Research Article

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Arterial Restenosis: Past, Current Status and Future Directions

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ABSTRACT

Relevance: *Restenosis is a pathologic response to vascular injury, characterized by neointimal hyperplasia and progressive narrowing of a stented vessel segment. At present arterial restenosis is the main problem of endovascular surgery. The repeated development of vessel lumen narrowing reduces the use of open and percutaneous arterial reconstruction methods. Actually, restenosis itself is a narrowing of the vessel lumen by more than 50% after damage of the arterial wall in the process of its reconstruction, usually developing 6-9 months after angioplasty. Although advances in stent design have led to a dramatic reduction in the incidence of restenosis, it continues to represent the most common cause of target lesion failure following percutaneous coronary intervention. Efforts to maximize restenosis prevention, through careful consideration of modifiable risk factors and an individualized approach, are critical, as restenosis, once established, can be particularly difficult to treat. According to the literature, the incidence of restenosis in coronary arteries ranges from 10 to 40% depending on angiographic and clinical situations. The occurrence of restenosis in lower limb arteries ranges from 34 to 46% with balloon angioplasty and from 1.6 to 19.4% with stenting, respectively.*

Aim: *The aim of the study was to review and analyze modern literature data devoted to the problems of arterial restenosis in patients after arterial reconstructions in lower extremities and coronary arteries, and modern approach to the prevention of this problem.*

Material and Methods: *We searched electronic databases including PubMed, Googleacademy, Cyberleninka, RSCI, HCC, Elibrary and Web of science with a search depth of 12 years for key aspects.*

Keywords
Arterial restenosis, Arteries, Drug-coated stent, Neointimal hyperplasia.

Introduction

The main links in the pathogenesis of arterial restenosis include elastic shrinkage of the vascular wall lumen, wall thrombosis and neointima hyperplasia, which lead to pathologic rearrangement in the stent. The beginning of this process is mechanical damage to the intima and media of arteries. Predictors of restenosis are divided into external (damage to the vessel from outside) and internal (reaction of the vascular wall, the response to which is inflammation and thrombosis with subsequent proliferation). Currently, several dozen genes associated with atherosclerosis have been characterized that also influence the frequency and severity of restenosis development. The first group of genes

encodes proteins regulating lipid metabolism and transport, the second - proteins regulating blood pressure levels, the third - proteins of inflammation, apoptosis and proliferation [1]. The severity of restenosis itself depends on the amount of damage to the inner vessel wall, the occurrence of restenosis after angioplasty due to excessive internal remodeling of the arteries is added to it. In addition, there are 4 phases of this process describing the process of regeneration of the vascular wall after damage:
- thrombotic (1-2 days);
- proliferation and migration of smooth muscle cells of the vascular wall into the intima (from 1-7 days to 1 month);
- matrix synthesis and development of neointima (fibrous sheath, on the inner surface of the vascular prosthesis as a result of altered endothelium sprouting into the prosthesis);
- formation of restenosis itself (from 7 days to 3-6 months).

It is known that during stent deployment and endothelial damage there is an interaction of platelets, collagen and Willebrand factor located in the subendothelium, which leads to their activation and aggregation. Then thrombin is formed, which gives rise to the coagulation cascade, inflammatory response, proliferation, and most importantly, activation of the blood fibrinolytic system and platelet apoptosis. The appearance of platelet complexes in blood with stromal progenitor cells expressing osteogenic differentiation marker - osteonectin, is a significant sign of stenotic arterial lesions. In the authors' opinion, in such patients the determination of osteonectin-positive cells with CD-40 positivity capable of binding platelets has the greatest prognostic value. Currently, the concept of endothelial dysfunction includes problems from the vascular endothelium to the source of its origin - progenitor endothelial cells. According to some authors, it is the deficiency of endotheliocyte-like cells, as well as impaired mobilization and adhesion of these cells that causes untimely endothelialization of the luminal surface of coronary stents, leading to the development of restenosis. One should not forget about nitric oxide (NO) deficiency, which entails increased synthesis of proinflammatory cytokines and chemokines, leads to proliferation of smooth muscle cells, increased interstitial growth and restrictive processes.

