Mechanisms and prevention of restenosis: from experimental models to clinical practice

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1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) was first introduced by Andreas Gruentzig in 1977 [1] as an alternative form of myocardial revascularization for patients with coronary artery disease. During the early years of its application, PTCA was limited to patients with single proximal coronary artery disease, well preserved left ventricular function, and stable angina refractory to medical treatment. Almost twenty years later, PTCA has become a well established technique for myocardial revascularization of patients with unstable angina [2], patients with an evolving myocardial infarction [3], patients with multivessel disease [4], and patients with depressed left ventricular function [5]. However, PTCA remains limited by restenosis that occurs in 30–60% of cases despite a successful procedure [6–9]. Assuming 500,000 PTCA procedures per year in the United States [10], more than 150,000 patients develop restenosis every year. Although some restenoses may be silent, most of these patients present with recurrent angina and a significant proportion will need a new revascularization procedure. Decreasing the rate of restenosis would sharply lower the long-term cost of PTCA; in the United States, a reduction of the rate of restenosis from an hypothetical 33% to 25% might save as much as $750 million annually [10]. Numerous agents have been used to prevent restenosis, and the results of more than 40 multicenter randomized clinical trials have now been published [11,12]. Despite intensive investigation in this area, no pharmacological therapy has yet been found to be useful in preventing restenosis. The purpose of this report is twofold: first, to review the available information relevant to the mechanisms of restenosis, and, second, to review the strategies currently being explored as possible approaches to the control of coronary restenosis after PTCA.

2. Mechanisms of restenosis

2.1. The healing process after arterial injury

2.1.1. Neointimal hyperplasia

In response to experimental arterial injury, medial smooth muscle cells (SMC) shift from a contractile to a synthetic phenotype, proliferate, migrate, and produce large amounts of extracellular matrix (Fig. 1). This growth response leads to the development of a neointimal thickening also known as neointimal hyperplasia [13] (Fig. 2).

Immediately after arterial injury with a balloon catheter, multiple factors (see below) lead to the activation of SMCs. Early markers of SMC activation such as expression of nuclear oncogenes are detectable as soon as 30 min after injury [14,15]. Induction of c-fos, c-jun, and c-myc proto-oncogenes is one of the earliest transcriptional events associated with growth factor stimulation [16] and the increased expression of these genes is a transient response to mitogenic stimulation persisting at most for a few hours after exposure to growth factors [17]. It has been recently demonstrated that the distribution of c-fos and c-jun products after arterial injury was concentrated in smooth mus-
Fig. 1. The cascade of events leading to neointimal thickening after balloon denudation. SMC = smooth muscle cell. ECM = extracellular matrix.

Many of these neointimal cells continue to proliferate for several cycles but nearly half of the migrating cells do not synthesize DNA [26]. Proliferation and migration should thus be considered as two distinct mechanisms leading to neointimal thickening; as discussed below, some factors may affect SMC migration but have no effect on SMC proliferation, and vice versa [27].

In animal models, the degree of intimal thickening is maximal after 3 months [28]; the additional volume that accumulates after 2 to 4 weeks reflects the adjunctive synthesis of extracellular matrix by synthetic SMCs [22-24,29]. Experimental balloon denudation is followed by a marked increase in expression of the genes that code for collagen and elastin in the arterial wall [30]. Similarly, the reexpression of embryonic forms of fibronectin occurs in the media and adventitia of rabbit arteries 24–48 h after injury; two weeks after balloon denudation, when the neointima is formed, fibronectin mRNAs as well as the fibronectin protein accumulate in the luminal layers of the neointima [31]. As pointed out by Schwartz et al. [32], cellular components constitute only about 11% of neointimal volume, and the remainder is extracellular matrix. Given the abundance of extracellular matrix in restenotic lesions, one potential “anti-restenosis” strategy would be to reduce the matrix volume surrounding each cell; a substantial reduction in neointimal volume might be obtained without the need to inhibit SMC migration or proliferation.

After 2 to 3 months, SMCs return to a contractile phenotype and no further significant increase in intimal thickening occurs [33].

