Current Perspectives

Intimal Hyperplasia, Vascular Modeling, and the Restenosis Problem

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At the recent Scientific Sessions of the American Heart Association, a plenary session was devoted to the problem of restenosis after percutaneous transluminal coronary angioplasty. The panel included five widely recognized and experienced physician-scientists who provided critical, comprehensive reviews of the problem. Two of the speakers dealt with the clinical, angiographic, and pathobiological aspects, one discussed the impact of new devices, and one reviewed the clinical trials designed to cope with each of several specific mediators of smooth muscle cell proliferation or thrombosis. The last speaker proposed an antisense gene delivery strategy to reduce or prevent the intimal proliferative reaction, which is a principal characteristic of the undesirable occlusive tissue response. The conclusions to be drawn from the presentations can be summarized in two brief statements. (1) We do not completely understand the natural history of the restenotic process. (2) None of the strategies attempted thus far has had a significant impact on the incidence of restenosis, which continues to complicate 30% to 50% of angioplasty procedures. Most of the pharmacological interventions attempted thus far have been based on common assumptions that the intimal smooth muscle proliferative response, intimal hyperplasia, is the consequence of the mechanical injury to the plaque and/or to the artery wall and that once initiated, it may proceed to restenosis unless one or more of the biochemical agents that have been shown to stimulate arterial smooth muscle cell proliferation is suppressed or antagonized. Although a proliferative reaction may be initiated by mechanical disruption of a plaque during angioplasty, this trauma may not be the critical determinant of progression to restenosis because 50% to 70% of the lesions do not restenose and have ostensibly been subjected to the same or similar trauma as those that do. Thus far, no definite relation has been established among plaque composition, plaque structure, or the nature and extent of plaque disruption and the eventual outcome. Indeed, unfavorable results have been attributed both to inadequate and to excessive plaque disruption.

Experimental animal models designed to illuminate the nature of intimal hyperplasia and of the restenotic reaction have relied mainly on characterization of the intimal healing response after balloon catheter injury of the endothelium and the immediately subjacent media. This maneuver induces a self-limiting intimal accumulation of smooth muscle cells that does not proceed to occlusion; nor is it occurring in the presence of an underlying atherosclerotic process that has resulted in a complex conglomerate of tissues of varied composition and different mechanical properties, nor is it occurring in the presence of a greatly modified local flow field due to deformities related to plaque configuration or disruption or to the presence of flow-limiting lesions elsewhere along the artery. The balloon injury denudation model has produced new knowledge concerning mediators of smooth muscle cell migration and proliferation but has not as yet reproduced the conditions prevailing at most angioplasty sites and has not provided information of preventive therapeutic value. However, some evidence has been forthcoming, even from this model, that flow may modulate the proliferative healing response after balloon injury, suggesting that evolution of the healing reaction is sensitive to wall shear stress.

Two of the speakers at the plenary session alluded to recent findings that suggest that restenosis or its prevention may be related, at least in part, to reactive-adaptive modeling processes, including those by which blood vessels tend to compensate for plaque formation. Our own findings that human arteries enlarge as plaques form, thereby preserving lumen cross-sectional area for extended periods, were cited in support of a possible role for modeling reactions in relation to restenosis. Also cited was a recent experimental study suggesting that vessel enlargement may follow angioplasty and that restenosis may be prevented if the enlargement exceeds the potentially occlusive intimal proliferative reaction. Indeed, a good deal of evidence is now available to indicate that the artery wall tends to adapt or remodel in such a manner as to maintain stability with respect to flow and tensile stress. For flow, the response is closely related to changes in wall shear stress; for tensile stress, the response is to alterations in pressure and/or vessel radius. These adaptive reactions are of necessity closely linked. For example, increased wall shear stress induces an increase in radius until wall shear stress is restored to mean baseline levels of about 15 dyne/cm² (References 13 and 14); the increase in radius induces modifications of wall thickness, structure, and composition in keeping with the associated increase in wall tensile stress. Conversely, reduction of wall shear stress below baseline values results in a reduction of radius and a corresponding adjustment of mural composition in response to the reduced tensile stress. The intima participates in these compensatory reactions in the form of intimal thicken-
ing, tending to narrow the lumen and increase flow rate when wall shear stress is reduced below normal baseline values\textsuperscript{18-20} or to augment total wall thickness, thereby reducing wall tensile stress when pressure or radius are increased.\textsuperscript{16} These reactions occur in the presence of atherosclerosis and participate in the modeling, which accounts for some of the features of plaque structure that tend to sequester the lesion, stabilize flow, and prevent plaque rupture.\textsuperscript{21,22}

It is reasonable, therefore, to suppose that disruptions and deformities introduced by angioplasty, by atherectomy, or by other direct mechanical interventions result in local and focal redistributions of both wall shear stress and mural tensile stress and elicit adaptive modeling reactions in intima, media, and plaque. These changes will appear as alterations of lumen configuration, lumen radius, and overall artery size. Should local levels of wall shear stress and tensile stress be prevented from reaching or reestablishing baseline conditions, the proliferative intimal reaction would be expected to continue and restenosis to supervene. Should baseline conditions be restored before the reactive intimal modeling process results in occlusion, the proliferative reaction would be expected to stop and stabilize with maintenance of a patent lumen. The factors preventing stabilization and persistence of a patent lumen would therefore include the presence or creation of irreducible deformities associated with dense plaque fibrosis and/or calcification as well as the persistence of low flow states due to proximal or distal atherosclerotic stenoses or to reduced cardiac output.