Arterial Coronary Restenosis

The frequency of surgical treatment of coronary heart disease (CHD) has increased significantly in recent years. Worldwide, more than 7 million percutaneous coronary interventions (PCI) are performed annually. Technical breakthroughs in coronary angioplasty have made this procedure routine and safe in patients with stable CHD. The risk of death during this procedure in stable patients does not exceed 0.5%. At present, PCI is an indispensable stage of therapy in patients with CHD, especially those with acute coronary syndrome. However, obvious successes of modern interventional cardiology and angiology in the treatment of patients with CHD are overshadowed by the occurrence of various complications, which increases the urgency of the problem of safety of interventions. With the advent of endovascular methods of IBS treatment there appeared problems associated with various complications of this type of treatment. According to the data of H.G. Fozilov, the total incidence of PCI complications is 4.35%. At the same time, specific complications occur most often, accounting for 3.0% (heart rhythm disorders - 0.71% of all cases). Complications related to the access site and hemostasis (0.52%), and complications related to the damage of other organs and systems (0.12%) occur less frequently [2]. To date, a large number of classifications of complications arising during the performance of X-ray endovascular interventions on the venous arteries have been proposed. Large and small, ischemic and non-ischemic, cardiac and extracardiac, central and peripheral complications are distinguished. According to literature data, in coronary artery stenting complications in the form of restenosis were observed in 10-40% of patients who underwent balloon angioplasty. It should be noted that with the replacement of angioplasty by stenting the restenosis rate decreased by about 10%. But as the number of PCI increased, the number of complications in the form of restenosis also increased.

Restenosis is a repeated narrowing of the coronary artery in the place of stent placement, resulting in reduction of its lumen diameter by more than 50%, occurring in the process of arterial wall repair after its damage. As a rule, restenosis development occurs 6-9 months after angioplasty. Unfortunately, the results of numerous studies still do not give a complete picture of the mechanisms of restenosis development as a complication of PCI. Factors predisposing to the development of restenosis are divided into external and internal. External factors are related to the impact on vessels from the outside. Internal factors, among which biological factors are of special interest, determine the activity of inflammatory reaction and thrombosis with subsequent activation of hyperplastic process in the intima of coronary arteries after intervention. During PCI there is a mechanical damage of the vessel wall with disruption of the endothelial layer. Platelets, monocytes and neutrophils begin to form an inflammatory response. According to A. Curcio et al., arterial hypertension, smoking, obesity are important factors of restenosis occurrence [3]. Vascular factors include the diameter of stented arteries, multiple stenting, duration of exposure and the extent of stenosis. Vessel diameter and stenosis extent are independent predictors of in-stent restenosis. It has been proved that restenosis is less frequent when using stents with smaller width of steel strip, while increasing the stent length from 20 to 35 mm and more increases the restenosis frequency twofold. A.G. Osiev notes that the design is of greater importance for uncoated stents and less significant for drug-eluting stents [4]. High level of low-density lipoprotein LDL cholesterol at the time of intervention and subsequently increases the incidence of this complication. The role of lipoprotein (a), similar in structure to LDL in the prediction of restenosis has been shown. It was found that its concentration is associated with the risk of such complications of PCI as neointimal hyperplasia and restenosis to a greater extent than LDL level. According to Yu.A. Shuvalova et al., of all the variety of clinical risk factors for cardiovascular diseases, type 2 diabetes mellitus is a predictor of restenosis after coronary artery stenting [5]. Obesity is also among the most important risk factors for cardiovascular pathology. In the work of O.V. Arsenicheva et al. it was proved that patients with CHD and presence of metabolic syndrome who underwent PCI had a higher total number of complications of

this procedure compared to patients without metabolic syndrome (29.8 and 14.1%, respectively). The frequency of restenosis in the group with metabolic syndrome reached 12.2%, while in patients without metabolic syndrome restenoses were observed much less frequently (in 3.1% of cases) [6,7]. Thus, the problem of restenosis development after PCI remains relevant. To date, despite a large number of studies, the issues of verification of key mechanisms of in-stent restenosis, methods of determining predictors and development of prophylactic measures to prevent this complication remain unsolved.