2.1.2. Arterial remodeling

Arterial remodeling is well described in de novo atherosclerosis. Glagov et al. [34] observed that human coronary arteries undergo adaptive enlargement in response to progressive plaque expansion and maintain the lumen area until the plaque occupies 40% of the area circumscribed by
the internal elastic lamina. This compensatory enlargement may thus limit the effect of plaque development on lumen narrowing.

There is increasing experimental evidence that neointimal hyperplasia is not the sole mechanism leading to lumen renarrowing after angioplasty, and that arterial remodeling also plays a major role in this process [35–37]. In the hypercholesterolemic rabbit model, Kakuta et al. [36] showed that compensatory enlargement of the vessel (increase in internal elastic lamina area) occurs in the weeks following experimental angioplasty; this process was able to accommodate nearly 60% of the neointimal formation in response to balloon injury and limit lumen narrowing. Surprisingly, restenosis was not related to neointimal formation but to a lack of compensatory enlargement or even to some degree of vessel constriction. Vascular remodeling is thus able to limit the effect of neointimal formation on chronic lumen diameter and differences in vascular remodeling, not differences in intimal formation, account for restenosis in this model. Other reports by Post et al. [35] and Lafont et al. [37] have also demonstrated the role of vascular remodeling in other models of restenosis.

2.2. Mechanisms of restenosis in humans

One important question is whether the pathophysiological mechanisms of restenosis demonstrated in experimental models also apply to the clinical situation. Obviously the arterial wall response after coronary angioplasty in humans is less well documented than the responses in experimental models. Nevertheless, histological studies have shown that intimal thickening in the restenotic lesion contains SMCs in an abundant extracellular matrix [38–40]. Immunohistochemical studies [41,42] have documented phenotypic modulations of SMCs after PTCA in humans; during the 2 months following PTCA, SMCs are in a synthetic phenotype and thereafter they revert to a contractile phenotype. Various degrees of proliferation have been demonstrated in atherectomy specimens from restenotic lesions [38–40]. Migration of SMCs has never been demonstrated after PTCA in humans; it should be noted, however, that in man there is not necessarily a need for SMC migration into the intima since SMCs are already present in the atherosclerotic plaque.

However, as in experimental models, neointimal hyperplasia is not the sole mechanism of restenosis in humans. There is preliminary intracoronary ultrasound evidence that vascular remodeling also occurs after angioplasty in humans [45,46]. Studies by Mintz et al. [45,46] suggested that most of the late lumen loss after balloon angioplasty was due to arterial remodeling and not to intimal formation. The contribution of remodeling to restenosis after nonballoon coronary angioplasty may, however, be different. Coronary stenting, for example, may eliminate any component of arterial remodeling, either enlargement or constriction (see below).

2.3. Potential regulators of the healing process

2.3.1. The endothelium

The endothelium plays a fundamental role in controlling vessel tone and SMC proliferation. After experimental angioplasty, reendothelialization of the denuded surface occurs within weeks and may be either complete [47,48] or incomplete [49–51] depending upon the animal model studied (Fig. 3); areas where the endothelial covering has rapidly regenerated have less marked intimal thickening than areas where endothelial regeneration occurs later [49,52,53]. Endothelial regeneration is probably delayed or may even be incomplete in humans. In one study, Gravanis and Roubin [54] did not find endothelial cells at the angioplasty site in patients who died within 1 month of PTCA but found substantial reendothelialization in the later specimens. Previous experimental studies support the notion that certain functions of the endothelium — including barrier regulation of permeability, thrombogenicity, and leukocyte adherence, as well as production of growth-inhibitory molecules — are critical to the prevention of luminal narrowing by neointimal thickening [55–57]. Nitric oxide (NO) has been identified as one of the relaxant factors synthesized and released by normal endothelium [58,59]. NO may theoretically interact with the process of restenosis at several levels. First, NO has an inhibitory effect on platelet adhesion and aggregation [60]; second NO has an inhibitory effect on SMC proliferation [56,61]; third, NO may exert a beneficial effect on arterial remodeling [62]. When L-arginine, the physiological precursor of NO, was administered to animals before endothelial denudation, the degree of subsequent neointimal thickening was significantly reduced compared to that observed in control animals that did not receive L-arginine [55,63,64].
2.3.2. Platelets and the thrombotic process

