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МИКРОСОСУДИСТАЯ СТЕНОКАРДИЯ: ПАТОФИЗИОЛОГИЯ СНИЖЕНИЯ КОРОНАРНОГО РЕЗЕРВА

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Microvascular Angina Pectoris: The Pathophysiology of Decreased Coronary Reserve

Резюме

Проведен обзор современной российской и зарубежной литературы, посвященной проблеме нарушенного коронарного резерва кровотока как проявления микрососудистой дисфункции. При поиске информации по этому вопросу использованы материалы следующих баз данных: РИНЦ, Best Evidence, Scopus, Elsevier, PubMed, Clinical Evidence, Cochrane Library. Нарушение коронарного резерва кровотока — важное проявление микрососудистой дисфункции и ключевой диагностический критерий микроваскулярной стенокардии. Оценка этого показателя имеет высокую прогностическую и терапевтическую значимость. Учитывая гетерогенность патогенеза, дальнейшие исследования необходимы для персонализированного подхода к лечению пациентов с микроваскулярной стенокардией.

Ключевые слова: микрососудистая дисфункция, коронарный резерв кровотока, ишемия, эндотелиальная дисфункция, гиперреактивность гладкомышечных клеток, ПЭТ, ОКТ, МРТ, CFR

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

A review of modern Russian and foreign literature on the problem of impaired coronary blood flow reserve as a manifestation of microvascular dysfunction has been conducted. When searching for information on this issue, materials from the following databases were used: RSCI, Best Evidence, Scopus, Elsevier, PubMed, Clinical Evidence, Cochrane Library. Violation of the coronary blood flow reserve is an important manifestation of microvascular dysfunction and a key diagnostic criterion for microvascular angina. The evaluation of this indicator has high prognostic and therapeutic significance. Given the heterogeneity of pathogenesis, further research is needed for a personalized approach to the treatment of patients with microvascular angina.

Key words: microvascular dysfunction, coronary blood flow reserve, ischemia, endothelial dysfunction, smooth muscle cell hyperreactivity, PET, OCT, MRI, CFR

Conflict of interests

The authors declare no conflict of interests

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MVA — microvascular angina, IHD — ischemic heart disease, CFR — coronary flow reserve, NO — nitrogen oxide, ED — endothelial dysfunction, CBF — coronary blood flow, ROS — reactive oxygen species, SOD — superoxide dismutase, IL-1, IL-6, IL-18 — interleukins 1, 6, 18, TNF- α — tumor necrosis factor alpha, CRP — C-reactive protein, NKcells — natural killer cells, TMAO — trimethylamine N-oxide, NF- κ B — nuclear factor kappa B, NLRP3 — NOD-like receptor family pyrin domain containing 3, CYP2C19 — cytochrome P450 2C19, HDL-C — high-density lipoprotein cholesterol, sST2 — soluble suppression of tumorigenicity 2, IL-33 — interleukin-33, hs-CRP — high-sensitivity C-reactive protein, suPAR — soluble urokinase plasminogen activator receptor, ET — endothelin, VCAM-1 — vascular cell adhesion molecule 1, ICAM-1 — intercellular adhesion molecule 1, PVAT — perivascular adipose tissue, PGI₂ — prostacyclin, EDHF — endothelium-derived hyperpolarizing factor, INOCA — ischemia with non-obstructive coronary arteries, CMD — coronary microvascular dysfunction

Introduction

Microvascular angina (MVA) is a specific form of ischemic heart disease (IHD), where clinical representation of angina is combined with the absence of angiographically significant stenosis of large epicardial coronary arteries [1]. Given clinical significance of microvascular angina, it is useful to discuss possible pathogenic mechanisms of its development. In their review, Kaski J-C et al. identify four key types of microvascular dysfunction: endothelial dysfunction, impaired regulation of resistance arteriole tonicity, structural vascular remodelling, and inflammatory and metabolic disorders [2]. These mechanisms can function both individually and in combination, forming a heterogenous clinical pattern of MVA in different groups of patients. One of the key pathophysiological mechanisms underlying MVA is an impaired coronary flow reserve (CFR), an important parameter of the coronary flow ability to increase myocardial perfusion in response to oxygen demand. The article describes contemporary ideas of CFR physiology, mechanisms of its impairment in microvascular dysfunction, diagnostic methods, and clinical significance of this phenomenon. CFR shows the ratio between the highest (hyperemic) and baseline (at rest) coronary flow [3]. Reduced CFR values demonstrate vascular system inability to adequately adapt to increased metabolic demand of the myocardium. Normal CFR value is > 2.5 . Any values below this level reflect microvascular dysfunction in the absence of anatomical stenosis of the main arteries.