Restenosis in The Vessels of the Lower Limbs

In general, endovascular intervention should not be performed prophylactically in patients with asymptomatic stenosis of lower limb arteries. The fundamental goals of stent implantation are to improve the primary results of angioplasty (reduction of residual stenosis, prevention of arterial wall collapse and dissection) and to preserve the patency of the artery in the long term. Stent implantation should be avoided in angioplasty of arteries in the area of hip and knee joints, although special stents designed for interventions in this area have recently been developed. The stent should also not be implanted in arterial segments that can be used for bypass surgery. Vascular stents should provide mechanical support to preserve the vessel's internal lumen. The stent resists elastic recession of the vascular wall and fuses the dissection planes formed during angioplasty. A vascular stent should have the following characteristics:

- High radial stability to resist elastic recession;
- Good longitudinal elasticity;
- Minimal shortening for precise placement;
- Resistance to external compression;
- Biological inertness;
- Thromboresistance;
- Extensibility;
- High radiopacity;
- Simple installation and reinstallation mechanism;
- Durability;
- High level of permeability.

In addition, it should promote endothelialization without neointima hyperplasia. Vascular stents can be divided into three main groups according to the methods of insertion: balloon-expandable, self-expanding, thermally expandable. Despite the variety of currently available options, unfortunately, there is no ideal stent that meets all requirements (Figure 1).

The incidence of complications related to stent placement, according to different data, varies from 1.6 to 19.4%. Restenoses in remote follow-up after balloon angioplasty of lower limbs arteries among patients with iliac arteries lesions were observed in 34% of patients, with postoperative lumen loss 58,3±4,29%, in the group of patients with stenoses of femoral and hamstring arteries - in 46%, with lumen loss 65,2±5,14%.

