow reserve <2.5) and residual diameter stenosis (diameter stenosis >35%) were suboptimal, a modest prediction of restenosis was possible.9 The DEBATE II and DESTINI trials further validated the importance of these flow measurements. The measurement of coronary flow reserve, however, has a number of limitations.10 If baseline coronary blood flow is reduced, then an abnormal
coronary flow reserve can occur that may be unrelated to the severity of the stenosis. Adjustment of the coronary flow reserve to other unaffected vessels may not fully compensate for this problem. In addition, coronary flow reserve is not a measurement of volumetric flow, and thus, it assesses only the contribution of the stenosis to flow rather than total flow. This might be important if high normal flow is better than normal flow in reducing restenosis.

An alternative method to assess the physiological significance of the residual stenosis is measurement of fractional flow reserve (FFR) or the ratio of mean coronary pressure distal to the stenosis and mean aortic pressure during maximal hyperemia. FFR is a measure of the percent of maximal blood flow that can be obtained in the presence of the stenosis. A number of studies have shown a close correlation with angiographic or perfusion imaging assessments of stenosis severity. A recent trial demonstrated that the combination of a residual stenosis <30% and FFR >0.90 predicted a favorable clinical outcome after balloon angioplasty. Thus, assessment of the hemodynamic, not anatomic, significance of the stenosis with coronary flow reserve or FFR pressure appears to more accurately predict outcome than residual stenosis or MLD.

In this issue of Circulation, Stankovic et al.12 evaluate a new index that combines flow and MLD in predicting restenosis after balloon angioplasty. Flow was assessed with the corrected TIMI frame count (CTFC), a measure of the time of contrast appearance at the distal vessel, and caliper-determined measurements of residual MLD after angioplasty. In this study, coronary flow reserve was also measured. In a multivariate analysis, the ratio of CTFC to MLD ratio was predictive of restenosis and was able to distinguish a group of patients with a relatively high restenosis rate (56%) versus those with a low rate (15%). The ratio was better than either measurement alone and better than coronary flow reserve.

The ratio reflects the relationship between flow and resistance and thus is an indirect measurement of the overall pressure gradient. Because it estimates flow at rest rather than during maximum vasodilatation, such as is done with FFR or with coronary flow reserve, it measures the combined effects of the residual stenosis and distal coronary reserve. The findings of this study suggest that both the stenosis and distal resistance to flow are important in predicting restenosis. In fact, a number of studies have demonstrated that after successful angioplasty, coronary flow reserve does not return to normal for some time, which implies that there may be slow recovery of autoregulation of the microvascular bed.15 Although not all authors have validated this observation, the importance of volumetric flow to coronary restenosis probably deserves greater scrutiny.

This study, however, does have a number of limitations. The study population was small and very restrictive, excluding, for example, stent use, total occlusions, and patients with multivessel disease or prior myocardial infarction. Whether this index would be valid in a broader, more clinically relevant group of patients undergoing coronary interventions remains to be demonstrated. The study also did not compare the CTFC/MLD ratio with FFR.10 This latter measurement does not suffer from some of the limitations of coronary flow reserve. This study, however, further emphasized the importance of coronary blood flow and coronary physiology. It seems clear that the use of pressure and flow assessment, in addition to residual stenosis, has significantly improved our ability to predict those patients at risk of developing restenosis.

References

Key Words: Editorials • restenosis • angioplasty • prognosis • coronary blood flow
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Circulation. 2000;101:946-947
doi: 10.1161/01.CIR.101.9.946

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/9/946

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