Immediately after experimental balloon injury, endothelial denudation induces platelet adhesion and aggregation resulting in release of the constituents of their alpha granules within a few minutes [7,65]. Numerous mitogenic substances, including PDGF (Platelet Derived Growth Factor), are thus released at the site of injury and may be involved in the process of SMC activation [66]. Experiments performed in thrombocytopoenic animals have demonstrated the fundamental role of platelets in determining the extent of neointimal thickening following arterial injury [67]. In a canine model of endothelial injury, the intensity of cyclic flow variations related to platelet accumulation was a major determinant of neointimal thickening [68]. Recent studies have shown that thrombocytopoenia inhibits migration of activated SMCs from the media to the intima but has no effect on the initial cycle of cell proliferation [65]. Coagulation proteins such as thrombin may also be implicated in the response of SMCs [69]. Thrombin has mitogenic properties for SMCs [70] and has been demonstrated to induce multiple growth-related signals in SMCs including the expression of the c-fos proto-oncogene [71]. Finally, the volume of thrombus at the PTCA site may also play a role in the subsequent restenotic process. An alternative proposal for the cellular mechanisms leading to neointimal hyperplasia has been recently advanced by Schwartz et al. [32]; this hypothesis based on the porcine coronary injury model suggests that the volume of intracoronary thrombus at the time of PTCA may determine the subsequent volume of neointima.

In humans, the presence of thrombus at the time of PTCA can be assessed using angioscopy [72]. We recently reported the relation of angiographic findings at the time of PTCA to subsequent restenosis [73]. Patients who had a luminal thrombus at the PTCA site had a much higher risk of restenosis than patients without thrombus. Similarly, when PTCA is performed in patients with an unstable coronary syndrome, a situation where intraluminal thrombus plays a major role [74], the risk of restenosis appears higher than that observed when PTCA is performed in patients with stable angina [75,76].

2.3.3. Growth factors

Growth factors released at the site of injury play a major role in the response of SMCs to balloon injury. Platelets are an important source of PDGF, but endothelial cells, macrophages, and SMCs may themselves secrete PDGF after arterial injury [22,77–79]. PDGF seems to be critical for SMC migration from media to intima, whereas its absence does not limit SMC proliferation [65,80]. Using an antibody to PDGF, Ferns et al. were able to reduce neointimal SMC accumulation after experimental angioplasty without affecting mitogenic activity [80]. Basic fibroblast growth factor (bFGF), an in-vivo angiogenic factor [81] with proliferative properties for both SMCs and endothelial cells through specific receptors [82,83], may also play a role in restenosis. SMCs within the tunica media, when damaged by an oversized balloon, may release bFGF due to stretch or crush injury; the liberated bFGF can then mediate the initial wave of cell division within this layer of the blood vessel. Infusion of an antibody that neutralises bFGF reduces the first cycle of SMC replication by up to 80% in the arterial media following balloon denudation but has no effect on the resulting neointimal thickening [84]. Among the other growth factors that may participate in the restenotic process are transforming growth factor β (TGFβ) and insulin growth factor type 1 (IGF-1). TGFβ mRNA is increased in SMCs following arterial wall injury and reaches a maximum before the phase of extracellular matrix synthesis [85,86]. TGFβ is known to modulate fibronectin expression [87] and may be important in the control of extracellular matrix synthesis [88,89]. TGFβ is produced by SMCs, platelets and endothelial cells [77,90]. The main source of IGF-1 is SMCs and its mRNA expression undergoes a 10-fold increase in the weeks following balloon denudation [91].