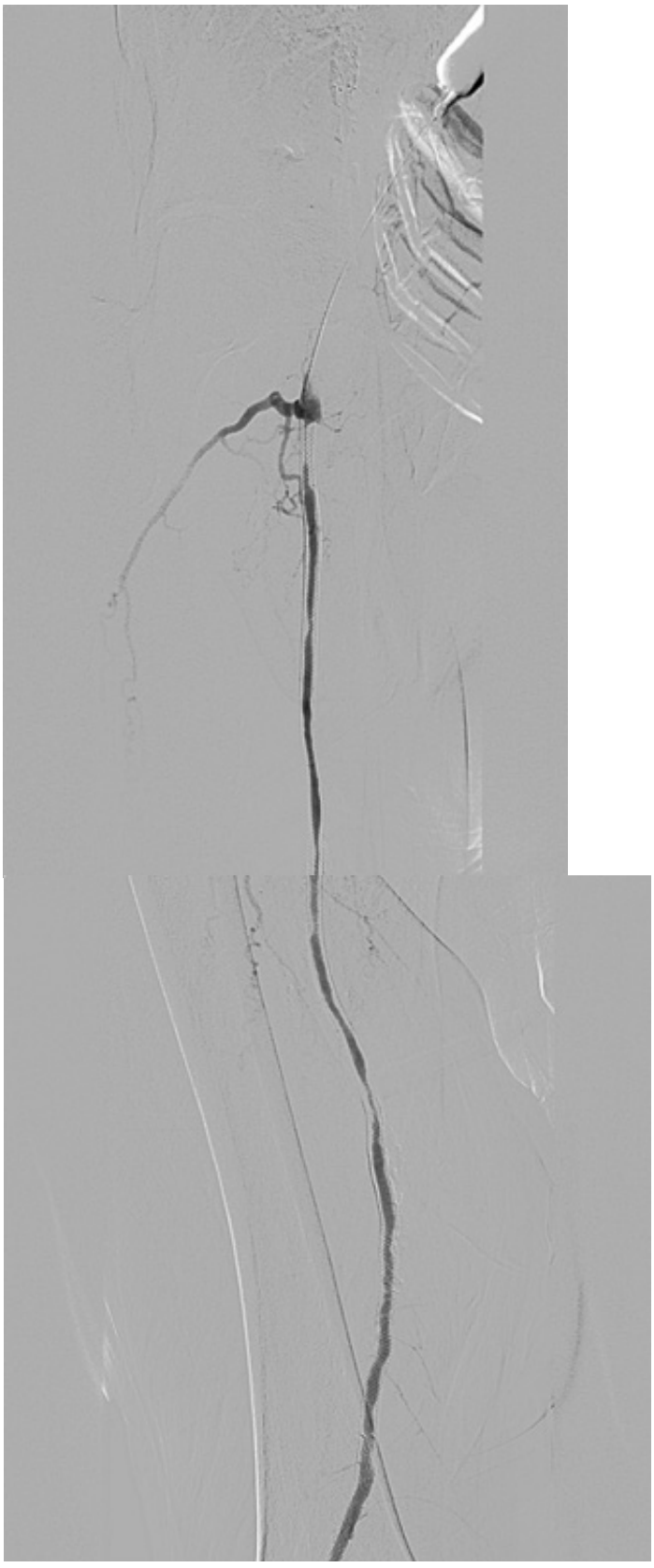

Figure 1: In-stent restenosis of superficial femoral artery. In anamnesis patient had multiple interventions in femoral-popliteal segment and tibial arteries, including rotational atherotomy.

In the early postoperative period, patients underwent exacerbation of chronic vascular inflammation in the form of a 1.8-fold increase in the concentration of proinflammatory blood factors with subsequent quiescence of inflammation in the distant period, with a decrease in the concentration of inflammatory markers and endothelial damage [8-17] (Figure 2).

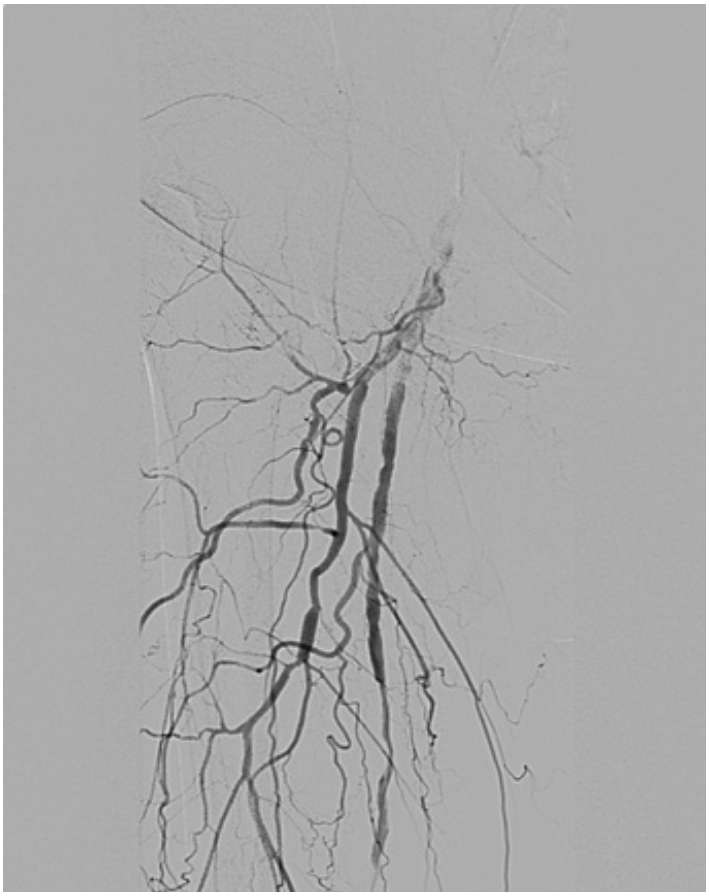

Figure 2: Restenosis in right superficial femoral artery.

