Acta Radiologica 43 (2002) 442–454
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ACTA RADIOLOGICA
0284-1851

Review Article

RESTENOSIS AFTER BALLOON ANGIOPLASTY AND/OR STENT INSERTION – ORIGIN AND PREVENTION

A review of the literature

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Key words: Arteries, stents; balloon dilation; angioplasty; intimal hyperplasia; interventional procedures.

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Accepted for publication 30 May 2002.

Due to research advances in vascular biology, assessment of the vasculature as a conduit for circulating blood has been successively revisited during the past century. At present, the vasculature is known as a complex organ, capable of synthesizing and secreting a wide variety of biological mediators and responding to numerous chemical and mechanical signals. Obstructive vascular disease, mainly atherosclerosis, can disturb these functions and cause serious clinical symptoms (42, 169, 170).

Diagnostic and therapeutic options have changed substantially during recent decades. Interventional treatment methods such as percutaneous transluminal angioplasty (PTA) and insertion of vascular metallic endoprostheses – stents (32, 37, 39, 57, 77, 106, 110, 145, 172) – have in many cases replaced traditional vascular surgery. However, PTA and/or the insertion of stents also causes injury to the vessel wall, followed by a healing process (48, 50, 101, 106, 165, 189). This reparative process can result in restenosis, caused by intimal hyperplasia (IH) and a remodeling of the artery, also called chronic spasm (128, 154, 155, 221). Significant restenosis develops in 20–50% of treated vessels, impairing the long-term result of treatment (60, 63, 91, 93, 94, 139, 175, 197). The restenosis can cause recurrence of symptoms, with serious consequences for the patient (99, 220).

The severity and the location of the atherosclerotic lesion are important factors for the outcome of interventional treatment. Development of restenosis is more frequent after treatment of long stenoses and of occlusions, while best results are obtained after treatment of short stenoses (78, 87, 106, 119, 133, 219). The lumen diameter of the treated artery is also important and is generally inversely proportional to the frequency of significant restenosis (78, 93). Several components from the circulating blood and the artery wall are involved in a complicated course of events following PTA and stenting. Some of these events are of particular importance for the development of restenosis (101). Different approaches to preventing restenosis have been evaluated in experimental and clinical studies and the results are reported in numerous publications. Effects, results and conclusions presented below are most often based on experimental animal studies; thus evaluation is dif-

ficult or impossible in the human arteries. The course of events can, to some extent, be different in the atherosclerotic human arteries.

Effects of PTA

The aim of PTA is a restoration of the vessel lumen and normalization of the blood flow. The dilation balloon, used for PTA, is commonly longer than the stenosis, to avoid its dislodgment during inflation. Consequently, both a stenotic segment of the artery and also a normal artery – adjacent to the stenosis – are dilated (62). The entire dilated segment is denuded of endothelium and about 20% of the smooth muscle cells (SMCs) in the media are damaged (42, 52, 64, 101, 130, 159). The circumferential stretching of the artery wall can cause disruption of the internal elastic membrane, and also of the media (27, 64). Originating from the plaque, intimal dissection can occur (64), and the severity of the injury correlates to the degree of the subsequent IH (85, 88). The atherosclerotic plaque intrudes into the wall of the artery, but can also fracture. Following PTA, several of the molecules described below are released (79), activating circulating blood components and cells in the vessel wall, and starting a process of repair (Figure).

Blood components: Following deflation of the angioplasty balloon, platelets adhere and aggregate to the endothelium-denuded subendothelial matrix, and fibrin is also deposited in the damaged area (101). Platelets secrete procoagulants, promoting further development of the thrombus, but also several others mediators (170). Two of these mediators – the platelet-derived growth factor (PDGF) and the transforming growth factor β (TGF β) – have important roles in the development of IH. The PDGF stimulates migration of the SMCs to the intima (91, 92, 134, 137) and the TGF β stimulates SMCs to synthesize extracellular matrix components (42).

Leukocytes entering the damaged portion of the artery promote the inflammatory response and can contribute to the formation of IH (166, 200). In the intima, monocytes are transformed to macrophages (69), which besides phagocytosis can secret TGF β, endothelial mitogens, and also factors inhibiting endothelial cell growth. Activated by PTA, neutrophils aggregate in the damaged area, and can contribute to damage of the peripheral tissues during reperfusion following angioplasty (123, 147). Leukocytes can also secrete growth factors, oncogenes and attractants stimulating further colonization of the vessel wall by macrophages.