2.3.4. Hormonal factors

The renin–angiotensin–aldosterone axis has been implicated in the pathogenesis of restenosis [92,93]. There is evidence that angiotensin II may modulate SMC growth in vitro [94,95]; angiotensin II infusion in rats is followed by marked SMC proliferation in the intima [96]. Powell et al. have reported that inhibitors of angiotensin converting enzyme (ACE) suppress myointimal proliferation after vascular injury [97]. The actions of ACE inhibitors are probably not solely related to an effect on angiotensin II levels but may in part be due to an effect on bradykinin metabolism [98,99] or to an effect mediated by aldosterone [100]. Serotonin and other vasoactive hormones (catecholamines, vasopressin) released at the angioplasty site are also able to induce SMC proliferation [101–104]. Recently, considerable interest has also been focused on endothelin, a potent vasoconstrictor peptide produced by vascular endothelial cells [105]. Endothelin binds specifically to human SMCs in culture and can induce nuclear oncogene expression [106,107]. Endothelin has been shown to have mitogenic activity for rat aortic SMCs [108] and endothelin antagonists reduce neointimal thickening after vascular injury in vivo [109,110].

2.3.5. Mechanical factors

Mechanical factors may also play a role in the degree of restenosis in experimental models. Large areas of endothelial denudation without trauma to the media lead to mild neointimal thickening despite late endothelial regeneration [111]; in contrast, focal endothelial denudation with substantial medial trauma, combined with rupture of the internal elastic lamina, is associated with marked neointimal proliferation, although the endothelium regenerates within a few days [112]. These results suggest that endothelial
denudation alone is not sufficient to produce major neointimal thickening and that direct injury of SMCs is also an important factor. Direct injury to SMCs may induce a greater neointimal response by (1) increasing the local release of growth factors by necrotic SMCs, and (2) activation of intracellular pathways leading to SMC proliferation [113,114].

Beside acute mechanical factors, chronic mechanical factors may also play a role. Blood flow in the injured vessel may be a determinant of subsequent restenosis; experimental studies by Kohler et al. have demonstrated greater neointimal hyperplasia in the case of decreased blood flow after angioplasty [115,116].

3. Prevention of restenosis

3.1. Discrepancies between experimental models and human restenosis

A large number of pharmacologic trials have examined whether systematically administered pharmacologic agents reduce the risk of angiographic restenosis [11,12,117]. The overwhelming majority of these clinical pharmacologic studies reported to date have failed to show a significant reduction in the incidence of restenosis in humans. These results are in sharp contrast with the often promising results obtained in experimental models [118].

3.1.1. Platelet antagonists

Platelet adhesion and activation is an important step in vascular healing during the first days after angioplasty. Friedman et al. [67] noted suppression of the intimal proliferative response to balloon injury in severely thrombocytopenic rabbits. Faxon et al. [119] observed a reduction in the incidence and severity of recurrent stenosis in the atherosclerotic rabbit model in animals treated with sulfinpyrazone or aspirin and dipyridamole. In humans, aspirin, the prostacyclin analogue ciprostene, the serotonin antagonist ketanserin, and several thromboxane A2 antagonists have been studied [120–125]. While antiplatelet agents have significantly reduced the risk of acute closure, there is no evidence that they may reduce restenosis. Moreover, the glycoprotein receptor antibody GP IIb/IIIa has been shown to reduce clinical events 6 months after PTCA [126]; angiographic studies are currently being performed to analyze the impact of these very potent antiplatelet agents on restenosis.

3.1.2. Anticoagulants

Heparin is one of the molecules that has been most widely used in experimental models of restenosis. Both non-fractionated heparin and the newer low molecular weight derivatives have demonstrated antiproliferative activity in animal models such as the rat and the rabbit [26,127,128]. However, in humans, short-term intravenous heparin [129] and 1- to 3-month treatment with subcutaneous low molecular weight heparin [130] have been shown to be ineffective. Recent clinical trials have evaluated the more powerful antithrombin hirudin; hirudin inhibits experimental restenosis [131] but does not appear to be effective in humans [132].

3.1.3. ACE inhibitors

A potential role for angiotensin converting enzyme (ACE) inhibitors in the limitation of neointimal proliferation has been suggested, based on the demonstration that angiotensin II plays an important role in the control of SMC growth [96]. After initially positive results in experimental models [97], two large clinical studies (MERCA TOR and MARCATOR), with over 2000 patients combined, examining the ACE inhibitor cilazapril have failed to show any significant impact on restenosis rates [133,134].

