Heparin
Will it Control Intimal Thickening After Angioplasty?

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Althought transluminal angioplasty has simplified the treatment of patients suffering from coronary arteriosclerosis and myocardial ischemia, its efficacy is significantly diminished by the early and high frequency of intimal hyperplasia and restenosis.\(^1\) Intimal hyperplasia is also an important cause of stenosis and failure of other forms of vascular reconstruction including atherectomy, endarterectomy, and vein or synthetic bypass grafting. These procedures all have in common an element of injury and a subsequent response of the vascular wall to that injury. The accumulation of vascular smooth muscle cells and associated matrix invariably accounts for the bulk of the intimal hyperplastic lesion. For this reason, clinical investigators have focused on pharmacological strategies for inhibiting smooth muscle cell migration and proliferation as a way of controlling intimal hyperplasia and restenosis.\(^2\)

A number of drugs have been tried in animal models and in patients undergoing coronary angioplasty. Most of the drugs, including aspirin and related inhibitors of platelet function, do not prevent restenosis.\(^3\) Heparin has been shown to be an effective inhibitor of intimal thickening in rat models of arterial injury and is currently undergoing testing in a number of clinical trials.\(^1,4\) It inhibits smooth muscle proliferation and migration in vitro and in vivo and produces a marked alteration in matrix composition. The drug needs to be given for only a brief time in the perioperative period (approximately 1 week) for maximal effect, and the smooth muscle cells do not start proliferating after the heparin is stopped. Fragments of heparin lacking anticoagulant activity are as effective as native heparin in inhibiting intimal thickening. Even though smooth muscle growth is inhibited by heparin treatment, endothelial regeneration proceeds normally and is not affected by heparin.

Why then did the studies of Gimple et al\(^5\) and Buchwald et al\(^6\) arrive at opposite conclusions with regard to the effect of heparin on intimal hyperplasia in animal models of atherosclerosis? In both situations, the animals were fed a diet containing 2% cholesterol, and marked hypercholesterolemia was noted. The artery studied was then subjected to injury and at a later time was treated with either angioplasty or stent. In the rabbit studies of Gimple et al, heparin did not appear to affect the intimal thickening after angioplasty, whereas in the studies of Buchwald et al, which used a minipig model of healing after placement of a stent, heparin had a marked impact.

There are a number of important differences in these two sets of experiments. For example, cholesterol-fed rabbits developed a level of hypercholesterolemia 20- to 25-fold above control levels (in the range of 1,000–1,500 mg%), whereas in the pigs, the cholesterol levels were much lower (300 mg%). Even though the rabbits were taken off the diet at the time of angioplasty, a high blood level of cholesterol was nevertheless sustained over the period of study. These differences in cholesterol levels might then be reflected in changes in the composition of the injury-induced lesion. The rabbit lesion might contain substantially more foam cells and fewer smooth muscle cells than the pig injury-induced lesion. It is of note that injury of normal rat carotid arteries produces an intimal thickening that is made up almost entirely of smooth muscle cells.\(^7\) If heparin were to have little or no impact on the accumulation of macrophages and lipid, then the differences might simply be related to the degree of hypercholesterolemia. There are many other differences of importance. The test vascular bed (rabbit femoral artery versus pig coronary artery), the local stimulus to produce fibrous plaque (air injury in the rabbit versus balloon injury in the pig), the type of treatment (angioplasty in the rabbit versus stent in the pig), and the type of heparin and protocol for delivery could be of great importance. We have noted, for example, that continuous intravenous heparin administration is the most effective way to inhibit intimal thickening after injury in rat carotid artery; intermittent injection of heparin is less effective and sometimes leads to thrombosis (AW Clowes, MM Clowes, unpublished results). Furthermore, the targeted vascular bed and the animal itself may alter the response to heparin. Using similar protocols in rats and rabbits, we have observed that intimal thickening in injured carotid arteries can be suppressed by heparin in both animals but less so in the rabbit; in the rabbit, healing vein grafts showed little or no response to heparin, whereas contralateral injured arteries showed diminished intimal thickening.\(^8\) Hence, it is possible that a combination of lack of responsiveness and an overwhelming stimulus including a high blood level of cholesterol in the rabbit yielded a recurrent lesion.

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relatively resistant to heparin treatment compared with the pig.

This analysis underscores several points. First, there are significant differences between different animals and between animals and humans. It is important to characterize the different responses in terms of stimulus and the type of lesion formed. There is little quantitative information regarding the participation of lymphocytes, macrophages, smooth muscle cells, and endothelial cells as well as the extent of thrombosis in each of the injury systems both acutely and during the reparative phase. Comparative studies need to be performed with human tissue retrieved by atherectomy and at autopsy to determine whether any of the animal models mimic the human response. Second, it is likely that there are many forms of injury and response. For example, it is possible that angioplasty has an acute effect and induces a short-lived healing response, whereas the presence of a stent or a sustained high blood cholesterol level may represent a protracted stimulus for intimal thickening. Finally, in regard to the pharmacological treatment, it is clear that different forms of heparin and different protocols of delivery will significantly influence the outcome. With a more detailed analysis of the mechanisms of heparin action and the response of diseased and normal arteries to injury and pharmacological therapy in several animal models, it should be possible to define features in common that will lead to the design of sensible clinical trials of heparin in patients undergoing coronary angioplasty.

References
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