Intima: In the normal artery the intima consists of a single layer of partly overlapping endothelial cells, creating a smooth, non-thrombogenic and non-adherent surface. Endothelial cells build up a permeable barrier to the deeper layers of the arterial wall and have a key role in the regulation of normal vascular function (33, 71, 138, 150). In response to mechanical stimuli and to circulating vasoactive substances, the endothelium regulates vascular tonus via several biological mediators. One of these mediators, the endothelium-derived relaxing factor (EDRF), causes relaxation of the artery, and inhibits proliferation of SMCs. Several investigators have suggested that EDRF is the nitric oxide (NO) molecule, or that NO is the active part of EDRF (42, 127). The vasorelaxant NO also

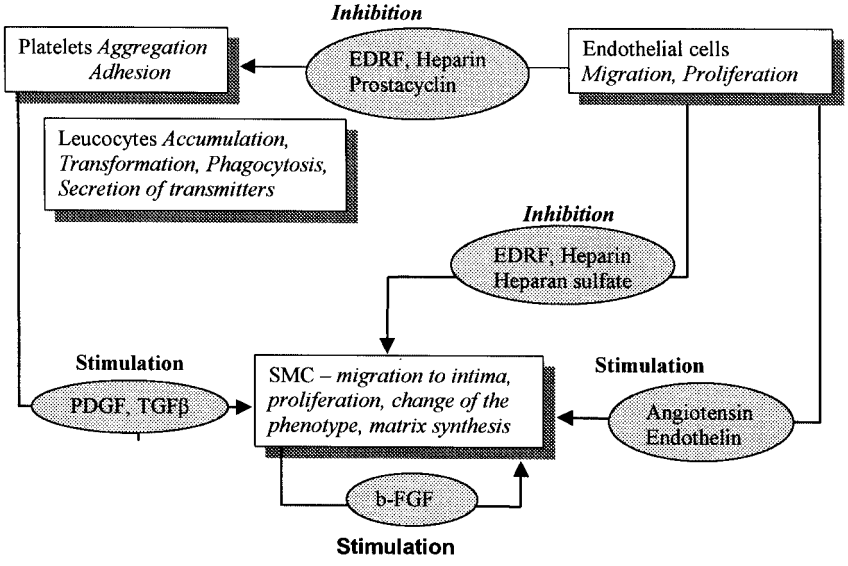

Figure. Some of the most important occurrences after PTA.

stimulates endothelial cell growth and inhibits aggregation of platelets (42, 46).

Endothelium-derived prostacyclin is another potent platelet antiaggregator (33). In contrast, the potent, endothelium-derived vasoconstrictors angiotensin II and endothelin stimulate proliferation of SMCs (73). The endothelium also synthesizes heparin and heparan sulfate, which, beside their anticoagulant effect, also have an inhibitory effect on SMC proliferation (42, 139). These effects are mediated by the different fractions of the heparin molecule. Secreted by endothelial cells, tissue plasminogen activator (TPA) and urokinase plasmin activator prevent thrombus formation, but can also participate in degradation of the extracellular matrix, which is necessary for the migration of the SMCs. Disruption of the internal elastic lamina probably facilitates migration of the SMCs to the intima; however, the SMC also migrates via channels in the intact lamina.

Media: The contractile SMCs are responsible for maintenance of vascular tonus. Injured SMC synthesizes the basic fibroblast growth factor (b-FGF), which stimulates transformation of these cells to the synthetic, proliferative phenotype (44, 80, 92, 101, 108, 208). The b-FGF also promotes endothelial regrowth (139). The extracellular matrix, composed of collagen, elastic fibers and proteoglycans, is affixed to the membranes of the SMC. The SMC can secrete proteolytic enzymes, which resolve these bindings and promote migration of the SMC cells to the intima (42, 130). After arterial injury, proliferation of the SMCs can be stimulated by other factors, such as the epidermal growth factor or Gbeta gamma (75, 86). The SMCs are of the same phenotype as the fibroblasts and are able to start the synthesis of extracellular matrix (80), which in the intima forms a large part of intimal hyperplasia.

Adventitia: The adventitia, divided from media by the external elastic lamina, is responsible for the nutritional support of the artery wall. Temporary hyperemia after PTA and changes in the vasa vasora in the adventitia have been observed (42, 152, 153). It was suggested that changes in the adventitia can contribute to the development of IH (11, 44).

