Arterial Injury and the Enigma of Coronary Restenosis*

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Despite dramatic improvements in the primary success rate of coronary balloon angioplasty (1), the long-term efficacy of the procedure has not increased since its inception in 1977 (2,3). This paradox has been due to an unabated 30% to 40% incidence rate of restenosis that has persisted despite multiple attempted pharmacologic (4) and mechanical interventions (5,6).

The problem of coronary restenosis. The pathogenesis of the restenotic response to mechanical injury is incompletely understood (7); clearly it is multifactorial and includes growth factor stimulation of smooth muscle proliferation (8-10), elastic recoil (11) and organization of thrombus adherent at the site of arterial injury (12). Our understanding of the problem has been limited by the lack of an animal model that adequately mimics the pathologic response of the diseased human artery to balloon trauma. The rabbit iliac and rat carotid artery models, for example, have suggested benefit from at least nine pharmacologic interventions, none of which inhibited restenosis in later human testing (albeit often at a lower drug dosage) (13). The use of other models, such as the nonhuman primate, has also been limited by high purchase and maintenance costs and by difficulties in handling the animals.

Our understanding of restenosis has been further hampered by inadequate methods for measuring its prevalence in humans. The previous reference standard, percent diameter stenosis determined by contrast angiography, is now recognized to be a poor one, in large part because measurement of the adjacent “normal” artery is required; this reference segment is seldom normal, but instead, is usually diseased (14). Similarly, measurement of absolute minimal lumen dimension by quantitative angiography is limited because multiple views are required to adequately define eccentric stenoses and the highly irregular lumen borders produced by balloon angioplasty (15,16). Consistent with this limitation is the observation that postangioplasty dimensions as measured by intravascular ultrasound, a technique still in infancy itself, are consistently 15% to 30% smaller than lumen diameters measured by quantitative contrast angiography (17).

The present studies. Two reports in this issue of the Journal add to our understanding of the problem. Schwartz and colleagues (18), using the depth of arterial wall penetration by the wires of tantalum stents introduced and overexpanded by a balloon angioplasty catheter, describe a proportional response between the degree of arterial injury and the severity of neointimal thickening in a porcine coronary model. This important observation extends the work of Steele (19) and Wilentz (20) and their coworkers, who described a proportional response between the degree of injury and early platelet deposition in other models. If validated, this concept might greatly increase the sensitivity for detecting potentially useful interventions by allowing correction of the severity of neointimal thickening for the variable degree of arterial injury. However, it is not clear if this model usefully mirrors the human response (in fact the response may be so exuberant that it is insensitive to potentially useful interventions). Further, although more late thickening was seen with greater damage, this finding does not give the interventional cardiologist any indication of how much damage to inflict, as some balloon stretch is required to achieve an initial dimensional gain. Finally, one must not conclude from this study that the stent itself causes prolific restenosis, as in this study the stent was intentionally very much oversized (stent/artery ratio 1.3 to 2) compared with the stent/artery ratio of 1 to 1.1 that is currently being evaluated in clinical trials.

The clinical correlate of the proportional response of Schwartz et al. (18) is described, also in this issue of the Journal, by Beatt and colleagues (21). They used computer-assisted quantitative coronary angiography to assess 490 lesions from 424 patients obtained 94 ± 43 days after coronary angioplasty. Restenosis, defined as a decrease in minimal lumen dimension from the postprocedure result by ≥0.72 mm, was found to be significantly correlated with both larger improvement at the time of dilation and with a larger absolute dimension after angioplasty. They conclude that increased mechanical stretch leads to more lumen renarrowing. Also, and very important, they conclude that a distinction should be made between clinical restenosis (as measured by the ≥50% stenosis definition) and the restenosis process (as measured by dimensional change after angioplasty). However, the clinician is again not provided with enough information to judge the angiographic result he or she should strive for, as the clinical result in relation to postangioplasty dimension is not given. Hence, the appropriate balance between sufficient trauma to produce an adequate platform to minimize the clinical effect of the anticipated myointimal regrowth and limited trauma so as not to trigger an exuberant response cannot be judged.
Optimal model for human restenosis. While one can speculate that the ideal model should have pathologic features similar to those of humans before and after arterial injury, and should perhaps also respond similarly to dietary manipulation, it remains unclear whether these factors are prerequisite. Most important, the optimal model for restenosis should accurately predict the impact of pharmacologic and mechanical interventions in humans. If an intervention is beneficial in the model then benefit should be clearly demonstrable in human studies and, conversely, its negative predictive value should also be high. Unfortunately, no intervention shown to be effective in an animal model has reproducibly been shown to have even a small benefit in humans. Although this is likely to be due primarily to the shortcomings of the animal models, it may also be a function of inadequacies of trial design and inappropriate use or incomplete assessment of the end points used in many clinical trials (see later).

