folia medica

Folia Medica 65(6):863-870
DOI: 10.3897/folmed.65.e109433

Review

Pathogenetic Mechanisms of Repeated Adverse Cardiovascular Events Development in Patients with Coronary Heart Disease: the Role of Chronic Inflammation

Irina Starodubtseva[1], Maria Meshkova[1], Anna Zuikova[1]

[1] *NN Burdenko Voronezh State Medical University, Voronezh, Russia*

Corresponding author: Irina Starodubtseva, NN Burdenko Voronezh State Medical University, Voronezh, Russia; Email: starodubtsevairina1@gmail.com

Received: 12 July 2023 ♦ **Accepted:** 3 Aug 2023 ♦ **Published:** 31 Dec 2023

Citation: Starodubtseva I, Meshkova M, Zuikova A. Pathogenetic mechanisms of repeated adverse cardiovascular events development in patients with coronary heart disease: the role of chronic inflammation. Folia Med (Plovdiv) 2023;65(6):863-870. doi: 10.3897/folmed.65.e109433.

Abstract

Stent restenosis is the most unfavorable complication of interventional treatment for coronary heart disease. We already know from various literature sources that the causes for stent restenosis in patients are both mechanical damage (partial opening, stent breakage, extended stented area, calcification, incomplete stent coverage of atherosclerotic plaque, weak radial stiffness of the stent metal frame, lack of stent drug coating), and the neointimal hyperplasia formation which is closely related to the *de novo* atherosclerosis development, being a predictor of the recurrent cardiovascular event.

Considering this event, it is necessary to understand all the pathogenetic and pathophysiological processes of atherosclerosis. This review aims to comprehensively highlight the main issues of pathogenesis and the development of stent restenosis in the coronary artery after percutaneous transluminal coronary angioplasty. The review is based on relevant publications found by a selective search of PubMed, Google Scholar, Scopus, Web of Science, and eLibrary, including works published within the last 20 years. The influence of various factors of the pathogenetic process on the risk of stent restenosis has been demonstrated.

Keywords

stent restenosis, pathogenesis, inflammation, percutaneous transluminal angioplasty.

INTRODUCTION

The introduction of percutaneous coronary intervention (PCI) has revolutionized the treatment of patients with obstructive coronary artery disease (CAD), including patients with acute myocardial infarction.[1] In addition, the development of drug-eluting stents (DES) is successfully aimed at the problem of neointimal excess growth in the stented segment.[2] However, this success was achieved at the cost of a significant delay in vascular healing due to the powerful effects of the released antiproliferative drugs.[3] According to the 2018 ESC/EACTS Guidelines on Myocardial Revascularization, restenosis associated with CAD should be treated with repeat revascularization, and repeat PCI remains the strategy of choice for most of these patients.[4] In-stent restenosis (ISR) is the healing process of the damaged vessel after stenting which is detected in approximately 10%–40% of patients.[5] Long-term stent-related events have not been significantly reduced, despite recent advances in stent technology.[6] High rates of ISR associat-

ed with bare-metal stents (BMSs) led to the development of DESs, which modified the healing process after stent implantation, attenuating neointimal formation, and resulting in a reduction of the incidence of ISR to rates ranging from 5% to 10%.[7,8] With the invention of various generations of coated stents, their frequency has significantly decreased to 12%-15%, but the problem of restenosis is still not completely solved.[9]

For the symptomatic treatment of atherosclerosis narrowing the lumen, percutaneous transluminal intervention was established, which has a high success rate, accompanied by low periprocedural complications. Despite proper technical success, the vascular events recurrence rate of up to 20% remains during the first 12 months.[10,11] Although there is a decrease in the number of late thrombotic events when using new generation DES, late stent insufficiency remains a problem after stent installation. Neoatherosclerosis in the stent has become an important factor contributing to late vascular complications, including very late stent thrombosis and late restenosis in the stent.[12] Histologically, neoatherosclerosis is characterized by accumulation of lipid foamy macrophages in the neointima with the formation of a necrotic nucleus and/or calcification, or without them. The development of neoatherosclerosis can occur months or years after the installation of a stent, whereas atherosclerosis in native coronary arteries develops for decades. Early development of neoatherosclerosis was identified not only in first-generation DES, but also in second-generation DES. The mechanisms underlying the rapid development of neoatherosclerosis remain unknown. Plaque rupture in the stent is probably the cause of most of the thrombotic events associated with neoatherosclerosis, while it can also be a substrate of restenosis in the stent, since thrombosis can occur either symptomatically or asymptomatically.

