Coronary stent technology and the role of inflammation in the atherogenesis: problems and prospects

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ABSTRACT

Coronary artery disease (CAD) remains one of the leading causes of death in developed industrial countries. Timely and effective medical care for CAD patients depends on availability and application of endovascular methods for CAD treatment. Percutaneous coronary intervention (PCI) using drug-eluting stents allows to achieve good clinical results even in most severe patients. The issues of personalized invasive treatment for patients with chronic coronary syndrome and optimal prevention of recurrent clinical events in survivors of acute coronary syndrome and PCI remain relevant.

One of most important and unresolved problems in the pathophysiology of CAD is assessment of the nature of the inflammatory reaction that develops in the coronary vessels and myocardium in response to ischemic damage and PCI. Clinical studies focused on exploring a correlation between the proinflammatory parameters of the patient's status and the rate of secondary adverse events and aimed at revealing triggers of systemic and local inflammation are of great interest. Such a trigger could be the intestinal endotoxin (ET) which is capable of inducing systemic inflammation and, therefore, plays a significant role in the atherogenesis. A relationship between the endotoxin and cytokine system parameters should be investigated to develop a therapeutic concept for supporting CAD patients, including individuals after PCI. Parameters of systemic endotoxemia could be used as additional factors in developing the biomarker-based approach to identify patients with active inflammation or fibrosis. This could result in development of specific therapy aimed at suppressing proinflammatory mediators and protecting the heart from inflammation.

Key words: coronary artery disease, percutaneous coronary intervention, inflammation, endotoxin, cytokines, systemic endotoxinemia.

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Source of financing. The authors state that they received no funding for the study.

For citation: Ryabov V.V., Kretov E.I., Popov S.V., Khassanov I.Sh., Yakovlev M.Yu. Coronary stent technology and the role of inflammation in the atherogenesis: problems and prospects. *Bulletin of Siberian Medicine.* 2021; 20 (1): 200–212. https://doi.org/10.20538/1682-0363-2021-1-200-212.

УДК 616.132.2:615.472.5.032.13]-002:616.13-004.6
https://doi.org/10.20538/1682-0363-2021-1-200-212

Технология коронарного стентирования и роль воспаления в атерогенезе: проблемы и перспективы

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РЕЗЮМЕ

Ишемическая болезнь сердца (ИБС) остается одной из ведущих причин смертности в развитых индустриальных странах. Своевременная эффективная помощь данному контингенту больных зависит от доступности и эффективности применения эндоваскулярных методов лечения ИБС. Чрескожное коронарное вмешательство (ЧКВ) с применением стентов с лекарственным покрытием позволяет добиваться хороших клинических результатов даже у самых тяжелых групп пациентов. Остаются актуальными вопросы персонализации планового инвазивного лечения пациентов с хроническим коронарным синдромом, а также оптимальной вторичной профилактики повторных клинических событий у пациентов, благополучно пережившим острый коронарный синдром и ЧКВ.

Одной из важнейших и неразрешенных проблем в патофизиологии ИБС является оценка характера воспалительной реакции, развивающейся в венечных сосудах и миокарде в ответ на ишемическое повреждение и ЧКВ. Представляют интерес клинические исследования, направленные на изучение корреляции показателей провоспалительного статуса пациентов с частотой развития повторных неблагоприятных клинических событий с целью выявления индуктора системного и местного (в стенте) воспаления. Вероятным кандидатом является кишечный эндотоксин, способный индуцировать системное воспаление и таким образом играющий существенную роль в атерогенезе. Необходимы исследования взаимодействия параметров эндотоксиновой и цитокиновой систем для выработки терапевтической концепции поддержки больных ИБС, в том числе после проведения процедуры стентирования коронарных артерий. Использование показателей системной эндотоксинемии в прогнозе течения заболевания может быть дополнительным фактором для выработки подходов, основанных на биомаркерах для идентификации больных с активным воспалением

или фиброзом, что привело бы к разработке специфической терапии, направленной на подавление провоспалительных медиаторов и защиту сердца от воспалительного повреждения.

Ключевые слова: ишемическая болезнь сердца, чрескожное коронарное вмешательство, воспаление, эндотоксин, цитокины, системная эндотоксинемия.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при написании статьи.

Для цитирования: Рябов В.В., Кретов Е.И., Попов С.В., Хасанов И.Ш., Яковлев М.Ю. Технология коронарного стентирования и роль воспаления в атерогенезе: проблемы и перспективы. *Бюллетень сибирской медицины.* 2021; 20 (1): 200–212. https://doi.org/10.20538/1682-0363-2021-1-200-212.