3.1.4. Lipid-lowering agents

Lovastatin, which blocks the production of mevalonic acid and the synthesis of cholesterol by inhibiting the enzyme HMG-Co A reductase, has been shown to inhibit both cell proliferation in culture [135] and restenosis after balloon angioplasty in rabbits [136]. In humans, however, a large double-blind placebo-controlled trial has recently been published showing, again, no benefit of the treatment in the prevention of restenosis [137].

Fish oils containing omega-3 fatty acids may decrease LDL cholesterol, increase HDL cholesterol, and alter platelet functions [138]. Several randomized clinical trials have been performed to examine if omega-3 fatty acids can reduce restenosis and have provided conflicting results [139–142].

3.1.5. Growth factor inhibitors

Several growth factor inhibitors such as trapidil and angiopeptin have been tested in models of restenosis. Trapidil is a platelet-derived growth factor antagonist shown to be effective in experimental models of restenosis [143]. Two trials have suggested that trapidil may have an effect on restenosis, and further study of this agent is warranted [144,145]. Angiopeptin, a synthetic cyclic octapeptide analogue of somatostatin, has been shown to reduce neointimal hyperplasia in several different animal models of angioplasty [146,147]. The mechanism of this effect is unknown but is thought to be related to a local inhibition of growth factors responsible for smooth muscle cell activation [146,148]. We have recently shown that, in a rabbit model of balloon denudation, pretreatment with angiopeptin is associated with a marked inhibition of c-fos and c-jun expression 30 min after injury and with a highly significant reduction in neointimal thickening 28 days after injury [149]. By contrast, if angiopeptin treatment is begun 1 h after injury, no effect on neointimal thickening is observed. These findings suggest that the inhibitory effect
of angiopeptin in this model may be, at least in part, related to an inhibitory effect on early (G1) events of the cell cycle. In humans, however, two large clinical trials, one in Europe and one in the United States, have recently been reported to show no effect of angiopeptin in the prevention of restenosis [150,151].

3.1.6. Other agents

Many other agents have been evaluated as potential inhibitors of restenosis. Calcium channel antagonists [152,153], corticosteroids [154], and colchicine [155] have failed in man in spite of encouraging results in animals. Recently, the results of the ACCORD study [156] suggested that molsidomine, a direct NO donor, may significantly reduce the risk of angiographic restenosis; these results are in agreement with the potential beneficial effects of NO donors on the restenotic process (see above). Further studies are needed with these agents to confirm this finding.

In summary, in spite of encouraging results in animal models, no systemic pharmacologic agent has been shown conclusively to produce a clinically worthwhile reduction in restenosis after PTCA. There are at least four potential explanations for these discrepancies.

A first explanation might be inter-species differences; a drug that inhibits neointimal thickening in rats or rabbits will not necessarily achieve the same effect in humans. This possibility has led to attempts to develop more representative models of restenosis, in particular the pig model [157,158]. Recently, however, various drugs such as angiopeptin [147] have been found to be effective in the pig model but not in humans [150,151] suggesting that the pig model will not be superior to previously developed models in terms of prediction of inhibition of restenosis in humans.

Secondly, many clinical trials have used low doses or inadequate duration of therapy that can also limit the ability to obtain positive results even with an effective drug. Very high doses of drugs have been necessary to inhibit restenosis in experimental models and in most of the negative clinical trials the doses utilized were much lower. The inhibition of experimental restenosis with ACE inhibitors, for example, has been achieved with doses of drugs 10–100 times higher than the doses that can be used in humans [97,133,134]. This has prompted interest in the potential role of locally delivered drug (see below). This method would allow the local release of greater quantities of drug while minimizing systemic effects.

Third, pretreatment before PTCA may also be an important issue. As already discussed above, drugs such as angiopeptin or ACE inhibitors can significantly inhibit the early (15–30 min) phase of the SMC response to injury [149,159]; this suggests that when using these agents in humans, pretreatment may increase the effectiveness of the therapy.