AIM

The purpose of this review is to highlight the main pathophysiological processes and to display possible markers of the diagnosis of CAD progression based on the analysis and review of domestic and international literature.

MATERIALS AND METHODS

The work with the literature included the search for up-to-date original papers in PubMed, Google Scholar, Scopus, Web of Science, and JACC describing the contribution of immune processes to the pathogenesis of various phenotypes of restenosis in the stent. The search period was 20 years, but preference was given to current studies. The following key phrases were used to search the literature: inflammation, restenosis, atherosclerosis, immune system, tumor necrosis factor (TNF) and interleukin (IL)-1, IL-6, lipoprotein-associated phospholipase A2 (Lp-LA2), myeloperoxidase, pentraxin-3, proteases such as matrix metalloproteinase-9, and C-reactive protein (CRP) measured by high-sensitivity analysis (hs-CRP), lipoprotein (a) [Lp (a)], apolipoprotein A-II, growth differentiation factor (GDF) in in-ISR, and proliferation and migration of vascular smooth muscle cells (VSMCs) in the development of neoatherosclerosis. The full-text sources were then analyzed to determine which publications were relevant to the review's aim and to assess their significance. The exclusion criteria were duplicate publications, review articles without a detailed description of scientific results, and authors' opinions. A total of 25849 papers were initially found in these databases according to the key words. After using the exclusion criteria, the review included 46 of the most relevant and significant papers **(Fig. 1)**.

There are several factors that may contribute to the development of stent restenosis. These include biological factors, such as stent drug-eluting resistance and hypersensitivity; mechanical factors: incomplete opening of the device, its breakage or rupture, uneven distribution of the drug in the stent, polymer peeling, and there are also technical reasons, namely, barotrauma of the outstented segment, and residual uncovered atherosclerotic plaques. Interestingly, the predictors that contribute to the formation of restenosis in a drug-eluting stent do not differ from those in the implantation of a metal one. Factors such as a history of diabetes mellitus (DM), complex injury, small vessel diameter, and a long or non-expanded stent are equally common in both groups.[13]

According to the literature, the metabolic syndrome is characterized by insulin resistance, endothelial dysfunction, in addition to low-intensity inflammation and oxidative stress, which are common risk factors (RF) for the development of atherosclerosis.[14]

Thus, according to Cheng et al.[15], RFs affecting restenosis after PCI in patients with CAD, a clinical study based on 1-year follow-up showed that 93 cases among 1132 cases had ISR with a total frequency of 8.21%.

One-dimensional and multidimensional logistic regression analyses showed that postoperative levels of hypersensitive hs-CRP (OR=2.309, 1.579–3.375 mg/L), postoperative levels of homocysteine (HCY) (OR=2.202, 1.268–3.826 mmol/L), history of DM (OR=1.955, 1.272–3.003), coronary bifurcation lesions (OR=3.785, 2.246–6.377), and stent length (OR=1.269, 1.179–1.365 mm) were independent risk factors for ISR after PCI.[15]

An increasing number of scholarly publications prove the significant contribution of the immune system to the development and progression of ISR, and the inflammatory theory has repeatedly been confirmed in experimental studies. Atherosclerosis is an important cause of morbidity and mortality in the world[16], and the studies of diagnostic markers are important for early diagnosis and quality treatment of CAD progression. Over the past decades, the efforts of scientists around the world have been focused on studying the role of various components of cellular and humoral immunity in atherogenesis. It is believed that dendritic cells (DC) located in the arterial wall are able to capture particles