INTRODUCTION

Cardiovascular diseases (CVD) account for the largest share of overall mortality in European Society of Cardiology (ESC) member countries [1]. A common group of risk factors underlying the cardiovascular pathology are associated with unhealthy life style and may cause cancer, diabetes mellitus, and chronic lung diseases, that account for 80% of overall mortality. According to the last European registry, CVD risk factors remain prevalent in patients with chronic coronary syndrome, and prescription of secondary prevention medications is not reasonable. Elderly patients and to some extent female patients have a lower chance of receiving appropriate therapy than young male patients [2].

Coronary artery disease (CAD) accounts for more than 50 % of CVD mortality and 25.9 % of overall mortality in Russia [3]. Timely and effective medical care for CAD patients depends on availability and application of endovascular procedures for CAD treatment, especially in acute coronary syndrome (ACS), and on primary and secondary prevention.

In recent years, a rapid increase in the number of endovascular diagnostic and therapeutic interventions has been registered in Russia. More than 740,000 procedures were performed in 2018, of which more than 220,000 were percutaneous coronary interventions (PCI) [4]. It must be noted that implementation of invasive methods for ACS therapy allowed to achieve prominent results in several Russian clinics. Nevertheless, despite the application of antiplatelet and invasive reperfusion therapy, the incidence of ACS and its complications remains high [5, 6].

PCI is the most common invasive method to treat CAD due to high early procedural success and relief of symptoms. Technological development of ultrathin passivated and drug-eluting stents enables to achieve good clinical results even in most high-risk patients with ST-segment elevation myocardial infarction (STEMI) [7].

The prognostic value of invasive therapy in patients with chronic coronary syndrome has been investigated for quite a long time. Thus, the ISCHEMIA clinical trial [8] failed to demonstrate that PCI with stenting resulted in a lower number of serious ischemic complications (death, myocardial infarction (MI), cardiac arrest with return of spontaneous circulation (ROSC), hospitalization due to heart failure (HF) or congestive HF (CHF)) in patients with moderate CAD, as opposed to optimal drug therapy. Consequently, the issue of personalization of planned invasive treatment for patients with chronic coronary syndrome, namely selection of patients that will benefit from invasive therapy to the largest extent, remains relevant.

It is worth noting that along with improvement of the stent technology, the problem of coronary event recurrence has come to the forefront. It is obvious that even with optimal secondary prevention in survivors of ACS and PCI, intervention in chronic coronary syndrome does not provide zero residual risk of recurrent clinical events, such as angina pectoris, MI, HF, and sudden cardiac death.

Irrespective of the therapy success, researchers more often confirm the inadequacy of the infiltration theory of atherogenesis and its consequences [9]. Drug therapy optimization is associated to a large extent with the anti-inflammatory effect

of medications. Today, assessment of the nature of the inflammatory reaction that develops in the coronary arteries and myocardium in response to ischemic injury is one of the most important and unresolved problems in the pathophysiology of CAD. In this respect, an obvious gap in knowledge is observed that was obtained in the clinical trials [10, 11] studying a correlation of proinflammatory parameters of the patient's status with the incidence of recurrent adverse events, including the rate of in-stent restenosis.

The role of the immune system in the pathogenesis of CVD is well known: body immune protection is triggered by any stress effect [12], and acute myocardial ischemia is not an exception. There are several interdependent components of immune response that can be engaged in CAD and HF pathogenesis. Low-grade chronic systemic inflammation is essential that manifests through chronic nonspecific diseases involving the cytokine system. Hyperactivation of this system accompanies degradation of extracellular myocardial collagen matrix, ventricular dilatation, and cardiomyocyte hypertrophy (CMH).

There are many hypotheses on how and why the level of proinflammatory cytokines, especially tumor necrosis factor alpha (TNFα), increases and what causes immune response activation while common symptoms of inflammation are absent. Besides the assumption on myocardial TNFα production stimulated by elevated blood pressure proportional to myocardial wall tension and left ventricular end-diastolic pressure [13] and the hypothesis on extramyocardial cytokine production facilitated by tissue hypoxia and the excess of free radicals [14], there is an endotoxin (ET) concept of atherogenesis [15]. It is based on experimental results [16] and is confirmed by clinical trials [17], which allowed to formulate the endotoxin theory of atherosclerosis [18]. Apparently, the intestinal endotoxin may play a significant role in the atherogenesis, because it is capable of inducing systemic inflammation [19]. Therefore, further clinical trials are required to study the possibility of using systemic endotoxemia (SE) parameters for prognosing the course of postoperative (after coronary stenting) and follow-up periods to improve the patient's quality of life after endovascular interventions.