Finally, most of the “anti-restenosis” therapies tested so far have been directed against neointimal hyperplasia. As discussed above, neointimal hyperplasia is not the sole mechanism of restenosis after conventional balloon angioplasty in humans and recent studies have suggested that late vessel constriction may be the major factor. Future studies will try to provide a better understanding of vessel remodeling and to identify drugs that might affect this process. In 1995, however, the use of alternative techniques of endovascular revascularization was increasing. Recent studies have shown that coronary stenting may significantly decrease the incidence of restenosis compared to balloon angioplasty [160,161]. The mechanism(s) of restenosis within coronary stents may also be different from that of restenosis after conventional balloon angioplasty; this implies that a treatment shown to be ineffective in preventing restenosis after PTCA will not necessarily be ineffective in preventing restenosis after coronary stenting (see Section 3.3).

3.2. Local drug-delivery

3.2.1. How to deliver?

In recent years, a variety of balloon catheter systems have been designed to allow the local delivery of therapeutic agents at the site of arterial injury. The first devices were the double-balloon infusion catheter and the Wolinsky balloon catheter [162] (a perforated balloon allowing high pressure infusion of fluids into the vessel wall). More recently, other delivery systems such as the hydrogel-coated balloon catheter [163] or the dispatch catheter [164] have been made available.

3.2.2. What to deliver?

3.2.2.1. Anti-proliferative drugs. Most of the antiproliferative drugs that have been effective in preventing experimental restenosis are potential candidates for the prevention of restenosis using local drug-delivery systems. As stated before, this approach may allow the local release of high quantities of drug while minimizing systemic effects. However, an important limitation of this technique is the rapidity with which the infused drug leaches from the arterial wall, and the short duration of therapeutic efficacy of this approach. In experimental models, high drug levels persist for less than 48 h after drug infusion [162]. It is probable, therefore, that if this approach is to be effective, it will be necessary either to use drugs that will interfere with the early steps of the restenotic process — such as angiopeptin [149,165] — or to develop a means by which drug efflux from the arterial wall can be retarded. One potential means of achieving this would be the delivery of drug-impregnated biodegradable microspheres into the vessel wall to obtain a more prolonged local drug activity [166,167].
3.2.2.2. Gene therapy. One genetic approach to the goal of inhibiting the smooth muscle cell response to injury is the use of antisense oligonucleotides. A single-stranded DNA sequence that is complementary to a known region of a particular mRNA is synthetized. Following introduction into cells, the DNA strand binds specifically to the complementary nucleic acids; the double-stranded DNA–RNA hybrid is then degraded. In most of the antisense studies performed to inhibit restenosis, the target gene has been a nuclear oncogene: c-myb [20] or c-myc [21] antisense oligonucleotides delivered in a site-specific manner inhibited smooth muscle cell accumulation at the site of injury when inspected a few weeks after treatment. Clinical trials will soon be designed to study the effect of local delivery of antisense oligonucleotides after PTCA in humans.

Another approach is to transflect locally a gene that may inhibit the restenotic process. Experimental studies by Steg et al. [168] have demonstrated efficient gene transfer into the vascular wall using percutaneous delivery of an adenoviral vector; they also showed that when administered with appropriate catheters the level of transfection of extravascular organs was very low. The expression of the gene was transient (a few weeks) but this may not necessarily be a limitation in this indication. The question of the gene to be transfected remains to be answered; recently, in vivo gene transfer of nitric oxide synthase has been shown to inhibit neointima formation in injured rat carotid arteries [169].

3.2.2.3. Indirect approach. Most of the “anti-restenosis” strategies are based on a direct inhibition of the SMC response to injury. Another strategy, the indirect approach, has recently been suggested. Asahara et al. demonstrated that a single local administration of vascular endothelial growth factor (VEGF) is sufficient to facilitate endothelial repair in a rat model of balloon injury [170]; in this study, the degree of neointimal thickening at 2 weeks and 4 weeks after balloon injury was correspondingly attenuated to a statistically significant degree in arteries treated with VEGF versus controls. These results are probably related to the inhibitory effect of the endothelium on SMC growth [56, 61].

3.3. Mechanical prevention

During the past several years, “new” angioplasty devices including atherectomy techniques, and stents have expanded the indication for angioplasty to patients with anatomy considered suboptimal for conventional PTCA. With these devices came the hypothesis that creating a more satisfactory immediate result would reduce the risk of subsequent restenosis.