Real-world incidence rates of in-stent restenosis (ISR) account for 12% of PCI [18]. Each patient requires a customized treatment strategy based on the extent and mechanism of their restenosis, requiring flexibility in your toolkit and approach [19,20] (Figure 3).

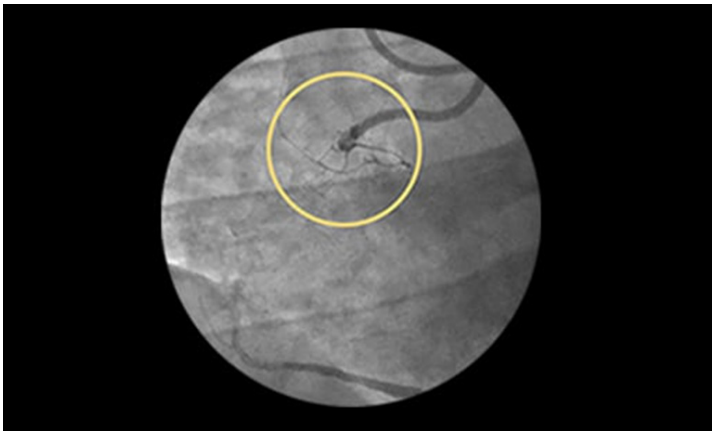

Figure 3: In-stent restenosis in coronary artery.

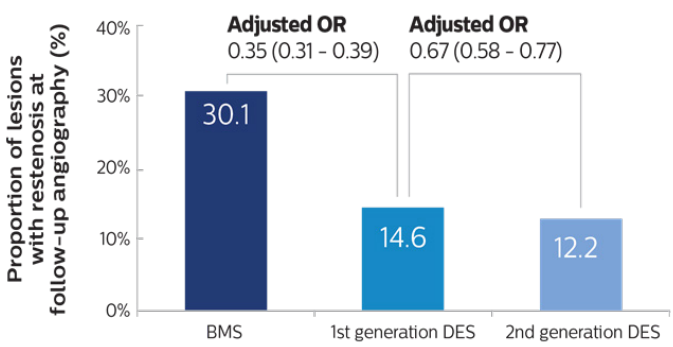

Figure 4: Rates of restenosis at follow up [21].

Treatment

According to the studies, oral administration of drugs did not lead to significant success in preventing restenosis, most likely due to poor access of drugs to the stent implantation site itself. However, 3 different methods have been presented for drug-drug interactions with the coronary stent. The first method involves binding of the drug by a polymer on the stent surface; the second involves binding of the drug by the inorganic coating of the stent (permanent or self-absorbing), and the third involves placing the drug on the stent surface without coatings. Drugs coating stents may contain antimycotics (sirolimus or its analogs paclitaxel and actinomycin); anti-inflammatory drugs (dexamethasone); drugs improving tissue repair (17β-estradiol and endothelial progenitor cell suspensions); immunosuppressors (sirolimus, tacrolimus, everolimus, mycophenolic acid). Gene-carrying stents with native plasmid DNA were also developed, which allowed to significantly reduce the rate of neointima formation and the development of reendothelialization. The use of such stents allows reducing the rate of restenosis due to a strong localized effect using a high concentration of drug at the site of the lesion.

In the TAXUS-I study it was shown that the restenosis rate after 6 months with paclitaxel-eluting stents compared to metallic stents was from 0 to 10% [22]. In TAXUS-IV, 6 months after intervention, the restenosis rate was found to be 7.9% with paclitaxel-eluting stents and 26.6% with metallic stents [23]. Unlike cyclosporine and tacrolimus, sirolimus has little effect on cytokine production. Sirolimus does not affect calcineurin phosphatase, but inhibits RAFT1/FRAP associated with G1 cell cycle progression of breast cells. A potential immunosuppressive effect of sirolimus is direct inhibition of T cells by blocking activation of p70s6 kinase, which is required for induction of mRNA for protein formation by the ribosome. When sirolimus is used, the potential for endothelial cell damage has been shown. The use of sirolimus-releasing stents, dexamethasone or their combination, compared with metallic stents, was accompanied by a 60 and 50% reduction in neointima proliferation after 7 days, respectively. After 28 days, the mean neointima area was 2.47±1.04 mm2 with sirolimus-eluting stents, 2.42±1.04 mm2 with the combination of sirolimus and dexamethasone, 5.06±1.88 mm2 with metallic stents, and 4.31±3.21 mm2 with dexamethasone-eluting stents.

