Editorial Comment

The Urge to Prevent Restenosis After Percutaneous Transluminal Coronary Angioplasty

Scylla and Charybdis in Disguise

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When Odysseus attempted to sail unharmed between Scylla and Charybdis, he could not have dreamt to ever be quoted in relation to restenosis after percutaneous transluminal coronary angioplasty (PTCA).

To be truly successful, balloon dilatation should change the preexistent stenotic lesion to the extent that sufficient luminal widening is achieved and restenosis does not occur. Nevertheless, approximately 30% of patients will develop restenosis despite an initially successful procedure. All clinical attempts to reduce the incidence have failed. The paradox of this apparent dismal outcome is that this may be the good news after all. Inhibition of the “response to injury” may be the bad news. Why so?

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Since the first documentation by Essed and colleagues1 of a fibrocellular intimal proliferation at the site of a previous PTCA that caused restenosis 5 months after the initial procedure, much research effort has been channeled into the study of the basic mechanisms involved. Animal experiments revealed that the response was due to a proliferation of vascular smooth muscle cells.2-4 A recent immunocytochemical analysis of the fibrocellular tissue causing restenosis in humans has shown unequivocally that the main cellular component is of smooth muscle cell origin.5 Furthermore, a study of coronary arteries of patients who died within 20 days after PTCA suggests that the proliferative response is due to an interaction of a platelet-fibrin thrombus and smooth muscle cells, with a possible role for macrophages.6 A recent editorial comment in this journal further emphasized the likely role of thrombus formation in the development of proliferative lesions after vascular injury.7 Hence, the problem of restenosis is solved once the mechanisms that cause the proliferative cellular response are successfully inhibited. Could it be that the logic behind this reasoning needs some nuance?

The fact that injury evokes a reparative response surely has contributed to the survival of mankind. We are, after all, discussing wound healing, albeit in a diseased artery. The dilating radial pressure of the inflated balloon may jeopardize tissue, may cause injury, and may set into place a reparative process. The response may cause restenosis, which is unfortunate, but the basic principle of the reparative phenomenon should not be blamed.

Is the response in patients who develop restenosis excessive compared with the response in patients who do not develop restenosis? Much depends on the clinical definition of restenosis. The presently promoted definition of restenosis is a 50% or greater loss of the initial gain, which hardly can be interpreted as an indication that patients who develop restenosis present a basically different response to injury from those that do not categorize as restenosis. Indeed, histopathological studies provide evidence that the response is rather similar but that the main difference in the extent of response relates to factors such as extent of laceration and type of tissue injured.8,9 The morphology of the stenotic lesion itself is already of paramount significance. It makes a difference whether the lesion is concentric or eccentric, since the extent of the laceration induced is different. In case of a concentric plaque, the chances are that any laceration induced will remain limited to the intimal plaque. On the other hand, eccentric lesions carry the risk that the plaque-free wall (the media and superimposed musculoelastic layer) gets involved or that the shoulder part of the plaque (the site where the plaque borders on the plaque-free wall) dissects from the underlying preexistent wall layers. Further relevant differences are introduced once the tissue component makeup is taken into consideration. Atherosclerotic plaques may vary from intimal elevations characterized by an extensive atheromatous pool with only scarce fibrous tissue enclosing the fatty debris to plaques almost solely composed of fibrous tissue with an almost acellular appearance. Injury to the former type of atherosclerotic plaque is hazardous in the sense that it may lead to an immediate thrombotic occlusion of the artery with all the acute and dramatic effects well known to the clinician, a “hit-and-run” situation of little relevance with respect to the fibrocellular proliferative response underlying restenosis. Occasionally, the procedure may lead to hemorrhage within the plaque, with or
without a partial washout of the atheromatous debris and subsequent organization. Nevertheless, injury to fibrous tissue may expose cells capable of responding. Under such circumstances, the nature of the cells involved becomes important. Are the cells exposed smooth muscle cells already transformed to dormant fibroblast-like cells, or are the cells exposed still “trigger happy”? In other words, the cellular composition of the plaques is an important feature when put into the perspective of the reparative response after PTCA. The same applies to laceration induced to vascular wall structures in case of an eccentric plaque. In those instances injury of the plaque-free wall or the flaplike injury or dissection at the site of the plaque shoulder will expose trigger-happy smooth muscle cells, and a rapid proliferative response almost certainly will ensue. In other words, injury induced by PTCA exposes tissue of variable composition, ranging from almost acellular “unresponsive” fibrous tissue to tissue loaded by trigger-happy cells. It is sobering to realize that the PTCA procedure, despite all technical refinements, remains an extremely crude and unpredictable procedure as far as its sequelae at the cellular level are concerned. In the real world, therefore, the logical sequence “thrombin deposition, release of growth factors, proliferation of vascular smooth muscle cells” needs some nuance. Contemplations initiated by reading the otherwise fascinating observations presented by Hanke and coworkers11 this issue of Circulation. In their experimental rabbit model, the use of low-molecular-weight heparin resulted in inhibition of smooth muscle cell proliferation after balloon angioplasty; surely this is another contribution to an understanding of basic mechanisms operative in vascular response to injury. Also certain is that it is another impetus for further attempts in humans to reduce the incidence of post-PTCA restenosis by inhibiting the proliferative cellular response via pharmacological interventions. The question, however, is not how to inhibit but rather how to modulate and control a response that basically is there to heal but, on the other hand, may produce restenosis. Hence, Scylla and Charybdis.

References

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