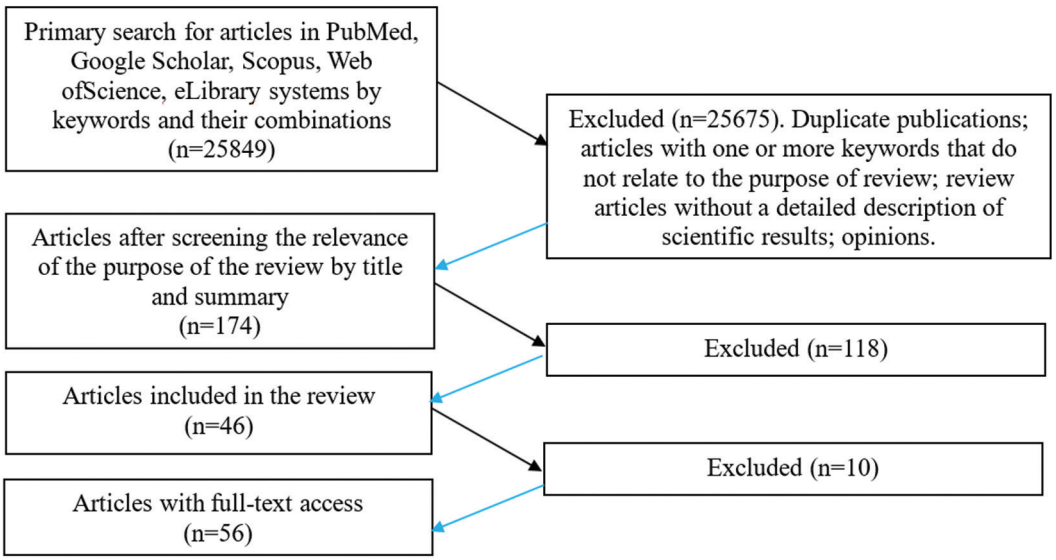

Figure 1. Selection of papers for the review according to the PRISMA methodology.

of oxidized low-density lipoproteins (Ox-LDL) and present them on their surface as an antigen for native T-cells. One of the key functions of DC is the production of the chemokine CCL17, under the influence of which CCR4 receptors located on the surface of T lymphocytes move to the location of DC.[17] According to the research of Karpov et al., a moderately positive correlation has been found between the number of T-helpers carrying the CCR4 receptor and the Gensini score, as well as a moderately negative correlation between the level of CCL17 chemokine in peripheral blood and the relative number of T-helpers expressing the CCR4 receptor.

The data obtained suggest that the chemokine CCL17 and the CCR4 receptor play a role in initiating the T-cell immune response in atherosclerosis.[17] It is worth noting that the effect of statins on the composition of immunocompetent cells could not be determined in this study because all of the patients were initially on cholesterol-lowering therapy. In the literature, the data on the effect of statins on the content of immunocompetent cells in the blood, in particular on the level of CD3+CD4+, are quite common.[18] A more in-depth investigation of the issue, as well as determination of the degree of CCR4 expression by T-lymphocytes of various subtypes, simultaneous determination of the level of DC in the blood, exclusion of the influence of RF for CAD and the treatment received, will allow us to better understand the mechanisms of immuno-inflammatory reactions in atherosclerosis and develop new methods of immunotropic therapy for the disease.

Studies by Kazemian et al. have shown that there is a link between high levels of LDL and Lp(a) in the bloodstream and the likelihood of restenosis in the stent; moreover, the studies show that Lp(a) can stimulate the proliferation of VSMCS.[19]

In many studies, type 2 DM repeatedly appears as one of the significant RFs for the development of cardiovascular events by 1.7 times with a single-vascular lesion, in the presence of multifocal atherosclerosis – already by 2.8 times.[20] And also in patients after myocardial revascularization in the presence of type 2 DM is already associated with an unfavorable cardiovascular prognosis. Patients with DM are characterized by high platelet reactivity in relation to thrombosis. The results of recent studies have shown that patients with DM have increased platelet volume, increased their sensitivity to the main inducers of thrombosis.[21] This factor was also noted in the study by Biazrova SV[22] which demonstrated that patients who undergo coronary stenting with drug-coated stents and have a higher blood level of platelets carrying the leukocyte antigen CD45+ (CD45+ platelets) on their surface have a higher incidence of restenosis compared to patients with lower level of CD45+ platelets. An increase in the level of CD45+ platelets in the blood of patients after coronary artery stenting using drug-coated stents has a closer relationship with the occurrence of restenosis in patients with diabetes mellitus compared with patients without this disease.[22]

Zhu et al. identified 10 genes (STAT3, IL1RN, C5AR1, CXCL16, IL17RA, SLC11A1, TLR2, IL1B, LYN, and CKAP4) that may be new diagnostic signatures for atherosclerosis.[23] However, there were some limitations in this study: firstly, due to the lack of information about cardiac RF of patients, such as age and gender, cardiac RF were not included in the WGCNA and logistic regression analysis. The selected genes may also be associated with cardiac RFs and not correlate directly with atherosclerosis. Secondly, although 10 potentially key genes have been identified, the specific biological functions and characteristics of these genes need to be further studied in the future. Thirdly, it is necessary to collect more clinical patients for further validation of this model.