The coronary blood supply has three functional components:

- Epicardial arteries ($> 500 \mu\text{m}$)
- Pre-arterioles ($100\text{--}500 \mu\text{m}$)
- Arterioles ($< 100 \mu\text{m}$), which regulate resistance to blood flow.

Regulation is based on metabolic, myogenic and endothelial mechanisms, with the participation of nitrogen oxide (NO), prostacyclin and endothelin-1.

Mechanisms of Coronary Reserve Impairment

Microvascular angina results from functional and/or structural changes in coronary microvessels, and a combination of both factors is not uncommon. Specifically, functional disorders causing MVA can manifest as impaired vessel dilation (abnormal vasodilation) and/or excessive narrowing of coronary microvessels (microvascular spasm). Impaired vasodilation can be a result both of endothelium-dependent and endothelium-independent mechanisms [9].

Endothelial dysfunction

Endothelial dysfunction (ED) means a pathological condition with imbalance between vasodilators, antimitogenic and antithrombotic substances (endothelium-dependent relaxants) and vasoconstrictors, prothrombotic and proliferative substances (endothelium-dependent constrictors) [11]. Besides, ED is associated with decreased bioavailability of nitrogen oxide (NO): its synthesis decreases and/or its degradation increases, thus restricting the vasodilative property of vessels. Studies showed that the presence of cardiovascular risk factors contributes to endothelial dysfunction, which causes persistent decrease in coronary blood flow (CBF) or vasoconstriction with evident myocardial perfusion impairment [9, 11]. Endothelial secretion imbalance leads to production of vasoconstrictors, such as endothelin-1, which cause changes in the systolic rhythm of coronary arteries and blood flow disturbances. These processes facilitate

deposition of metabolites in the myocardium, aggravate vascular endothelium dysfunction and can cause MVA [13].

Oxidative stress (ROS) and impaired arteriola autoregulation

Studies show that decreased bioavailability of nitrogen oxide (NO) together with higher production of reactive oxygen species (ROS) relates pro-inflammatory condition to endothelial dysfunction, observed in MVA [8]. Vasodilator-resistant endothelial dysfunction can lead to myocardial ischemia, especially during physical exercises.

MVA patients have vasoactive substance imbalance: higher levels of intercellular adhesion molecule 1, endothelin-1 and superoxide dismutase (SOD) activity, resulting in excessive accumulation of ROS. These vasoconstrictive factors are not compensated by endogenous NO and other vasodilators [3]. Although studies have partially invalidated the theory of endothelial causes of MVA, by showing reduced peripheral vessel response to endothelin in MVA patients, non-invasive methods of pulse-wave velocity evaluation showed similar disorders in vascular reactivity in patients with MVA and IHD [2, 3]. Endothelial dysfunction also stimulates precursor cell mobilisation from bone marrow, but their functional activity is impaired, causing incorrect proliferation [3]. Inflammation and impaired immune response speed up atherosclerosis development by impacting the microvascular system. The key role in the inflammatory cascade is played by interleukins IL-1, IL-6 and tumour necrosis factor alpha (TNF- α) [8].

Higher C-reactive protein (CRP) levels in MVA patients show the connection between disease pathophysiology and chronic inflammation. Immune system disorders, including NK cell activation and higher pro-inflammatory cytokine levels, contribute to vessel constriction and lymphocyte recruiting and increase oxidative stress.

In addition to immune diseases, chronic infections, e.g., *Helicobacter pylori*, are more often observed in MVA patients and can cause endothelial dysfunction because of incorrect immune regulation [3]. The interest in the role of intestinal microbiota in atherosclerosis has been recently increasing [8]. Metabolites, for instance trimethylamine N-oxide (TMAO), are produced from choline, betaine and L-carnitine in the presence of intestinal bacteria. Higher TMAO levels trigger NF- κ B signal path, boosting expression of pro-inflammatory genes, including cytokines, adhesion molecules and chemokines. TMAO also stimulates oxidative stress and activation of NLRP3-inflammasome and release of IL-18 and IL-1 β . Therefore, diet has a huge impact

on TMAO values and atherosclerosis progression [8]. A recent study in obese IHD patients showed that the use of probiotics, synbiotics and functional probiotic products contributed to control of plasma TMAO and HDL-C levels. Further studies are needed to assess the efficacy of TMAO inhibition in the management of atherosclerosis [8].