DEVELOPMENT OF THE CORONARY STENT TECHNOLOGY

As the PCI technology with stenting (stent technology) evolved, it became a common minimally invasive method to cure different CAD forms due to high procedural success, quality of life, and survival rate comparable to those coronary artery bypass grafting (CABG). Development of drug-eluting stents (DES) created on the basis of bare-metal stents (BMS) with addition of an anti-proliferative medication resolved the problem related to restenosis progression [20]. Release of the drug from the stent surface allows to regulate the intensity of inflammation occurring after coronary angioplasty and stent implantation and thereby inhibit neointimal hyperplasia in the region of blood vessel wall damage [21]. Clinical data confirm the long term (5-year follow-up) [22, 23] benefit of DES implanted in millions of CAD patients [24].

Technological progress led to development of DES with a unique hybrid coating combining passive and active components [25, 26]. The stent skeleton made of cobalt-chromium alloy with ultrathin 60 mm struts allows for perfect wall apposition, that is very important for regional blood flow [27] and stent endothelialization [28].

The metal body of the stent is completely covered with a thin passivation layer of amorphous silicon carbide (aSiC:H) that promotes stent endothelialization. The passivating effect of aSiC:H, which is a wide-bandgap semiconductor, consists in inhibition of electron transfer from the fibrinogen molecule with zero total electric charge in the non-excited state to the metal surface. Thereby, conversion of fibrinogen to fibrin (through electrostatic interaction of charged excited fibrinogen molecules) and its deposition on the stent surface are reduced [29]. Clinical studies [30] demonstrated that the passivation layer reduces adhesion and activation of blood platelets and leukocytes and significantly reduces release of potentially allergenic ions from the metal stent skeleton, the latter being especially important in long-term follow-up after stent implantation and total drug dilution.

Besides the silicon carbide layer, the stent body is completely covered by a biodegradable poly l-lactic acid (PLLA) polymer for limus delivery. PLLA has been approved for many medical applications since 1960s, and its advantages include high biocompati-

bility [31–33] and well-controlled solubility within 1–2 years, which contributes to gradual limus release, minimizing the inflammatory response over a longer period of time [34].

Sirolimus, a natural macrocyclic lactone isolated from *Streptomyces hygroscopicus* in the mid-1970s and approved by FDA for prevention of kidney transplant rejection in 1999, has immunosuppresive, anti-inflammatory, and strong anti-proliferative effects [35]. It inhibits activation of the rapamycin protein target and stops the cell cycle (progression from phase G1 to S). Therefore, sirolimus restricts proliferation of cells, including T-cells, and proliferation and migration of smooth muscle cells, thereby suppressing restenosis [36].

Sirolimus-eluting stents, as opposed to bare-metal stents, reduce neointimal hyperplasia [36]. Re-endothelialization of human coronary arteries occurs to the same extent in the BMS and DES groups [37, 38]. In various animal models and clinical studies [39–41], sirolimus-eluting stents, as opposed to BMS and polymer-coated stents, reduce neointimal hyperplasia. Additionally, early effective neointimal tissue maturation takes place [42, 43], and the risk of stent thrombosis drops by 25% in comparison to other new-generation DES [44].

According to the results of the BIOSTEMI trial, sirolimus-eluting stents with ultrathin struts showed excellent clinical results in most high-risk STEMI patients [7]. As the stent technology develops (approaches perfection) and related clinical outcomes improve, the problems of postoperative complications and optimization of drug therapy are coming to the forefront.

Myocardial remodeling in acute MI mediated by cytokines and inflammatory cells includes myocardial healing encompassing phagocytosis and resorption of necrotic tissue, hypertrophy of survived cardiomyocytes, degradation and synthesis of collagen, proliferation of myofibroblasts, angio- and vasculogenesis, and proliferation of progenitor cells. Death of cardiomyocytes and degradation of the extracellular matrix induce release of signals activating innate and adaptive immunity and determine the intensity of the inflammatory response. Inflammatory mediators are involved in adverse cardiac remodeling (dilatation) and HF progression. Timely suppression of proinflammatory mediators can protect the heart from excessive inflammation-induced damage. New approaches are required based on detection of biomarkers (first of all inductors) of systemic inflammation for identifying patients with high risk of restenosis. Drug treatment of these agents could improve clinical outcomes for patients after PCI during a long follow-up period [9, 45].

