A Symposium: Restenosis After Percutaneous Transluminal Coronary Angioplasty

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Mechanism of Angioplasty and Its Relation to Restenosis

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Balloon angioplasty enlarges atherosclerotic narrowings in the vast majority of patients in whom it is attempted at an acceptably low complication rate. Experimental and human pathologic studies have confirmed that angioplasty enlarge the lumen by stretching the vessel wall. Often this stretching process causes plaque fracture due to inelastic components of the atheroma. Denudation of the endothelium is also a consistent observation. While enlarging the lumen, this vascular trauma promotes marked platelet adhesion and aggregation that is dependent on the degree of vascular damage. Most platelets accumulate early within the first few hours. Subsequently, thrombus formation and smooth muscle cell proliferation can occur with the formation of a new fibrocellular occlusive process. Experimentally, antiplatelet therapy can significantly reduce platelet deposition and can reduce the incidence of restenosis. Although restenosis is a multifactoral process, prevention seems possible when platelet accumulation, thrombus formation and smooth muscle cell proliferation can be inhibited through drug or mechanical means. (Am J Cardiol 1987;60:5B-9B)

In 1964, Dotter and Judkins described the nonoperative technique of transluminal angioplasty to treat patients with severe femoral and popliteal atherosclerotic obstructions. They envisioned that angioplasty worked by remodeling and compressing the atheroma because initial pathologic studies revealed little intimal destruction and no evidence of dissection. However, subsequent pathologic studies did not confirm these observations; in fact, they suggested that marked vessel damage occurred after balloon angioplasty with neointimal tears and occasional perforation. Castenada-Zuniga et al reported vessel stretching, cracking of the intima and separation between the intima and media in human postmortem studies. The results of postmortem studies have not been uniformly accepted because of variability in findings and inherent differences between viable atherosclerotic tissue and postmortem pathologic specimens.

Studies in normal canine arteries showed that balloon dilatation caused marked intimal damage with extensive endothelial desquamation. However, normal vascular tissue is not likely to respond to injury in the same way as atherosclerotic plaque. In order to circumvent this problem, we and others adapted a rabbit model of atherosclerosis in which significant focal iliac atherosclerotic lesions could be developed that were suitable for the study of the effect of angioplasty. Atherosclerotic lesions were induced in 3 kg white New Zealand male rabbits by balloon deendothelization of both iliac vessels followed by 6 weeks of a 2% cholesterol diet. Cholesterol levels on this diet averaged 1,000 to 1,500 mg/dl. Angiography disclosed significant focal midiliac stenosis ranging from 50% to 90% in severity (Fig. 1).

Angioplasty was performed retrograde from the femoral artery using a 2 to 2.5 mm balloon catheter. Repeat angioplasty disclosed angiographic improvement in all animals. The animals were then killed and perfused at 80 mm Hg to permit histologic examination. Nondilated segments showed concentric foam cell lesions with a fibrous cap typical of this model. Using an indwelling catheter technique fibrocellular eccentric lesions could also be developed. Histologic changes at the angioplasty site included vessel stretching when eccentric lesions were present and neointi-
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FIGURE 1. Significant iliac stenosis is evident in the left iliac artery of a rabbit after balloon deendothelization and a 2% cholesterol diet for 6 weeks. Middle panel shows a 2.5 mm angioplasty balloon catheter inflated in the stenosis with angiographic improvement evident after angioplasty in the right panel. Reproduced with permission from Atherosclerosis.6

FIGURE 2. An example of histological changes seen immediately after angioplasty. Marked neointimal fracture is evident with the creation of neointimal flaps extending into the vessel lumen. Reproduced with permission from Circulation.9

FIGURE 3. Morphometric analysis of serial histologic sections through the angioplasty site and control segments show enlargement of the lumen and vessel area without change in the area of the arterial wall (intima and media). This finding is consistent with vessel stretching without compression of the atheroma. *p ≤0.05. Reproduced with permission from Circulation.9