Course of events after PTA: During and after PTA, the vasoconstrictors endothelin and angiotensin II are released from endothelial cells and b-FGF is simultaneously released from the injured SMCs. These molecules contribute to the proliferative response of the SMCs (92, 206). As soon as blood flow is restored, platelets and fibrin adhere to the molecules presented at the denuded subendothelial matrix (25). Platelets release PDGF, stimulating migration of the SMCs to the intima, and TGF β stimulates the production of extracellular matrix (22). The aggregation of platelets on the surface can continue promoting thrombus formation, but usually stops within hours. After 1 day the surface is no longer thrombogenic, probably due to an overlying coat of plasma proteins (101).

A transient decrease in fibrinolytic activity in the arterial wall can promote further building of the thrombus (174). Monocytes, macrophages and neutrophils accumulate in the injured part of the artery, secreting mitogenic factors (69, 123). Proliferation and migration of endothelial cells start from the borders of the injured area and from arterial side branches (200). About 50% of uninjured SMC changes from the contractile phenotype to the proliferative. DNA synthesis starts in proliferative SMCs within 48 h (26, 92, 101, 118, 129). SMCs and endothelial cells support lysis of the extracellular matrix by the secretion of proteolytic enzymes (101, 129).

Migration of the SMCs to the intima usually begins 4–7 days after PTA. Proliferation of SMCs reaches a maximum after 7 days, subsequently decreases, and is practically terminated after 4 weeks (18, 25, 189). At this time endothelialization of the damaged area is also terminated (118). The new endothelial cells are immature, with partly insufficient function (211, 218). Synthesis of the components of the extracellular matrix by SMCs in the intima continues for up to 3–6 months (66, 101). At this time extracellular matrix represents up to 80% of the volume of the neointima. During the following year, partial regression of the IH may occur in about 10% of cases (120, 124). After a few years, the neointima changes form and resembles an atherosclerotic plaque (25) with foam cells, collagen, and calcifications. Whether this process is a natural event, or represents recurrence of atherosclerosis, is unclear (216).

Recently, attention has also been focused on chronic elastic recoil, another important factor contributing to restenosis after PTA (60, 216). This event has been observed during intravascular ultrasonography (IVUS) examinations of human coronary arteries and has also been investigated in an experimental study (116).

Effects of stent insertion

A stent is usually used if the effect of PTA is unsatisfactory (68), but stents are also used for treatment of arterial occlusion, dissection and restenosis (14, 145, 158). The benefit of primary stent treatment of arterial stenosis is still under discussion (203), but the clinical use of stents and

their applications are still increasing (220). Different stents have been developed and tested (3, 39, 40, 144, 145, 168, 196, 197) and new stents are becoming available. Stainless steel and nitinol are the most common stent materials, but other metals have also been used (39, 98, 110, 179, 197). Metal implants cause mechanical and chemical irritation (45) and gold-coating of stents, for example, has caused a significant increase in IH (98, 179). Due to the lack of comparative clinical studies, it is difficult to estimate the importance of the stent material for long-term results. The development of IH can be partly related to the type or construction of the stent (12, 24, 41, 54) and to the number of inserted stents (149).

On the basis of the delivery system, stents can be divided into balloon-expandable and self-expanding stents. The artery is balloon-dilated during deployment of the balloon-expandable stent. The balloon, which is always longer than the stent, causes endothelial damage also outside the stent (62). Self-expanding stents are inserted after PTA and subsequently balloon-dilated (198). Thus, PTA starts processes in the wall of an artery as described above, but the stent has several additional effects. The stent prevents vascular spasm and elastic recoil and keeps the atherosclerotic plaque and/or the intimal flap, in case of dissection, away from the lumen of the artery (145, 184). The self-expanding stent can continue expanding due to radial forces, which can also stimulate the development of IH (112). The metallic stent can disturb the electrostatic equilibrium (45) and increase the number of platelets and neutrophils in the treated part of the artery (147). Compared to PTA the stent can also prolong disturbances to endothelial function (211). Changes in vasa vasorum were observed after stenting (152, 153, 188).

The elastic properties of the stent and the artery are different, and the artery loses compliance after stent insertion (7, 168). A relatively stiff stent cannot follow the movement of surrounding tissues in the body as the artery does. The temporarily compressed and folded self-expanding stent can regain its shape, whereas external forces can irreversibly deform the balloon-expandable stent (4).