Support of the inflammatory component in MVA pathophysiology is evidenced by reduced levels of serum dihydroxyeicosatrienoic acid, one of the key epoxyeicosatrienoic metabolites, possessing anti-inflammatory and vasodilatory properties. This metabolite is formed in the presence of cytochrome P450 (CYP) 2C19, and in MVA patients a share of "bad metabolites" of this enzyme is higher, causing impaired vascular tone regulation and unrestricted vasoconstriction of small coronary vessels [3]. Platelet activation, which depends on eicosanoid reaction, is associated with increased expression of their soluble ligand CD40, stimulating further release of pro-inflammatory cytokines and facilitating development of pro-atherogenic processes [3]. At the same time, the serum concentration of soluble suppression of tumorigenicity 2 (sST2) receptor for interleukin-33 (IL-33) rises. Activation of this receptor is associated with development of heart fibrosis and endothelial dysfunction in MVA patients.

Another factor, which aggravates anti-inflammatory mechanisms in MVA patients, is vitamin D deficiency. Imbalance between pro- and anti-inflammatory agents is worsened even more by lower levels of high density lipoprotein cholesterol, which acts as endogenous inhibitor of vascular inflammation [3]. Studies showed that MVA patients have significantly lower serum vitamin D levels vs. healthy individuals, making it possible to consider vitamin D deficiency as a potential risk factor contributing to intensification of inflammatory processes, endothelial dysfunction and development of MVA [1]. Systemic inflammation is aggravated even more by circulating pro-inflammatory microparticles, which are thought to be responsible for NO modulation and release of cytokines, as well as monocyte recruiting [8]. Although the theory of inflammation is quite convenient, the data on beneficial effects of anti-inflammatory drugs on MVA pathogenesis are insufficient [3, 8]

Smooth muscle cell hyperresponsiveness and abnormal vasoconstriction in acetylcholine provocation tests

Acetylcholine is a vasoactive mediator, which triggers a vasospasm by activation of cholinergic receptors on smooth muscle cells of the vascular wall. In normal endothelium, acetylcholine causes vasodilation due to

stimulation of nitrogen oxide (NO) release. However, in endothelial dysfunction, the ability of endothelium to produce NO decreases significantly, leading to dominance of muscarine receptors of smooth muscles and development of vasoconstriction. In a microvascular spasm during an acetylcholine provocation test, the patient experiences ischemic changes on the electrocardiogram, and typical clinical symptoms of angina can be observed; at the same time, there are no angiographic signs of epicardial coronary artery stenosis [6].

Catecholamine hypersensitivity

The dominance of the adrenergic system in MVA patients is also evidenced by results of radionuclide scanning, which demonstrated impaired uptake of the tracer, an analogue of adrenalin, competing with endogenous catecholamines in vegetative nerve terminals of the heart muscle [2]. A similar conclusion is confirmed by disorders in the system of neural regulation of cardiac activity, which were assessed using a spectral analysis of RR segments and metabolic studies. Symptoms of adrenergic activation in MVA patients can partially result from tissue hypersensitivity to an unstable level of endogenous catecholamines. This adrenergic receptor hypersensitivity is likely not to be limited to cardiac and respiratory disorders and reflects the stimulating action of receptors in the bronchial tree and pulmonary blood flow in these patients. During physical exercises, intramuscular pH values and phosphocreatine levels drop rapidly, and it takes time for them to get back to normal values [3]. There are evidences of sympathetic dysfunction in vascular remodelling and microvascular complications. Some publications describe data on impaired parasympathetic tone and sympathetic dominance in MVA patients [14]

Microvascular inflammation and remodelling: the role of cytokines

Chronic low-level inflammation plays a key role in pathogenesis of microvascular dysfunction (MVD). Endothelium-dependent MVD, assessed via microvascular response to acetylcholine, correlates with higher levels of inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) and soluble urokinase plasminogen activator receptor (suPAR) [8]. The central mediators of an inflammation process are pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF- α) [3].

Immune cell activation is associated with release of endothelin (ET) and immunomodulatory activators of ET, causing endothelial dysfunction. During

inflammatory activation, higher expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) occur, boosting interaction between monocytes and endothelium. Higher monocyte integrin affinity contributes to their adhesion and migration via vascular wall, causing endothelial cell damage.

The signaling pathway, mediated by NOD-like receptor family pyrin domain containing 3 (NLRP3), has also a role to play in pathogenesis of microvascular damage. In ischemic reperfusion, heart microvessel cells (CMEC) demonstrate increased NLRP3 expression, caspase-1 activation, and significant rise in pro-inflammatory interleukin IL-1 β and IL-18 levels, resulting in localised inflammation and facilitating endothelial dysfunction [10]. Besides, damages in the signalling function of perivascular adipose tissue (PVAT) impact localised inflammation, atherosclerotic process and microvascular function regulation. Studies of isolated vessels showed that PVAT inflammation disturbs normal control of the microvascular function of skeletal muscles [7].