The histological features of the intimal proliferative response after angioplasty are indistinguishable from those that occur about surgically produced anastomoses in association with revascularization procedures. Appearances are similar in vessels with markedly reduced flow, in saphenous veins or other vessels used as bypass grafts, and in vascular constructions for dialysis access.\textsuperscript{15,23,24} The intimal thickening associated with these situations may be either self-limiting or proceed to stenosis. In specimens of nonatherosclerotic reactive intimal thickening obtained from many human vessels and anastomotic junctions, we have noted two principle forms: intimal hyperplasia and intimal fibrocellular hypertrophy.\textsuperscript{25} We have suggested that the term intimal hyperplasia be reserved for tissue appearances that connote an ongoing predominantly proliferative response. The component cells tend to be fairly widely separated without any definite common orientation. The intervening matrix, although abundant, contains few distinct elastin or collagen fibers. We have used the term intimal fibrocellular hypertrophy for appearances that connote structural differentiation and stabilization. In this form, common orientation of the component cells is a prominent feature, as is the reduction in the relative proportion of matrix to cells, but with formation of commonly oriented and prominent elastin and collagen fibers. The morphological characteristics of the two forms of reactive intimal modeling are shown in the Figure. The intimal adaptive-reactive response appears initially as the mainly proliferative form, intimal hyperplasia. With the reestablishment of baseline wall shear stress, the predominantly proliferative phase is curtailed, and transition to the architecturally differentiated intimal fibrocellular hypertrophy response occurs, most likely closely modulated by local tensile stress conditions.\textsuperscript{15,16} The organizing intimal reaction then tends to merge with the adjacent artery wall and may exhibit structural features of media. The proposed role for mechanically induced modeling reactions as determinants of restenosis or patency and the relation of the forms of intimal thickening to the possible outcomes are outlined in the Table. Both forms of nonatherosclerotic intimal thickening may appear in atherectomy material after previous angioplasty but also may be found in atherectomy specimens without previous intervention.\textsuperscript{26} The latter findings probably represent focal adaptive modeling reactions after plaque fissuring or other changes in configuration due to changes in plaque composition or thrombosis. Transitional or superimposed forms, connoting intermediate changes presumably in response to alterations in mechanical conditions, are often noted in surgical and autopsy material.\textsuperscript{23,26}

The implications of these considerations with regard to the restenosis problem may be summarized as follows.

(1) Artery enlargement is in general a reaction to increased flow and/or to the formation of an atherosclerotic plaque. In the case of angioplasty or atherectomy,
Mechanically Induced Modeling in Relation to Patency and Restenosis

**Stenosis→Intervention→Proliferative Healing Response**

Persistent or subsequent progressive low flow (WSS ↓)

- WSS ↓ → IH → r ↓ → WSS ↑
- Baseline WSS not restored → Continuing IH → restenosis

Postinterventional low local flow (WSS ↓)

- WSS ↓ → IH → r ↓ → WSS ↑
- Baseline WSS restored → Stabilization (arrest of IH) → IFH → patency

Higher than baseline local flow (WSS ↑)

- WSS ↑ → r ↑ → WT ↑ → TS ↑
- TS ↑ → SMC response (media: intima: IH)
- Stabilization (appropriate TS and baseline WSS)
- IFH → patency

Semidiagrammatic outline summary of the proposed role for mechanically induced reactive modeling responses as determinants of restenosis or patency after direct interventions on stenotic plaques. IFH indicates intimal fibrocellular hypertrophy; IH, intimal hyperplasia; r, effective local radius; SMC, smooth muscle cell; TS, total tensile stress; WSS, wall shear stress; and WT, wall tension.

(4) The postangioplasty intimal proliferative response that may eventuate in restenotic intimal hyperplasia is not a late event. It is the unfavorable continuation of an adaptive-reactive process, which, although usually evident to various degrees and at various intervals during plaque morphogenesis, is set into progression as a modeling response, not by the angioplastic injury per se but by the suddenly imposed local changes in configuration and in local flow conditions caused by disruption of the plaque and artery wall. Thus, the "magic bullet" approach based on the manipulation of mediators of smooth muscle cell proliferation, including gene targeting at the time of angioplasty, is unlikely to reduce the incidence of restenosis if the mechanical-hemodynamic conditions do not permit a favorable self-limiting remodeling outcome.

(5) More and better clinical-pathological correlative studies of human material should be undertaken to test the observations and suggestions that form the basis of the present communication. Determinations of flow rate at the site of angioplasty before, immediately after, and periodically after angioplasty, assessment of corresponding local configurational changes, and documentation of plaque distribution and progression proximal and distal to the lesion under treatment are likely to provide insights into the critical flow-related determinants of restenosis. Such studies could help to establish criteria for the identification of patients likely to benefit from angioplasty and those who are more likely to benefit from other procedures.

(6) Some of the determinants of restenosis may be patient specific. Excessive tissue reactivity of some individuals to postangioplasty conditions, rapid progression of atherogenesis, and the development of plaque complications at the angioplasty site and at locations distal or proximal to the intervention site are mechanisms worthy of further investigation.

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