There are two main mechanical atherectomy devices with sufficient clinical experience to evaluate their potential to limit restenosis: rotational atherectomy (the Rotablator) and directional coronary atherectomy. Although randomized studies are still needed, the rates of restenosis observed with the Rotablator do not appear to be substantially lower than that observed after conventional PTCA [171, 172]. It must be pointed out that adjunctive balloon angioplasty is now performed in the majority of cases after rotational atherectomy in order to achieve the largest possible acute gain; this may offset the theoretical benefits of the Rotablator (i.e., preferential ablation of fibrous or calcified tissue with minimal damage to normal structures [173]). Directional coronary atherectomy (DCA) effectively removes atherosclerotic tissue but also frequently constituents of the normal vascular wall [174]. DCA allows a higher acute luminal gain than conventional PTCA; the late luminal loss, however, is also higher after DCA suggesting that atherectomy may stimulate the proliferative process [175]. Recently, the one year follow-up of patients randomized to either DCA or PTCA has demonstrated a significantly higher mortality in patients treated by DCA [176]; although the mechanism(s) of this unfavorable long-term effect is unknown, these results may limit the use of this technique of revascularization in humans.

The coronary stents currently under clinical evaluation are metallic devices that are implanted permanently into the vessel wall [177, 178]. Recent studies have shown that implantation of an intracoronary stent in conjunction with balloon angioplasty is not only highly effective in treating acute vessel closure due to balloon-induced dissections, but may also reduce the risk of restenosis. Two large randomized trials, the Benestent study and the Stent Restenosis Study (STRESS) have been recently completed and published [160, 161]. Both trials showed that at 6 months the need for repeated revascularization (the primary clinical end point) was reduced with stenting, as compared with standard angioplasty. The rates of angiographic restenosis were also lower in patients randomized to coronary stenting than in patients treated with conventional balloon angioplasty (22 vs 32%, respectively in the Benestent trial, and 32 vs 42%, respectively in the STRESS trial. These angiographic results were mainly related to a larger increase in the diameter of the lumen immediately after stenting. In spite of a significantly higher late loss during follow-up in the stent groups, the net result at 6 months was still better with stenting than with standard angioplasty.

The mechanism of restenosis within coronary stents is not completely understood but preliminary intravascular ultrasound studies [179] suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss occurring after stent implantation is due to plaque growth (probably related to neointimal hyperplasia). This observation, taken together with the fact that the late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty, suggests that restenosis within coronary stents might be much more sensitive to therapies
designed to inhibit neointimal hyperplasia rather than restenosis after standard angioplasty.

Thus, the future prevention might well be the combination of a mechanical device that produces the widest possible lumen and prevents vessel constriction with a pharmacologic approach to inhibit the proliferative process. Although systemic administration of "anti-restenosis" drugs has not yet been tested to prevent restenosis after coronary stenting, it is very likely that pharmacologic inhibition of neointimal hyperplasia within coronary stents will take advantage of local delivery techniques. In addition to local drug delivery catheters described above, the stent itself may be coated with polymers and serve as a platform for drug delivery over relatively long periods of time [180].

A remaining and important question is whether complete inhibition of neointimal thickening is desirable. Acute coronary events are mainly the consequence of plaque rupture and thrombus formation [74]. Proliferation of SMCs and matrix production after angioplasty may prevent persistent instability. When angioscopy is performed a few months after PTCA of unstable plaques [181], the angiographic appearance is almost unvaryingly that of a stable smooth white plaque without thrombus. Some degree of neointimal thickening may thus be beneficial. If inhibition of neointimal hyperplasia becomes feasible, it will be important to determine how much should be inhibited.

4. Conclusion

In conclusion, restenosis remains an important clinical problem. The results of large pharmacologic trials have been disappointing. Restenosis which is now known to be due to both vessel remodeling and neointimal hyperplasia may be limited in the future by a combined mechanical and pharmacologic approach. The continued attractiveness of PTCA as an alternative to medical treatment and bypass surgery for patients with coronary artery disease will depend upon our ability to control the restenotic process.

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