Course of events after stent insertion: The surface of the metal implanted in the vessel will be covered by a strongly adherent monolayer of proteins after only 5 s. After 1 min, the surface is uniformly coated by five layers of proteins, predominantly fibrinogen (9). The holes between the stent wires are filled with the thrombus, composed of fibrin, platelets, and white and red blood cells (147, 163). The amount of adherent platelets and leukocytes increases during the first few hours after stent insertion (147, 160). The balloon-expandable stent keeps the lumen of the artery open, stretching the media. The self-expandable stent, which does not expand to full diameter after insertion, can expand further during the following days, progressively dilating the artery (30).

The primary response of the vessel wall is, however, caused by PTA and is similar to the events described above, with proliferation and migration of SMCs and formation of neointima (8). The thrombus formed between the stent wires is successive replaced by proliferating neointima. In animal studies the stent was covered by IH after 4 weeks (30, 214), but development of IH usually stops after 6 months. IH can cause restenosis in the stent lumen and/or at the edges of the stent. Later progress of IH has also been observed (4). Endothelialization starts immediately after the procedure and will continue until the stent and the stented part of the artery are covered by immature endothelium, which takes approximately 3–4 weeks (97, 163, 190). A mild inflammatory reaction can persist during this time (12). Side branches of the artery that are covered by the stent usually remain open (3). The stent prevents chronic elastic recoil, but also causes progressive atrophy of the media, a phenomenon which has been observed 3–6 months after insertion (174). Regression of atherosclerotic plaques in stented arteries has been reported in studies based on autopsy (64).

Prevention of IH

After PTA and stenting, a reparative process is necessary to regain normal vessel function and should not be eliminated completely. Prediction of the severity of IH is currently not possible, but would be very valuable, since 50–80% of patients do not develop significant restenoses. Prevention of IH is unnecessary for this group of patients.

Various strategies to prevent IH have been tested in experimental animal studies, frequently with the aim to reduce SMC migration and proliferation, and to accelerate endothelialization (121). Experiments have been performed in both healthy vessels and in the 'experimental atherosclerosis' model, used in animal studies, which develops over weeks or months (24, 49, 113, 171, 172). The lesion is histologically similar to the human atherosclerotic lesion, which takes years to develop (113). Balloon denudation of the artery wall, used in the experimental atherosclerosis model, has been used by other investigators for creation of 'intimal hyperplasia' (206). The single experimental atherosclerotic lesion was located in the artery of a healthy

animal, with good inflow and distal outflow of the blood. Use of a different experimental technique in causing the injury can affect the outcome of the study (125, 129, 176, 195).

Anatomic variations in the structure of the vessels also play an important role (12, 139), and use of different vessels in the same animal can contribute to diversity of the obtained results (36, 198). The response to vascular injury varies between different species, e.g., dogs and pigs (36, 121, 183). Numerous stent models have been used in different studies (12, 13, 56, 74, 168, 171, 180, 196). It was suggested that development of IH is dependent on the shape of the stent (3, 12, 54, 58, 180), while the diameter of the stent is less important (82). However, high inflation pressure during insertion of the balloon-expandable stent may promote IH (81).

The results of pharmacological therapy can be influenced by different dose/response effects in different species (122). Evaluation of the results of PTA and stenting and of restenosis has been done using angiography, ultrasonography and histopathologic examinations, but all these methods have their drawbacks. The introduction of IVUS during the last decade made possible a more adequate evaluation of the lumen and the arterial wall *in vivo* (57, 82, 84, 116, 181, 212, 219, 222). However, placement of the IVUS catheter through a severe stenosis or occlusion can be difficult. It is also difficult or impossible to study most of the events in the wall of the artery of patients treated by PTA or stent insertion.

Most of events described above, and of methods preventing intimal hyperplasia proposed below, are based on animal studies. This could partly explain why these methods are seldom beneficial in clinical trials. Several of these methods are also relatively complicated, and can have substantial adverse effects for the patient. However, different proposed approaches to prevent IH are summarized below:

Diet is one of the most important factors in the development of atherosclerosis and was shown to have a role in the development of restenosis in an animal study (191). Supplementation of the diet with unsaturated fatty acids was tested in clinical studies (35, 161), but the considerable disagreement regarding the obtained results is representative of the problems meeting scientists working with prevention of IH.

Pharmacological approaches: Several drugs, delivered systemically or locally, have been tested (6, 27, 101). Unacceptably high doses (157) or requirement for a long delivery time (102) for prevention of IH do, however, exclude some of these drugs from clinical use.