Perivascular fibrosis and vascular wall thickening

Structural abnormalities, related to coronary microvascular dysfunction, are mostly represented by narrowing of arteriole and capillary orifice, perivascular fibrosis and capillary depression, often with higher left ventricle weight. These events have been documented in patients with hypertrophic cardiomyopathy and hypertensive heart disease. In both conditions, observed morphological changes are described by unfavourable arteriole remodelling, causing medial wall thickening (mostly because of smooth muscle hypertrophy and increased collagen accumulation), and various degrees of intima muscle thickening, resulting in altered coronary physiology and CBF. An important common feature of these conditions is diffuse microvascular remodelling, involving the entire left ventricle [7].

Coronary microvascular dysfunction is associated with structural and functional remodelling of microcirculation, leading to impaired self-regulation of coronary blood flow. Endothelium is essential for CBF regulation through modulation of vasorelaxants, such as nitrogen oxide (NO), prostacyclin (PGI $_2$) and endothelium-derived hyperpolarizing factors (EDHF). Dysfunctional endothelium is a result of the action of pathological vasoconstrictors (such as endothelin-1, superoxide, hydrogen peroxide and thromboxane), which cause vascular imbalance. Besides, microvascular spasm involves impaired vasomotion (physiological beating) and is closely connected with the presence

of endothelial dysfunction [6]. Decreased CFR is associated with:

- A higher cardiovascular risk

Sixteen studies in 8,446 patients showed 3.7-fold increase in the risk of death in patients with abnormal CFR. This conclusion is important because total mortality is resistant to bias and is a clinically significant result. Also, abnormal CFR causes 3.4-fold increase in cardiovascular risk even with correction of some other prognostic factors in individual studies, such as age, hypertension, diabetes mellitus, dyslipidemia, smoking, and a history of myocardial infarction. On the average, decrease in CFR by 0.1 unit is associated with 16% increase in the risk of death. This conclusion demonstrates that CFR is a risk continuum, where lower levels predispose patients to more unfavourable clinical results [5].

- Poor prognosis in INOCA patients

INOCA (ischemia with non-obstructive coronary arteries) is a clinical syndrome with ischemic symptoms in the absence of a primary stenosis of the epicardial coronary artery of $\geq 50\%$. In the majority of cases, INOCA is caused by CMD (coronary microvascular dysfunction, including microvascular spasm), epicardial coronary spasm or a combined pathology. INOCA patients have worse quality of life and a higher long-term cardiac risk, recurrent hospital admissions and high healthcare costs. Predictive effects of CFR changes were studied in INOCA patients. In patients with abnormal CFR, long-term results, such as primary unfavourable cardiac events and target vessel insufficiency, rise vs. patients with normal CFR [4]. It was demonstrated that INOCA patients have lower quality of life. Moreover, the annual costs for INOCA patient management are very high because of frequent hospitalisations and repeated invasive tests [12].

- Resistivity to conventional antianginal therapy

Other drugs, such as ranolazine, ivabradine, nicorandil, can be used in MVA patients resistant to conventional therapy. Their main mechanism of action in MVA is boosting antianginal effects. Nicorandil can contribute to higher CFR levels. Studies of the use of trimetazidine in MVA patients show various results. All these drugs are considered to be stage 2 and 3 in the management of patients with refractory MVA [2, 12].

Therapeutic Approaches in Abnormal CFR

Despite heterogeneity of pathophysiologic mechanisms of MVA, baseline drug therapy is an important element of treatment. Conventional antianginal drugs, including β -adrenoceptor blocking agents, angiotensin-converting enzyme inhibitors (ACE inhibitors)/

angiotensin II receptor blockers (ARB), as well as calcium channel blockers (CCB), are currently the first-line therapy in MVA patients. If monotherapy is not efficient enough, a combination of agents can be used, particularly β -blockers and CCB.