Detection at the outpatient stage continues to be extremely low, even in the presence of clinical signs of the disease, not to mention asymptomatic forms.[24] A number of studies have recently been published in which it has

Folia Medica

been repeatedly stated that the type, composition, morphology, and immunohistochemical characteristics of an unstable (vulnerable, prone to rupture) atherosclerotic plaque are more important than the size of the atheroma or the degree of arterial stenosis.[25] The search for effective therapeutic targets and early diagnosis of restenosis inside the stent leads to a high interest in the pathogenesis of this condition. The main pathogenetic mechanisms of the development of RVS are elastic collapse of the vessel lumen, parietal thrombosis and hyperplasia of the neointima, leading to pathological remodeling of the vascular wall. Mechanical damage to the intima media of the arteries and hypersensitivity to stent materials are considered as the starting moment.[26] It was previously known that injury to the vascular wall during the intervention leads to the development of a local inflammatory reaction, adhesion, activation and aggregation of platelets with the formation of a parietal thrombus, migration and proliferation of smooth muscle cells (MMC) and reendothelization, as well as to the synthesis of extracellular matrix components (hyaluronic acid, fibronectin, osteopontin and vibronectin). All these processes are physiological and necessary to restore the anatomical and functional integrity of the vascular wall. However, in some cases, they acquire a pathological character and lead to the appearance of neointima hyperplasia and chronic vasoconstriction. According to a number of authors, stenting prevents elastic recoil, but does not prevent the development of thrombosis, inflammation, and hyperplasia of the neointima.

The structure of the covering of an atherosclerotic plaque includes many components of the extracellular matrix (collagen, elastin, proteoglycans and glycosaminoglycans), factors affecting the formation and destruction of these components are of great importance in stabilizing the plaque. At the same time, the listed macromolecules of the extracellular matrix can capture lipoproteins and contribute to the accumulation of lipids in the intima. It is known that atherosclerotic plaques rich in lipids, and not a connective tissue elements and uncalcined become more 'soft' and dangerous in terms of damage and thrombosis development. Cytokines are able to stimulate the secretion of matrix metalloproteinases (MMPs) by atheroma cells (mainly macrophages, but also endothelial, smooth muscle, foam cells). MMPs (collagenases, gelatinases, stromelysins, etc.) obtain a degrading ability towards almost all components of the extracellular matrix. Pronounced stimulating effect on the transcription and synthesis of MMPs was found in neurohumoral agents traditionally associated with remodeling processes: angiotensin II, endothelin, catecholamines. The secretion of MMPs can be influenced not only by cytokines, but also by growth factors, some chemical agents, etc. The activity of MMP in the plaque is parallel to an increase in inflammatory cell infiltration in it and an increase in the level of cell apoptosis.[27,28]

It was already noted earlier that neointimal hyperplasia is one of the main factors contributing to restenosis after angioplasty procedures. The development of restenosis is based on the complex interaction of various mechanical and biological factors caused by the revascularization procedure of the affected vascular network and concomitant vascular trauma. The mechanism by which postangioplastic restenosis develops seems to depend on whether the intervention was performed with a stent or balloon angioplasty. In the case of a procedure without a stent, early arterial recoil and negative vascular remodeling are important factors. On the contrary, restenosis after stent implantation (restenosis in the stent) primarily contributes to neointimal formation and neoatherosclerosis.[29,30]

In their work, Ebert et al.[31] described in sufficient detail the generation of neointimal hyperplasia on the example of various small animals, creating a vascular injury, as a consequence of which, an inflammatory reaction occurs with an increased set of immune cells, especially monocytes and macrophages, which quickly accumulate and differentiate into foam macrophages. Oxidative stress and increased release of cytokines and chemokines lead to proliferation and migration of VSMCs from the medium to the intima.

A detailed study of the cardiovascular system immune homeostasis is necessary to search for early predictors of noninvasive diagnosis of ISR and it is possible in the future to create and justify specific targets for immunotropic therapy. Currently, a number of clinical studies and meta-analyses are devoted to the investigation of new surface-decomposable DES with the functions of anticoagulation, antiproliferation and endothelialization.[32] DES are widely used in the clinic because of their impressive ability to reduce restenosis. However, conventional biodegradable drug-coated polymers undergo volumetric erosion, which can induce internal catalysis that leads to high local acidity during the degradation process and causes adverse side effects.[33]