Identification of factors that increase the risk of in-stent restenosis, including cellular and inflammatory factors and blood markers, is a topical issue [10]. The role of SE (in its pathogenic form – ET aggression (EA)) in induction of atherogenesis is becoming more prominent [46, 47]. Therefore, studying the role of the lipopolysaccharide (LPS) factor in initiation of systemic inflammation, development of postoperative complications, and the rate of restenosis progression becomes more relevant.

INFLAMMATION AS A FACTOR OF CARDIAC PATHOLOGY

The immune aspect of CVD pathogenesis is well known: immune defense mechanisms are activated not only in any infection, but also in response to any stress impact [12], including ischemia, hemodynamic overload, intoxication, etc. There are several inter-dependent immune system components that can be involved in the pathogenesis. The main of them are proinflammatory cytokines, the durable effect of which leads to gradual destruction of myocardial extracellular collagen matrix, ventricular dilatation, and cardiomyocyte hypertrophy. These cardiac remodeling processes can become irreversible [48] and facilitate HF progression along with cytokine-induced enhancement of cardiomyocyte apoptosis.

Cytokines can be defined as a new autonomous system that regulates the main body functions, exists along with nervous and endocrine regulatory systems, and is primarily aimed at maintaining homeostasis upon penetration of pathogens and disruption of tissue integrity. Death of cardiomyocytes and degradation of the extracellular matrix in the infarcted myocardium induce signal release for activating innate and adaptive immunity and determine the intensity of the inflammatory response. The role of post-infarction inflammation in progression of ischemic inflammation is contradictory, and inflammatory mediators are involved in adverse cardiac remodeling (dilatation) and HF advancement.

The main cause of immunity activation in patients without commonly recognized attributes of inflam-

mation remains unclear. Along with neurohumoral factors, realizing their effect through activation of renin-angiotensin-aldosterone and sympathoadrenal systems, the key role in the pathogenesis belongs to proinflammatory cytokines, such as TNFα [49–52] and interleukins IL-1 and IL-6, that modulate cardiovascular system functions [12, 53]. The source of excessive cytokines can be "overstressed" cardiomyocytes [54] or peripheral muscle cells. However, data are available that cytokine release is provoked by endotoxins (ET), i.e. lipopolysaccharides (LPS) of Gram-negative bacteria, which are capable of penetrating into the systemic circulation through the impaired intestinal barrier.

Stagnation of venous circulation in the intestine, which is inevitable when the myocardium is damaged and the cardiac output drops, facilitates wall permeability for bacteria and/or their toxins, which, penetrating the circulation and interacting with the CD14-receptor (CD – cluster of differentiation) of immunocompetent cells, trigger synthesis of TNFα and other cytokines [13, 14]. The intestinal origin of ET and its transport into the circulation of patients without signs of active infection are confirmed by the fact that ET concentration in hepatic veins is significantly higher than in the left ventricle (LV) and pulmonary veins [55]. Absence of any difference between the TNFα levels in the pulmonary veins and in the LV presumably excludes the heart as the source of systematically increased cytokine level [56].

Endotoxin is considered as a fundamental trigger of cytokine storm, and chronic ET load is at least one of the reasons for immune response activation [57–59]. However, ET is also capable of causing a hypo-response to successive loads known as ET tolerance: repeated stimulation of monocytes leads to reduced production of TNFα, IL-1α, and IL-6 cytokines via the negative feedback mechanism [60–62]. The ET tolerance phenomenon, being a complex regulatory response of the body to inflammation, was studied at the level of changes in cellular membrane molecules, signaling proteins, pro- and anti-inflammatory cytokines, and other mediators [63, 64]. Therefore, the ET activity in the blood plasma, being a potential stimulator of immune activation, has pathogenic effects.

The ability of LPS to activate the immune response results from its interaction with TLR4, the key receptor of innate immunity, which is cardio-pathogenic in nature [65]. TLR4-mediated innate immune responses [66, 67] are capable of triggering myocardial defense after the ischemia-reperfusion sequence (I/R) [68, 69], but they are also involved in myocardial damage in the I/R sequence and HF advancement [66, 67, 70–72]. Lack of TLR4 [70, 71] or modulation of TLR4-mediated activation of the factor kappa-B (NFκB) [66] significantly reduces myocardial damage caused by I/R, improves restoration of the cardiac function, and reduces expression of inflammatory cytokines and adhesion molecule genes [72].