The SIRIUS study demonstrated a low rate of restenosis development with sirolimus-eluting stents compared to metallic stents (3.2 and 35.4%, respectively), and the rate of repeated interventions due to restenosis development, according to the ARTS II project, amounted to 8.5% per year [24]. Figure 4.

First Generation Stents

According to the innovative but still suboptimal experience with localized antistenotic irradiation, the concept of a metallic stent coated with an antiproliferative drug reached its apogee. Despite initial failure, this approach was soon recognized as effective in several studies, marking the era of drug-coated stents. The results of the RAVEL and SIRIUS studies led to the FDA approval of the sirolimus-coated stent in the USA (Cypher, Cordis, Miami, FL, USA), also data from the TAXUS I, II and IV studies allowed the FDA to recommend the paclitaxel-coated stent for clinical use [22-26]. Both stents are based on a combination of a metal platform, a biocompatible polymer, and an antiproliferative drug. A large amount of clinical data has focused on these two drug-coated stents: according to PubMed, more than 1000 studies have been published since 2007. Although many studies have confirmed the early and mid-term safety and efficacy of these devices, clinicians have not reached a consensus on long-term safety, particularly the potential risk of late stent thrombosis and restenosis.

II generation stents

All first-generation stents clinically and statistically significantly reduced the incidence of restenosis compared with holometallic stents, but none of them had all of the following characteristics: thin, biocompatible or biodegradable polymer; optimal elasticity, conformability, contrast, delivery and resistance to structural failure; negligible late narrowing of the vessel lumen; no hypersensitivity reactions or risk of late thrombosis. Generation II stents were developed and soon became available in Europe and somewhat later in the United States. The first device was the zotarolimus-coated Endeavor® stent (Medtronic, Minneapolis, MN, USA), which was tested in the ENDEAVOR I and II trials and showed a low rate of late thrombosis and other adverse events compared to the holometallic stent [27-29]. This stent was developed using phosphoryl choline polymer, zotarolimus and Driver cobalt stent platform. Another representative of this class is the everolimus-coated Xience V stent (Abbott Laboratories, Abbott Park, IL, USA). The drug-coated everolimus is a derivative of the mTOR inhibitor rapamycin (mammalian target of rapamycin, the target of rapamycin in mammals). Rapamycin is an antibiotic and immunosuppressant used to combat rejection of transplanted organs and tissues, especially kidneys [6,30]. Subsequently, competition among medical companies has led to an avalanche growth of the drug-coated stent market and demonstrated that drug-eluting antiproliferative stents have gained a major place in clinical practice over the last decade.

Generation III and IV stents

The desire of device manufacturers to improve long-term outcomes, as well as frequent evidence of adverse effects of polymer coating of the stent, has led to a new concept of using biosoluble materials. Thus, in a recently published metaanalysis [31-33] it was shown that stents with biodegradable coating demonstrate results no worse and sometimes even better than their predecessors. The next step was the production of fully biodegradable vascular scaffolds. Absorb due to its biocompatibility serves as a powerful factor of physiological vascular remodeling [3,35-39]. At first, the world community accepted the IV generation of vascular devices with enthusiasm, but controversial immediate results, complexity of implantation technique and impossibility of routine use of the new device led to the return to the III generation devices. A modern representative of drug-eluting stents of III generation of Russian production is the Calypso stent (Angioline, Russia).

Clinical Challenges

Target lesion revascularization rates remain an issue even today when using multiple overlapping stents.