In addition, human autopsy analysis showed that drug-eluting stents show greater deposition of proteoglycans compared to restenotic BMS, which may be a potential enhancer of neoatherosclerosis in DES, since extracellular matrix components such as proteoglycan are known to be associated with lipoprotein retention.[34] Persistent apoptosis of macrophages and smooth muscle cells in stented lesions additionally contributes to the development of the necrotic nucleus.[35] Pathological thickening of intima with a lipid pool is a sign of native atherosclerosis and plaque progression, whereas in neoatherosclerosis, the formation of a necrotic nucleus is mainly due to apoptosis of macrophages in the absence of a lipid pool, which ultimately leads to plaque rupture in the stent. It has already been noted that atherosclerosis in native coronary arteries develops for decades, while neoatherosclerosis in the stent appears to occur months or years after the stent is installed and quickly and more often in DES compared to BMS.[31]

The mechanisms responsible for accelerated atherosclerosis in stented segments, especially in DES, remain little known; however, it is assumed that incompetent and dysfunctional endothelial coating of the stented segment contributes to this process.

The formation of neointima shows several parallels with the formation of *de novo* atherosclerosis. Talking about this process, it is necessary to understand all the pathophysiological stages.

Damage and activation of the endothelium

When the endothelium is exposed to various damaging factors (chemical or biological in nature, mechanical, metabolic, or immunocomplex), its function is disrupted, resulting in a decrease in the release of vasodilating factors [nitric oxide (NO), prostacyclin, and hyperpolarizing endothelial factor] and an increase in the synthesis of constrictor factors (endothelins, thromboxane A2, etc.). Thus, endothelial dysfunction is an inadequate (increased or decreased) formation of various biologically active substances in the endothelium. Endothelin-1 interacts with the ETA receptors of smooth muscle cells, prompting them to contract immediately, thereby counteracting the endothelial ET_B-receptor, which usually induces vascular relaxation stimulating the endothelium to release NO.[36]

NO and prostaglandin I2 in a normal physiological state have vasodilating, antiproliferative and anti-adhesive effects on the endothelium. As previously noted, this disorder occurs if the physiological balance is affected by pathological stressors in the form of continuous and stable release of NO into the vascular microenvironment, which has a significant inhibitory effect on platelet activation, thrombus formation, migration and proliferation of SMC, as well as a positive healing effect on the atherosclerotic lesions[37], and endothelial glycocalyx can directly modulate interactions of ECs-blood for inhibiting the adhesion of platelets, leukocytes, erythrocytes, as well as high-molecular plasma substances[38]. Thus, vascular stents with NO-releasing properties and endothelial glycocalyx molecules constructed on the surface can provide highly biomimetic endothelial functions for the prevention of thrombosis, hyperplasia and restenosis. Glycoprotein tenascin-C promotes the proliferation of smooth muscle cells by interacting with many different growth factors and adhesion molecules, such as platelet-derived growth factor (PDGF), as well as fibroblast growth factor (FGF), and fibronectin.

Platelet-derived growth factor (PDGF)

PDGF is the most well-studied representative of the group of protein growth factors. PDGF can change the proliferative status of a cell, affecting the intensity of protein synthesis, but without affecting the transcription enhancement of early response genes such as c-myc and c-fos.[39] Platelets themselves do not synthesize protein. PDGF synthesis and processing is carried out in megakaryocytes - bone marrow cells, platelet precursors - and is stored in platelet α-granules. While PDGF is inside platelets, it is inaccessible to other cells; however, when interacting with thrombin, platelets are activated, followed by the release of the contents into the serum. Platelets are the main source of PDGF in the body, but, at the same time, it has been shown that some other cells can also synthesize and secrete this factor: these are mainly cells of mesenchymal origin.[39]

Accumulation of monocytes

Various adhesion factors, such as selectins and vascular cell adhesion molecules, are expressed by the activated endothelium, which causes leukocytes, especially monocytes, to roll and stick to the endothelium, where a complex cluster of integrins and cadherins leads to transmigration into the subintimal space.[40] These monocytes differentiate into macrophages that exhibit an inflammatory response that releases cytokines (for example, tumor necrosis factor-α or interleukin-1β), which enhances the weakening of the endothelial barrier by chemotaxis of lymphocytes and additional mononuclear phagocytes. It can be assumed that the deficiency of an endogenous inhibitor of the interleukin-1 receptor antagonist contributes to intimal hyperplasia after arterial injury. This additionally increases the permeability of the endothelium leading to an altered influx of lipid droplets, forcing transmigrated macrophages to mature into foam cells, which also contributes to the formation of *de novo* atherosclerosis.[41] The dying foam cells accumulate, forming a necrotic center encapsulated by a VSMC-made fibrous lid of collagen, proteoglycans, and elastin, which accelerates restenosis.[42]