Anticoagulant therapy is commonly used during and after endovascular interventions. Heparin is routinely injected prior to PTA and stent placement to prevent early thrombus formation. Due to the supposed thrombogenic properties of the stent, an additional dose of heparin is often given after stenting (16, 136, 160). Medication with ASA or dipyridamole after intervention has been proposed and experimental studies have demonstrated that anticoagulant therapy reduces the risk of thrombosis and restenosis (6, 29, 43, 162, 172, 187). In other clinical and experimental studies, a reduction in the severity of lesions was observed, while the frequency of restenosis was not influenced by anticoagulant treatment (49, 50, 59, 167, 182, 187, 221, 223). Prolonged administration of heparin had an effect on IH in experimental studies. However, heparin does not inhibit proliferation of SMC *in vitro* (209), and has also been considered a possible causal factor of stent thrombosis (100). Cilostazol, a relatively new anti-platelet agent, showed preliminarily promising effects on IH after stent insertion (207, 224), but this effect could not be confirmed in a larger group of patients (146). There is no obvious evidence that prolonged systemic administration of anticoagulant therapy has any significant effect on the development of intimal hyperplasia.

Following an arterial injury, angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II – a potent vasoconstrictor, stimulating proliferation of SMCs (169). ACE inhibitors reduced IH in animal experiments, but clinical evaluation could not confirm these findings (107, 156, 157).

The inhibition of calcium transportation through the cell membrane can reduce proliferation of the cells. Inhibition of IH by calcium channel blockers was tested successfully in animal experiments, but these drugs had no obvious effects in clinical trials (139, 177).

Steroids should reduce the inflammatory reaction in the artery after intervention. Systemic administration of steroids to patients did not prevent the development of IH (151), although local deposition of steroids was reported to have a positive effect on IH (132, 196).

Cholesterol is necessary for cell membrane synthesis, and decreased cholesterol levels can reduce proliferation of SMCs (61). However, a desirable proliferation of endothelial cells can be reduced simultaneously. Lovastatin reduces serum cholesterol, but supplementation with lovastatin had no obvious effects on the development of IH (139). Another lipid-lowering substance, probucol, showed positive effects on the restenosis rate and reduced IH in clinical and experimental studies (90, 126, 164). The mechanism of action of probuc-

ol is not known, but seems to be mediated by free radicals.

The entry of cells into the proliferative cycle can be reduced by angiopeptin, an analogue of somatostatin. In an animal study, angiopeptin decreased IH in about 50% of cases (53). A poor clinical effect of angiopeptin can be explained by a mode of action that is different to that of somatostatin (2).

The vasorelaxant NO has an inhibitory effect on SMC proliferation. Promising results have been achieved with methods increasing levels of NO (47, 127, 185, 213). NO is synthesized in the endothelial cell by the enzyme nitric oxide synthetase from L-arginine. Administration of the NO precursor L-arginine markedly diminished the development of IH (21, 34, 65, 111, 122, 201). NO also suppresses the aggregation of platelets and promotes endothelialization (67), but slow release of NO from coated stents had no effect on the development of IH (17). Neither did oral administration of an NO-releasing drug have any effect on SMC proliferation (76).

Suppression of Na^+-H^+ exchange (102), inhibition of remodeling of the artery (109), local delivery of ethanol (117), and administration of antiallergic drugs, pemirolast potassium (142), or taxol (188), also showed promising results in preventing intimal hyperplasia in experimental studies.

Local drug delivery from drug delivery balloons and from coated stents has been tested experimentally, with encouraging results. Anticoagulant and antiinflammatory drugs, agents stimulating endothelialization and inhibiting SMC proliferation, receptor antibodies and ethanol were tested (1, 5, 6, 17, 51, 95, 105, 109, 117, 131, 132, 148, 195). However, clinical randomized studies evaluating experimental results have seldom been performed. A multicenter clinical trial, comparing the local delivery of heparin to intraluminal administration, showed that the method was safe, but did not have any advantages regarding the development of IH (222).

Biological technology methods for prevention of IH: Research advances in biological technology have opened possibilities to form molecules interacting with components in the artery wall. Different approaches have been tested in animal studies.

Attempts were made to reduce platelet adhesion and aggregation by local delivery of the platelet glycoprotein IIb/IIIa receptor antibody (1, 204, 205). Acceleration of reendothelialization was stimulated by the delivery of a vascular endothelial growth factor (5, 19, 210) or by blockage of the matrix glycoprotein thrombospondin-1 (22).