Optimal definition of restenosis. As noted previously (22), the incidence and clinical implications of the restenosis process vary considerably according to the criteria used to define this entity. In the study of Beatt et al. (21), the definition of a ⩾50% diameter stenosis at follow-up angiography identified a different group of patients from the group with restenosis defined by a change in minimal lumen diameter ⩾0.72 mm. Both definitions have important limitations. The rationale for the former criterion is that a measure of stenosis severity should reflect coronary flow reserve and thus be functionally and physiologically relevant (23). However, the definition assumes that the proximal or distal reference segment is not diseased and that no change has occurred in its caliber, assumptions that have been clearly shown to be invalid (14,22). Moreover, this definition may exclude patients with a considerable degree of neointimal thickening after an optimal angioplasty result but include patients with only a mild degree of neointimal thickening after a suboptimal angioplasty result. Finally, the arbitrary definition of ⩾50% diameter stenosis does not take into consideration the effects on coronary flow of stenosis length or angulation, dynamic changes in vessel caliber due to compensatory dilation, or the inaccuracies in measuring diameter stenosis in patients with diffuse coronary disease.

Although some of these difficulties are addressed using the change in minimal lumen diameter definition, this too has limitations. First, 0.72 mm is twice the standard deviation for repeated measures of nondilated coronary artery stenoses. This measurement has not been validated for angiography performed after coronary balloon dilation, a procedure that frequently causes lumen irregularities and haziness at the site of dilation. Second, a change of 0.72 mm has no physiologic meaning unless it is corrected for the caliber of the reference segment; it is thus also limited by the changes in caliber that may occur at this site. Third, the numeric change in minimal lumen diameter does not identify the nature of the "restenosis process" in any given individual. In the absence of ancillary investigations such as intracoronary ultrasound or local biopsy, however, it is unlikely that any angiographic measurement will distinguish between intimal proliferation, organized mural thrombus and elastic recoil. Finally, although measured as a continuous variable, the use of the binary outcome ⩾0.72 mm change in minimal lumen diameter, like the use of ⩾50% diameter stenosis, limits the statistical power of the observation. This has important implications for clinical trial design. If a binary definition is used, 696 patients must be enrolled with complete angiographic follow-up to have an 80% certainty of detecting a reduction in the incidence of restenosis in a given population from 35% to 25% with 2p = 0.05. If, on the other hand, a continuous variable is used, only about 100 patients would be required to demonstrate the same difference with the same statistical certainty. Using this approach a small difference in minimal lumen dimension might be statistically significant but its clinical relevance would have to be tested.

With these limitations in mind, we would recommend that the primary end point for angiographic trials assessing pharmacologic interventions should be absolute dimensional change, rather than "percent diameter stenosis." For mechanical interventions, that may intentionally trade off some lumen regrowth for a larger postprocedure platform, an end point of follow-up minimal lumen dimension would be more appropriate. Normalization for the diameter of the adjacent vessel at the time of the initial intervention should also be performed for interventions that are used in arteries of widely varying caliber.

Strategy for testing interventions. A number of large clinical trials have already been performed on the basis of little solid pretrial evidence that the intervention might actually work. The cost of this practice to the pharmaceutical industry, and eventually to society, is immense. Conversely, if a given intervention can be shown to have even a small impact on the incidence of restenosis, the potential savings in health care costs would be considerable. A three-stage testing scheme could be advanced as a rational, and probably most cost-effective, approach. First, any intervention considered to be effective on the basis of cell culture testing, or response in related disease processes, should be tested in at least two animal models. Second, if shown effective in animal models, the intervention should then be tested in a relatively small scale angiographic trial (for example, 100 patients restudied at 6 months) with minimal lumen dimension, measured as a continuous variable, as the primary end point. Only then is a full scale clinical trial in order. This would likely require 600 to 1,000 patients. Contrast angiography cannot adequately serve as the sole end point for such a trial because other clinically meaningful events, such as myocardial infarction and stroke, might also be influenced by individual pharmacologic interventions. Response to formal exercise testing has also been advocated as an end point for such a study because of the imperfect relation between stenosis dimensions and physiologic variables (22). Such testing may be invalid, however, because of progression of other nondilated stenoses, or unreliable be-
cause of other exercise limiting variables (for example, chronic pulmonary diseases). Perhaps more appropriate would be a composite clinical end point, similar to that advocated by Califf et al. (24) as an end point for thrombolytic trials. One could envision the following hierarchy of clinical outcomes: death, nonfatal myocardial infarction or stroke, repeat intervention (angioplasty or bypass surgery for documented recurrent stenosis at the dilated site), an abnormal stress test result without angiography, loss of patient to follow-up, negative functional test with suboptimal restenosis problem will almost undoubtedly be found in the future using the tools of molecular biology or possibly gene therapy, rational testing for benefit can probably be improved on by using fundamental knowledge available today.

Thus, although the ultimate answer or solution to the restenosis problem will almost undoubtedly be found in the future, the ultimate answer or solution to the restenosis problem will almost undoubtedly be found in the future using the tools of molecular biology or possibly gene therapy, rational testing for benefit can probably be improved on by using fundamental knowledge available today.

References