Transformation of smooth muscle cells of the vascular wall of VSMC

Migration and proliferation of fibroblasts in combination with growth factors and redox factors also promote stimulation and transformation of smooth muscle cells in the vascular wall of VSMCs to respond in a similar way.[43] The TGF family, in particular TGF-β1, plays a significant role in this process, stimulating the transformation of VSMC via the PI3K/AKT/ID2/mTOR pathway.[44] Three recently discovered adipokines – visfatin, LCN-2, and FABP – represent another link between adipose tissue and atherosclerosis due to their ability to activate macrophages and regulate their phenotypes. It has been demonstrated that visfatin is secreted by PVRT and stimulates the proliferation of VSMCs through extracellular signal-regulated kinases (ERK) 1/2 and p38 MAPK signaling pathways. The FABP4, locally produced by perivascular fat, increased the expression of inflammatory marker genes and was an independent predictor of the severity of coronary stenosis.[45] In addition, VSMCs demonstrate enhanced proliferation and migration. Subsequently, the modified VSMCs act differently than when they are in physiological conditions, since they are able to synthesize and secrete the extracellular matrix to a greater extent, and can also turn into foam cells.[46] The detailed sequence and interaction of altered endothelial permeability, monocyte influx, VSMC proliferation and migration, and increased extracellular matrix synthesis are still under study.

CONCLUSIONS

The attention of health workers should be directed not only to the timeliness and completeness of medical high-tech care provision, but also to the improvement of pre-

ventive measures in atherosclerosis progression. Since the pathogenesis of restenosis inside the stent is multifactorial, differentiated risk stratification is necessary. The identification of predictors associated with the patient, stent and the lesion is especially important, since the most effective way to combat restenosis inside the stent is to prevent it. The patients with a higher risk of neointima formation in the stent should receive routine follow-up at the dispensary and intensive medication after percutaneous coronary intervention to control risk factors and reduce restenosis in the stent.

This review can be used to create a risk prediction model and develop an intervention strategy in the formation of in-stent restenosis in patients after very high-risk percutaneous coronary intervention.

Acknowledgements

The authors have no support to report.

Funding

The authors have no funding to report.

Conflict of Interest

The authors declares that there is no conflict of interest.