Seeding of cultivated endothelial cells on the artery wall (28) or on stents (38) has been tested. However, cell seeding after PTA can be difficult in the clinical situation. Preservation of undamaged endothelial cells on the most important, inner surface, of the stent seems to be as difficult as carrying out PTA without damage to the endothelium.

Inhibition of degradation of the extracellular matrix prevents migration of SMCs to the intima. It can be achieved by blocking molecules involved in such degradation (15), or by blocking integrins – cell-surface receptors of the SMC – which preserve attachment of SMCs to the extracellular matrix (21, 23, 36).

In another experimental study, blockage of PDGF-β receptors by specific neutralizing antibodies inhibited PDGF stimulation of SMC proliferation (72). Epidermal growth factor receptor-targeted cytotoxin had a similar effect (148).

Genetic therapy after vascular injury is a relatively novel, interesting approach to prevent IH (89, 185, 193, 194, 213). Introduction of genetic information into SMCs made them sensitive to treatment with antiviral drug (ganciclovir), resulting in the death of the dividing cells (141).

The vascular endothelial growth factor (VEGF), a potent, endothelial cell-specific mitogen, has been used to promote angiogenesis. Experiments showed a clear therapeutic benefit after a single injection of VEGF. Also the FGF can promote angiogenesis (135, 199). Clinical trials will show if therapeutic angiogenesis can replace interventional or surgical treatment of patients with peripheral obstruction (89).

The biological technology is a relatively new, but rapidly growing, scientific area. Possible side effects and clinical importance of the developed molecules and specific substances must be carefully evaluated.

Other methods: Sympathectomy is used in treatment of patients with arterial occlusive disease, with the aim of preventing vasoconstriction. Sympathectomy also had an inhibitory effect on the development of restenosis (104). This effect can be secondary to prevention of remodeling of an artery after PTA.

Suppression of IH can be achieved by reduction of the number of proliferating SMCs in the vessel wall. Thermal methods, photodynamic therapy, external irradiation and brachytherapy have been used (55, 62, 96, 103, 114–116, 143, 178, 186, 202, 215). Radioactive stents were also constructed (179, 217). All these methods cause destruction of the SMCs in the media, which are subsequently replaced by fibrotic tissue. The beneficial effect of brachytherapy on IH has been documented in clinical studies (114, 115, 202). β-particle-emitting

gold stents had, however, the opposite effect (179, 198). Due to relatively short follow-up, the long-term effect of brachytherapy and irradiation from radioactive stents is still unknown. The common use of irradiation for prevention of IH is also controversial, due to the practical problems, the costs and the selection of patients – restenosis occurs only in 20–50% of treated arteries.

The coating of stents with fibrin may have a positive effect on the development of IH, the opposite to coating with polyurethane (83). Stents covered by an autologous graft (192) or synthetic material can prevent IH in the lumen of the device. However, restenosis in the stent–graft lumen has been observed (10). Development of IH at the edges of surgical grafts is a well-known problem (20, 87), and the problem for intraluminal stents–grafts may be similar (106). The stent–graft will also close arterial side-branches, decreasing the possibilities of development of collateral circulation.

The endothelium inhibits development of IH, but preservation of endothelium in the treated segment of the artery is practically impossible during PTA (70, 101). IH can be diminished by perivascular implantation of endothelial cells (140), but the practical clinical value of this experiment can be questioned. Insertion of a self-expanding stent without balloon dilation reduces injury to the endothelial cells and SMCs, and decreases the number of proliferating SMCs (31, 70, 173). Hypothetically, self-expanding stents strong enough to dilate a stenosis could be used without additional balloon dilation instead of PTA, to diminish traumatic injury to the vessel wall and, consequently, to reduce the development of IH.

Restenosis is commonly treated by a new PTA and/or insertion of a stent. Retreatment increases costs, carries the risk of complications and is troublesome for the patient. The prevention of IH is not possible today, but several promising alternatives are being tested. Increased knowledge about processes within the vessel wall after PTA and stent insertion, and further progress in research, are essential for further improvement of the results of interventional treatment.

Summary

Results of PTA and stent insertion are affected by restenosis, which causes a recurrence of symptoms, leading to a need for renewed treatment in a substantial number of patients. IH is the most important factor in the development of restenosis. Processes within the vessel wall responsible for development of IH, and different approaches to prevent restenosis discussed in this review, are most often based on animal studies and a randomized clinical testing is required. Despite substantial efforts by scientists and clinicians, the problem of restenosis cannot be solved today by a single, commonly available, method and further research and technical development is necessary.

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