Restenosis, the phenomenon of renarrowing of the vessel early after PTCA, has been reported to occur in 25% to 50% of patients, averaging 33%.13 The incidence of restenosis has changed little since PTCA was first introduced nearly 10 years ago. Restenosis is an early phenomenon with the vast majority of patients requiring repeat procedures within 6 months. However, repeat angioplasty is highly successful and can result in long-term patency in the majority of pa-
tients. While clinical, angiographic and procedural factors can predict a higher incidence of restenosis, the most likely cause of restenosis is the response of the vascular tissue to the often dramatic injury that can occur after PTCA. Vascular injury of the type seen after angioplasty would be expected to result in 4 separate but interactive processes: vasospasm, thrombosis, platelet adhesion and cellular perforation. In order to evaluate these potential mechanisms, we again used the atherosclerotic rabbit model. After induction of iliac atherosclerosis and successful angioplasty, animals were maintained on a high cholesterol diet for 4 weeks at which point they underwent repeat angiography. Angiographic evidence of restenosis was documented in all animals. Histologic studies also confirmed restenosis with evidence of organized thrombus and cellular proliferation (Fig. 5).

Further studies were undertaken to evaluate the potential role of vasospasm as a contributing factor. In separate groups of animals with angiographically documented lesions, nifedipine or placebo was randomly administered. Angioplasty was performed and the animals followed for 4 weeks. Repeat angiography showed no significant differences between groups. Likewise histologic examination also showed no significant difference. These findings have been verified by randomized clinical trials. While calcium antagonists may not play a role in preventing restenosis in most patients, clinical studies would suggest that they are important in patients with variant angina.

Although the injury hypothesis of atherosclerosis, popularized by Ross and Glomset, is not presumed to be a primary mechanism of de novo atherosclerosis, it is highly likely that it plays a prominent role in angioplasty. This hypothesis states that repeated vascular injury results in endothelial denudation with platelet adhesion, thrombus formation and monocyte infiltration, which can lead to smooth muscle cell proliferation, in part due to stimulatory effects of platelet derived growth factor. Subsequently increased uptake of cholesterol within arterial wall and formation of atherosclerosis can occur. As previously mentioned, animal studies have demonstrated deendothelialization of the vessel wall after PTCA with a dense platelet “carpet” laid down immediately after the procedure. We have recently quantified platelet accumulation at various time frames after experimental angioplasty in the rabbit model using chromium-51-labelled platelets (Fig. 6). The degree of platelet accumulation at the angioplasty site was significant and nearly 10-fold greater than that reported with milder forms of vascular injury. Of note was that platelet adhesion occurred principally within the first 2 hours after angioplasty. The degree of platelet accumulation was directly related to the degree of vascular damage quantified histologically. Efforts to reduce this marked platelet deposition have been somewhat unrewarding as the usual platelet regimens are only partially effective. Studies from our laboratory have demonstrated that intravenous aspirin and a thromboxane synthetase inhibitor significantly reduced platelet accumulation 30 minutes after angioplasty while oral aspirin and heparin were not effective. Longer term experimental studies have demonstrated that aspirin and dipyridamole as well as sulfinpyrazone significantly reduce the occurrence of restenosis as determined angiographically; however, neither drug regimen was completely successful as one-third to one-half of the animals showed some degree of restenosis. Histologic correlates have also confirmed the benefit of these agents in that less neointimal proliferation, and thrombus formation, occurred (Fig. 7). While platelet accumulation and thrombus formation are prominent features of experimental studies, cellular proliferation appears to be the most common and consistent finding. Human autopsy studies, although scant, have also demonstrated fibrocellular proliferation. In a report by Essed et al., histologic...
As we have shown, the degree of platelet aggregation is directly related to the degree of vascular damage. If greater platelet aggregation leads to a greater proliferative response as well as greater fibrin deposition, then the propensity for restenosis through either cellular proliferation or thrombus would be increased. This concept is supported by the observation that other forms of vascular damage such as the laser-heater probe causes less vascular damage and less restenosis than angioplasty in the same animal model.20

In summary, restenosis is a multifactorial process and while clinical, anatomical and procedural factors are important, it appears that the primary element is the response of the vascular wall to the acute injury. Prevention seems possible when platelet accumulation, thrombus formation and smooth cell proliferation can be inhibited through drug or mechanical means.

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