REFERENCES

1. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001; 344:1879–87.
2. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346:1773–80.
3. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006; 48(1):193–202.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019; 40(2):87–165.
5. Shlofmitz E, Case BC, Chen Y, et al. Waksman in-stent restenosis classification: a mechanism-based approach to the treatment of restenosis. Cardiovasc Revasc Med 2021; 33:62–7.
6. De Gregorio J, Tateishi K. Un-dilatable in-stent restenosis: an ounce of prevention... Cardiovasc Revasc Med 2022; 34:38–9. doi: 10.1016/j.carrev.2021.10.018
7. Bønaa KH, Mannsverk J, Wiseth R, et al., for the NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. N Engl J Med 2016; 375(13):1242–52.
8. Shlofmitz E, Iantorno M, Waksman R. Restenosis of drug-eluting stents: a new classification system based on disease mechanism to guide treatment and state-of-the-art review. Circ Cardiovasc Interven 2019; 12(8):e007023.
9. Urban P, Gershlick AH, Guagliumi G, et al. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. Circulation 2006; 113(11):1434–41.
10. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006; 48(1):193–202.
11. Fumiyuki O, Robert A, Byrne, et al. Neoatherosclerosis: review of histopathological findings and implications for intravascular imaging assessment. Eur Heart J 2015; 36(32):2147–59.
12. Lee S, Choi DV, Su Wu, et al. Long-term clinical results between biodegradable and long-lasting drug-coated polymer stents: a nationwide cohort study. Front Cardiovasc Med 2022; 9:873114.
13. Marjan B, Magdalena O. In-stent restenosis in drug-eluting stents: issues and therapeutic approach. J Cardiol Curr Res 2016; 6(3):00206. doi: 10.15406/jccr.2016.06.00206
14. Barbarash OL, Voyevoda MI, Galstyan GR, et al. Pre-diabetes as an interdisciplinary problem: definition, risks, approaches to the diagnostics and prevention of type 2 diabetes and cardiovascular complications. Russian J Cardiol 2019; 4:83–91.
15. Cheng G, Chang FJ, Wang Y, et al. Factors influencing stent restenosis after percutaneous coronary intervention in patients with coronary heart disease: a clinical trial based on 1-year follow-up. Med Sci Monit: Inter Med J Experiment Clinic Res 2019; 25:240–7.
16. Libby P, Bornfeldt KE, Tull AR. Atherosclerosis: successes, surprises and future challenges. Circ Res 2016; 118(4):531–4.
17. Karpov AM, Rvacheva AN, Masenko VP, et al. Взаимосвязь уровня содержания в крови Т-хелперов, экспрессирующих рецептор CCR4, и концентрации хемокина CCL17 с тяжестью коронарного атеросклероза [Interrelation of CCR4 receptor-expressing T-helper blood levels and chemokine CCL17 concentration with coronary atherosclerosis severity]. Cardiological Bulletin 2018; (2):53–8 [Russian].
18. Rodríguez-Perea AL, Montoya CJ, Olek S, et al. Statins increase the frequency of circulating $CD4^{+}FOXP3^{+}$ regulatory T cells in healthy individuals. Immunol Res 2015;762506.
19. Kazemian MR, Solouk A, Tan A, et al. Preventing in-stent restenosis using lipoprotein (a), lipid and cholesterol adsorbent materials. Med Hypotheses 2015; 85(6):986–8.
20. Li MF, Zhao CC, Li TT, et al. The coexistence of carotid and lower extremity atherosclerosis further increases cardio-cerebrovascular risk in type 2 diabetes. Cardiovasc Diabetol 2016; 15(1):43.
21. Barbarash OL, Kashtalap VV. Управление риском развития ишемических событий у пациентов с мультифокальным атеросклерозом и сахарным диабетом 2-го типа [Management of ischemic risk events in patients with multifocal atherosclerosis and type 2 diabetes mellitus]. Atherothrombosis 2020; 1:34-44 [Russian].
22. Biazrova SV. Исследование новых биомаркеров рестеноза после имплантации стентов с лекарственным покрытием у больных ишемической болезнью сердца и сахарным диабетом 2 типа [Study of new biomarkers of restenosis after drug-eluting stent implantation in patients with coronary heart disease and type 2 diabetes mellitus] Abstract 2017, 113 [Russian].
23. Zhu F, Zuo L, Hu R, et al. A ten-genes-based diagnostic signature for atherosclerosis. BMC Cardiovasc Disord 2021; 21(1):513.
24. Barbarash OL, Kashtalap VV. A patient with ischemic heart disease