- 2nd stent 12-16% at 12 months and 33% at 3-5 years [40].
- 3rd stent 25% at 6 months [41].
- Angiography alone cannot provide the information necessary to fully understand the mechanism and extent of ISR [42].
- Difficult to identify under-expansion or mal-apposition
- Challenging to determine if it is geographical miss or under-sizing
- Inability to discern between neointimal hyperplasia or neo-atherosclerosis
- Traditional mechanical tools have limitations for treating ISR.
- Mechanical tools, from angioplasty to rotational or orbital atherectomy, are largely ineffective in restenotic lesions [43].
- The unique soft, aqueous morphology of neointimal hyperplasia tissue presents a challenge to mechanical intervention [44].

The risk of restenosis is growing with each layer of stent [40]. Figure 5.

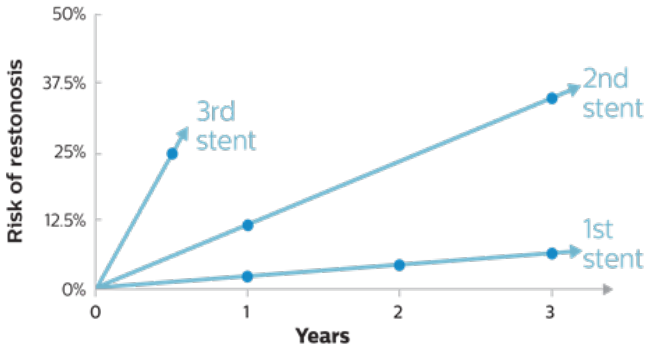

Figure 5: Risk of restenosis.

Genotherapeutic Methods

Recently, a molecular therapy targeting the proliferative component of in-stent restenosis has been developed. It is based on the premise of site-specific delivery of cell cycle inhibitor genes to prevent the formation of intimal lesions after stenting.

The data obtained to date show a clear prospect for the development and implementation of gene therapy technologies in the treatment of

many multifactorial processes, including restenosis. Gene therapy aimed at thrombosis suppression consists in local hyperexpression of NO-synthetase, which leads to an increase in NO synthesis in the vascular wall, as a result of which platelet aggregation is reduced and neointima growth is suppressed. Literature data show that gene therapy is mainly realized by direct injection of exogenous DNA embedded in vector system into vessel wall or myocardium.

The realization of this direction involves the solution of three fundamental problems:
- Identification of genes whose modification is able to achieve the desired therapeutic effect;
- Improvement of vector systems in terms of their safety and productivity of the injected gene material;
- Development of methods of targeted delivery of vectors to appropriate targets.

Vascular endothelial growth factor (VEGF) gene transfer using a catheter into a coronary vessel allowed significantly reducing (up to 6% of cases) the development of restenosis in 6 months after PCI and significantly increasing myocardial perfusion. The results of gene therapy using other genetic materials are ambiguous. Encouraging effects were obtained in the experiment when using a mutant gene encoding proteolytically inactive urokinase. Indirect (cellular) (ex vivo) and direct (*in vivo*) gene therapy are used to introduce exogenous DNA into human or animal vascular cells. In vivo gene therapy is based on direct injection of therapeutic genes embedded in a vector system into the vessel wall, myocardium. Vector systems include non-viral and viral vectors. The former are represented by plasmid DNA, which is injected in complex with liposomes, positively charged lipid vesicles that envelop the negatively charged DNA and promote better penetration through the negatively charged cell membrane. But the *in vivo* tissue transfection efficiency of plasmid DNA is very low and does not exceed 0.1% [5,45-49]. Plasmid DNA is not incorporated into the host genome and provides only temporary gene expression - 2-4 weeks. Viral vectors are represented by replication-defective retroviruses, adenoviruses and a number of other viruses. Retroviral vectors can provide long-term expression of the introduced gene. Their use for direct gene therapy is limited by low transduction efficiency, the danger of possible oncogenicity due to random insertion of promoters and the fact that they introduce DNA only into proliferating cells. Efficient transduction of vascular cells is achieved with adenoviral vectors that can target both dividing and non-dividing cells. They do not integrate into the host genome, but cause short-term gene expression - no more than 4 weeks. The main disadvantage is the development of adverse immune and inflammatory reactions. Mechanical approaches are used to deliver vectors into the vessel using intravascular systems - perivascular and myocardial.