Inflammation in some form and with some severity grade is present almost in all main types of cardiac pathology. The pathogenetic and morphological patterns of inflammation are almost identical and independent of its localization, except for small variations in involvement of cellular elements in the process. It was shown that the risk of developing acute MI in CAD patients increases during outbreaks of influenza [18] and after surgical interventions. Recipients of transplanted hearts suffer from dramatically accelerated atherosclerotic damage to the coronary system.

Clinical studies demonstrate that low-grade inflammation is associated with the pathogenesis of serious chronic diseases, such as atherosclerosis [46], diabetes mellitus, and age-specific neurological diseases [73].

A correlation was discovered between the inflammation process and arrhythmias, in particular, paroxysmal atrial fibrillation (AF), often occurring after different interventions on the heart [74–76]. Increased levels of C-reactive protein (CRP) and proinflammatory TNFα and IL-6 cytokines in the blood plasma were found both in patients with paroxysmal and persistent AF [77–82], while higher CRP level was observed in persistent AF [77, 78]. Furthermore, the CRP level can be used to predict sinus rhythm restoration or AF recurrence in patients undergoing cardioversion [83, 84].

CRP and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), almost undetectable in healthy arteries, can form a cyclic mechanism with oxidized LDL (OxLDL) or L5 in proatherogenic conditions, while elevated LDL level induces CRP expression by endothelial cells [85]. In turn, that can increase LOX-1 expression, facilitating atherogenic

LDL capture by endothelial cells and appearing as a key phagocytic receptor (macrophage receptor) to bind OxLDL in atherosclerosis [86]. LOX-1 receptors mediate proatherosclerotic effects of OxLDL that lead to endothelial dysfunction, proinflammatory monocyte recruitment to the arterial intima, formation of foam cells, apoptosis of endothelial cells and vascular smooth muscle cells (VSMC), and destabilization and rupture of plaques [86].

Atherosclerosis and vascular restenosis develop with VSMC proliferation. Recent studies have demonstrated that VSMC proliferation is stimulated by LDL via TLR4 receptors, however, the signaling pathways are not completely studied [87]. It is necessary to understand their role and molecular mechanisms involved into control over VSMC proliferation stimulated by LDL via the signaling pathways of TLR4 receptors. ET can stimulate different signaling pathways, such as PI3K/Akt, MAPKs, and IRAK1/4, which then facilitate NF-kB expression for VSMC proliferation. Studying potential TLR4 signaling pathways of VSMC proliferation remains relevant, which can be a new therapeutic target for proliferative vascular diseases.

For further increase in the efficacy of CAD treatment, especially its severe forms, such as acute MI, new approaches based on biomarkers to identify patients with active inflammation or fibrosis are required, that could result in development of specific therapy. Timely suppression of proinflammatory mediators can protect the heart from excessive inflammation that can be a direct cause of plaque destabilization.

PROBLEMS AND PROSPECTS

Development of the stent technology has enabled to solve one of the problems of PCI, namely prevention of in-stent thrombosis and restenosis in early postoperative period. The problem of preserving the patient's quality of life in the longer term apparently cannot be solved only by improving the quality of the stent and the implantation procedure, for example, by applying control and visualization methods like optical coherence tomography [43]. Further efforts are needed to study the mechanisms of stenosis and restenosis, find inducers of atherogenesis, and search for measures to prevent or at least slow down the process. Identification of the role of systemic inflammation in atherogenesis is relevant, from the mechanism of its induction through SE (and the role of LPS and antibodies to it in this process) [18, 46, 47] to inclusion of the cytokine system in the process.

This topic is investigated in the Russian national prospective multi-center non-randomized non-interventional clinical study "BIOFLOW-III VIP Registry" organized for clinical evaluation of DES implantation efficacy in daily clinical practice [11]. One of the secondary endpoints of the study which is of great scientific interest is a working hypothesis on whether patient's inflammation status correlates with clinical outcomes – serious adverse events (SAE).