and multifocal atherosclerosis. How to optimize the forecast? Medical Council 2018; 16:32–8.
25. Nus M, Mallat Z. Immune-mediated mechanisms of atherosclerosis and implications for the clinic. Expert Rev Clin Immunol 2016; 12(11):1217–37.
26. Svedman C, Ekqvist S, Möller H, et al. A correlation found between contact allergy to stent material and restenosis of the coronary arteries. Contact Dermatitis 2009; 60(3):158–64.
27. Johnson JL. Metalloproteinases in atherosclerosis. Eur J Pharmacol 2017; (816):93–106.
28. Cancel LM, Ebong EE, Mensah S, et al. Endothelial glycocalyx, apoptosis and inflammation in an atherosclerotic mouse model. Atherosclerosis 2016; (252):136–46.
29. Gray WA, Granada JF. Drug-coated balloons for the prevention of vascular restenosis. Circulation 2010; 121(24):2672–80.
30. Van Beusekom HM, Whelan DM, Hofma SH, et al. Long-term endothelial dysfunction is more pronounced after stenting than after balloon angioplasty in porcine coronary arteries. J Am Coll Cardiol 1998; 32(4):1109–17.
31. Ebert MLA, Schmidt VF, Pfaff L, et al. Animal models of neointimal hyperplasia and restenosis: species-specific differences and implications for translational research. JACC - Basic to Translational Science 2021; 6(11):900–17.
32. Hou R, Wu L, Wang J, et al. Surface-degradable drug-eluting stent with anticoagulation, antiproliferation, and endothelialization functions. Biomolecules 2019; 9(2):69.
33. Hou R, Wu L, Zhu Y, et al. Study of functional drug-eluting stent in promoting endothelialization and antiproliferation. J Biomater Sci, Polymer Edition 2020; 31(2):244–60.
34. Nakano M, Otsuka F, Yahagi K, et al. Human autopsy study of drug-eluting stents restenosis: histomorphological predictors and neointimal characteristics. Eur Heart J 2013; 34(42):3304–13.
35. Tabas I. Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: the importance of lesion stage and phagocytic efficiency. Arterioscler Thromb Vasc Biol 2005; 25(11):2255–64.
36. Kim HR, Gallant C, Leavis PC, et al. Cytoskeletal remodeling in differentiated vascular smooth muscle is actin isoform dependent and stimulus dependent. Am J Physiol 2008; 295(3):C768–78.
37. Chatterjee A, Catravas JD. Endothelial nitric oxide (NO) and its pathophysiologic regulation. Vascul Pharmacol 2008; 49(4-6):134-40.
38. Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. Annu Rev Biomed Eng 2007; 9:121–67.
39. Kade AK, Zanin SA, Gubareva EA, et al. Physiological functions of the vascular endothelium. Basic research 2011; 11(3):611–7.
40. Gerhardt T, Lei K. Transport of monocytes through the vessel wall. Cardiovasc Res 2015; 107(3):321–30.
41. Kuo A, Lee MY, Sessa WC. Lipid droplet biogenesis and function in the endothelium. Circ Res 2017; 120(8):1289–97.
42. Yang Y, Luo NS, Ying R, et al. Macrophage-derived foam cells impair endothelial barrier function by inducing endothelial-mesenchymal transition via CCL-4. Int J Molec Med 2017; 40(2):558–68.
43. Li DJ, Fu H, Tong J, et al. Cholinergic anti-inflammatory pathway inhibits neointimal hyperplasia by suppressing inflammation and oxidative stress. Redox Biol 2018; (15):22–33.
44. Zhu SB, Zhu J, Zhou ZZ, et al. TGF-β1 induces human aortic vascular smooth muscle cell phenotype switch through PI3K/AKT/ID2 signaling. Am J Translat Res 2015; 7(12):2764.
45. Furuhashi M, Fuseya T, Murata M, et al. Local production of fatty acid-binding protein 4 in epicardial/perivascular fat and macrophages is linked to coronary atherosclerosis. Arterioscler Thromb Vasc Biol 2016; 36(5):825–34.
46. Durham AL, Speer MJ, Scatena M, et al. Role of smooth muscle cells in vascular calcification: significance in atherosclerosis and arterial stiffness. Cardiovasc Res 2018; 114(4):590–600.

Патогенетические механизмы развития повторных неблагоприятных сердечно-сосудистых событий у больных ишемической болезнью сердца: роль хронического воспаления

Ирина Стародубцева[1], Мария Мешкова[1], Анна Зуйкова[1]

[1] *Воронежский государственный медицинский университет имени Н.Н. Бурденко, Воронеж, Россия*

Адрес для корреспонденции: Ирина Стародубцева, Воронежский государственный медицинский университет имени Н.Н. Бурденко, Воронеж, Россия; Email: starodubtsevairina1@gmail.com

Дата получения: 12 июля 2023 ♦ **Дата приемки:** 3 августа 2023 ♦ **Дата публикации:** 31 декабря 2023

Образец цитирования: Starodubtseva I, Meshkova M, Zuikova A. Pathogenetic mechanisms of repeated adverse cardiovascular events development in patients with coronary heart disease: the role of chronic inflammation. Folia Med (Plovdiv) 2023;65(6):863-870. doi: 10.3897/folmed.65.e109433.

Резюме

Рестеноз стента является наиболее неблагоприятным осложнением интервенционного лечения ишемической болезни сердца. Из различных литературных источников уже известно, что причинами рестеноза стента у пациентов являются как механические повреждения (частичное открытие, поломка стента, удлинение площади стента, кальцификация, неполное покрытие стента атеросклеротической бляшкой, слабая радиальная жёсткость металлического каркаса стента, отсутствие лекарственного покрытия стента), а также формирование неоинтимальной гиперплазии, которая тесно связана с развитием атеросклероза de novo и является предиктором повторного сердечно-сосудистого события.

Учитывая это событие, необходимо понять все патогенетические и патофизиологические процессы атеросклероза. Целью данного обзора является комплексное освещение основных вопросов патогенеза и развития рестеноза стента в коронарной артерии после чрескожной транслюминальной коронарной ангиопластики. Обзор основан на соответствующих публикациях, найденных с помощью выборочного поиска в PubMed, Google Scholar, Scopus, Web of Science и eLibrary, включая работы, опубликованные за последние 20 лет. Показано влияние различных факторов патогенетического процесса на риск рестеноза стента.

Ключевые слова

рестеноз стента, патогенез, воспаление, чрескожная транслюминальная ангиопластика