Perivascular delivery of genes into the vessel is performed using special catheters, which completely avoids systemic gene delivery. In addition, intramyocardial injections of vector solutions are used, which are performed during aortocoronary bypass surgery using a small thoracotomy, as well as from the left ventricular cavity using special catheters with needles for trans endocardial injections.

The cytostatic approach involves the introduction of genes encoding proteins that are natural inhibitors of proliferation, the expression of which is suppressed in proliferating cells, in an adenoviral vector into the damaged area of the vessel. Such genes are retinoblastoma gene, which blocks the cell entry into the cell cycle, forming a complex with transcription factor E 2F, which prevents DNA synthesis; a gene encoding a protein p21-inhibitor of cyclin-dependent kinases, providing the cell passage into S-phase, and one of homeobox genes gax, encoding a cytostatic protein. For the same purpose we used a mutant inactive proto-oncogene from the ras family, the product of which is one of the links in the mitogenic signal transduction chain. In all cases effective suppression of neointima growth by 50-80% was achieved [50] Figure 6.

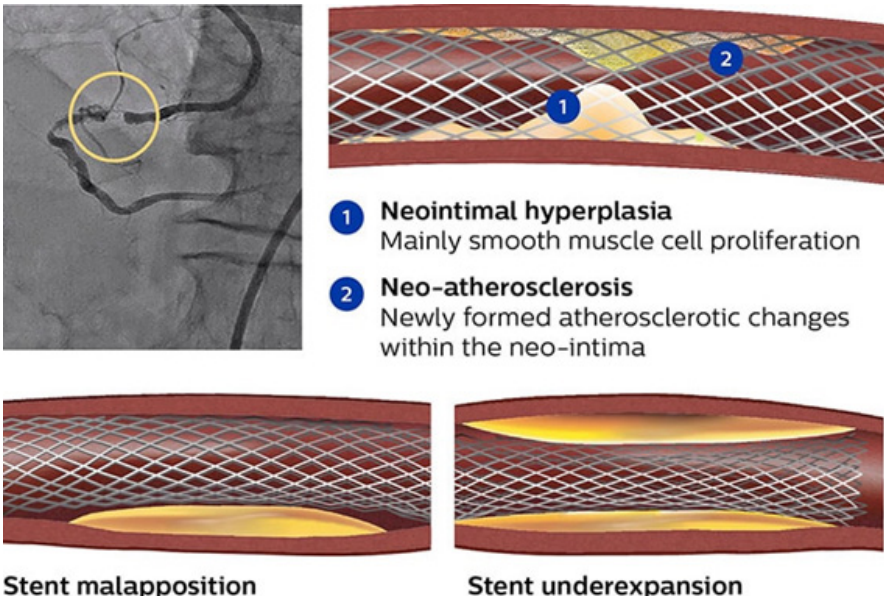

Figure 6: Neointimal hyperplasia and Neo-atherosclerosis.

Another cytostatic approach is to suppress the expression of proteins that determine the entry of the cell into the cell cycle and the passage of cell cycle phases. For this purpose we used administration of antisense oligonucleotides suppressing the expression of proto-oncogenes c-myc and c-myb, cyclin-dependent kinase 1 and 2 (CDK) and proliferating cell nuclear antigen (PCNA). The most significant suppression of neointima formation was achieved when oligonucleotides against PCNA and CDK2 were co-administered [51,52]. Thus, the genotherapeutic direction in the prevention of restenosis after PCI is in the stage of intensive development. With the solution of the issues of multifunctional candidate gene selection, improvement of vectors and methods of targeted gene delivery to target cells, gene therapy of restenosis will undoubtedly take a leading position in the prevention of adverse events after PCI.

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