To prove the hypothesis, besides standard clinical and biochemical blood parameters, vulnerable inflammation parameters (VIP) are measured in the blood serum of patients upon inclusion in the study: IL-1, IL-6, CRP, cortisol, ET (LPS), antibodies (AB) to the hydrophobic region of the ET molecule (AB-LPS-PHOB), AB to the hydrophilic region of the ET molecule (AB-LPS-PHIL). These laboratory measurements are performed twice: during PCI and if the patient has serious adverse events in the course of 36-month follow-up.

The primary endpoint of the study is identification of target lesion failure (TLF) within 12-month follow-up due to cardiac death, target vessel Q-wave or non-Q wave MI, emergency CABG, and clinically driven target lesion revascularization (TLR).

Secondary endpoints also include TLF at 6 and 36 months of follow-up; target vessel revascularization (TVR) at 6, 12, and 36 months; target lesion revascularization (TLR) at 6, 12, and 36 months; stent thrombosis at 6, 12, and 36 months; clinical device success; clinical procedural (PCI) success; VIP registered during inclusion in the study; VIP registered during SAE.

Acquisition of data on the correlation between blood parameters and the frequency of SAE in patients will be relevant for optimizing dynamic FU of CAD patients after PCI. Along with the possibility to resolve the problem for a definite patient cohort, the study results might be promising due to general pathological meaning of VIP for developing a dynamic predictive algorithm of life- and health-threatening adverse events (including vascular catastrophes, HF decompensation, and different life-threatening forms of arrhythmia) with

the use of integrative data bases and digital health platforms [88]. The "BIOFLOW-III VIP Registry" findings will allow to gain insight into the problem of stent lifespan extension and could provide the basis for developing a follow-up algorithm for PCI patients using methods to normalize integrated SE parameters.

MEASURES OF ENDOTOXIN AGGRESSION PREVENTION AND ELIMINATION

Systemic inflammation is an attribute of life itself and an obligatory factor of homeostasis (intestinal LPS activates adaptive body systems, including the immune system) [19]. Its pathogenic form resulting from excessive LPS in the circulation is considered as a pre-disease or a universal pathogenic factor of human and animal diseases [89]. This approach is confirmed by clinical observations of patients with allergic disorders, autoimmune diseases, female infertility, idiopathic and viral uveitis, anorexia, obesity, type 1 and 2 diabetes, chronic viral pathology (including AIDS), and physical and psycho-emotional stress [19, 90–98].

The list of drugs, foods, food additives, and procedures that are able to lower the ET concentration in the systemic circulation is quite long [99–101]. It includes enterosorbents and foods rich in fiber; Bifidobacterium-containing products (live cultures) and foods (starch drinks, etc.) that envelope the intestinal mucosa; choleretic medications, products (garlic, etc.), and procedures (gallbladder cleanse etc.); antiviral medications with rectal administration; antibiotics (gentamicin, etc.) binding LPS in the circulation; bacteriophages and foods selectively eliminating various Gram-negative bacteria, which cause EA development; moderate physical and aquatic exercises; intravenous laser blood irradiation as a method to increase anti-endotoxin immunity; selective hemoadsorption (LPS filters) and immunodrugs – concentrate human AB to LPS (in critical states). Furthermore, development of new selective hemo- and enterosorbents on the basis of oligonucleotides appears to be promising [102].

CONCLUSION

Advances in endovascular methods of CAD therapy and prevention of acute cardiac pathology using coronary stents are evident. Achievements in stent technology refinement based on development and application of new materials allowing for a significant decrease in the rate of inflammatory complications (primarily thrombosis) in early postoperative period are impressive. This has permitted to decrease mortality and preserve work capacity of a large population cohort.

Further progress in vascular surgery can be achieved in extending stent lifespan. A clear understanding of the key role of systemic inflammation in development of restenosis in the stented coronary artery has appeared, that apparently develops according to the mechanisms similar to those in atherogenesis. Systematic understanding of the role of microbiota in the homeostasis and general pathology and the contribution of intestinal ET to adaptation and atherogenesis induction was shaped.

Methodological and methodical basis for studying the role of endotoxemia in the pathogenesis was developed. We identified the range of drugs, foods, additives, and procedures capable of preventing and/or stopping EA and systemic inflammation induced by it by affecting the inflammation inductor. The relevance of creating a new generation of anti-endotoxin agents using selective hemo- and enterosorbents on the basis of oligonucleotides was substantiated.

Due to the general pathological significance of the inflammatory process, further studies on the relationship between ET and cytokine system parameters are promising for developing a therapeutic concept of CAD patient management, including individuals after coronary stenting.

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Received 18.05.2020
Accepted 29.09.2020