In patients with an unstable angina threshold due to physical exercises, combined drug therapy with individually selected medications may be preferable. In the absence of clinically significant response to conventional therapy, it is recommended to consider alternative drug strategies with the use of nicorandil, ranolazine, ivabradine and estrogens, proton pump inhibitors, taking into account individual clinical and functional characteristics of the patient [16]. RAAS blockers (ACE inhibitors/ARB) facilitate improved endothelial function, increase CFR values in patients with microvascular dysfunction [17], while β -blockers reduce oxygen demand of the myocardium. Ivabradine prolongs diastole and improves coronary perfusion. Nitrates demonstrate limited clinical efficacy in MVA patients, which is the difference between the management of this pathology and conventional angina [16]. Ranolazine and nicorandil are promising drugs for the management of refractory MVA. Nicorandil, which can activate ATP-sensitive potassium channels and nitrate component, has a combined effect: it dilates blood vessels, improves coronary blood flow, reduces pre- and afterload, and decreases platelet aggregation. Protective effects of nicorandil are a result of antioxidative activity, inhibition of apoptosis and inflammatory myocardial response to ischemia, which is confirmed by preclinical and clinical studies [15]. The antianginal effect of ranolazine is possible due to late sodium current (late I_{Na}) inhibition in cardiac cells. In ischemia, pathological late sodium current is activated, causing Na^+ accumulation in the cell. It activates Na^+/Ca^{2+} exchange and leads to secondary intracellular accumulation of Ca^{2+} [18].

Therefore, reasonable selection of a drug therapy in microvascular angina should take into account individual characteristics of the disease and variability of clinical response to conventional antianginal agents. If the conventional approach is not efficient, alternative drugs can be used, for instance ranolazine, nicorandil, ivabradine, and RAAS blockers. Special attention should be paid to medications affecting pathological elements of microvascular ischemia, particularly to ranolazine, which treats ion imbalance at the cellular level, and nicorandil, which combines vasodilatory, antioxidant and cytoprotective properties [19, 20]. Combination therapy adjusted for the clinical and functional characteristics of the patient ensures more efficient control of symptoms and contributes to better prognosis in microvascular angina.

Discussion

More recently, MVA has been considered a clinically significant form of IHD, which is associated with dysfunction of coronary microvessels in the absence of epicardial artery obstruction. According to the results of recent randomised studies and large registries, the incidence of MVA in patients with suspected IHD, but without significant coronary artery stenosis is 30 to 50 % [21, 22]. One of the most large-scale studies describing the role of MVA in ACS is ISCHEMIA, where some patients with initially minor damage to large vessels were diagnosed with marked microvascular dysfunction with prognosis worsening and higher cardiovascular risk [23]. Similar data were confirmed in study CorMicA (Coronary Microvascular Angina), a randomised controlled study, demonstrating that the use of functional stratification of microvascular tone and an individual approach to therapy improved the quality of life and angina symptoms in this patient group [24]. Moreover, results of a subset analysis of women in WISE (Women's Ischemia Syndrome Evaluation) registry shows that microvascular ischemia in women is associated with a higher risk of cardiovascular death and cardiac insufficiency, underlining the clinical significance of MVA as a predictor of severe outcomes [25, 26]. Therefore, microvascular angina is no longer considered a benign condition. Recent data show its significance in the development of ACS and other unfavourable cardiovascular events and the need in early diagnosis and target therapy.

The main challenge of MVA is the array of clinical presentations and lack of understanding of pathogenesis of this condition. When assessing therapy efficacy, it is essential to consider not only antianginal therapy, which was discussed earlier, but also approaches to prescription of prognosis-modifying drugs [27]. Numerous studies prove that several renin-angiotensin-aldosterone system blockers can improve endothelial function and decrease cardiovascular risks, while statins have modulatory action in regard to cholesterol levels and inflammatory processes [28, 30]. Calcium antagonist therapy also has a role to play, because it can relieve symptoms by relaxing vessels and improving coronary blood supply [29, 30]. Antiplatelet drugs can be useful in reduction of the risk of clotting, which is particularly important in patients with comorbidities [30, 31]. The use of antioxidants is also very important, because they can decrease oxidative stress, which contributes to pathophysiology of microvascular angina [33]. Thus, a comprehensive therapy approach taking into account all various drug classes can considerably improve the quality of patients' life and reduce cardiovascular risks.

Conclusion

Chronic low-level inflammation is a key factor in the development and progression of microvascular dysfunction, which is proven by increased levels of proinflammatory cytokines and markers of systemic inflammation. Activation of immune cells and associated signalling paths, such as NLRP3 inflammasome, causes endothelial cell damage and impaired vascular homeostasis. Defective regulation of perivascular adipose tissue aggravates localised inflammation and functional microvascular disorders. These data emphasise the importance of a comprehensive approach to diagnosis and therapy of microvascular dysfunctions with due account of proinflammatory strategies, aiming at endothelial function normalisation and prevention of vascular complications. Further studies are needed for the development of efficient therapeutic interventions to modulate inflammatory processes and facilitate microvascular remodelling.

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