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БЕЗБОЛЕВАЯ ИШЕМИЯ МИОКАРДА У ПАЦИЕНТОВ ПОСЛЕ ПРОВЕДЕННОГО ЧРЕСКОЖНОГО КОРОНАРНОГО ВМЕШАТЕЛЬСТВА

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Silent Myocardial Ischemia in Patients after Permanent Coronary Intervention

Резюме

По данным литературы были проанализированы частота и срок возникновения ишемии миокарда, в том числе безболевой ишемии, у пациентов после проведенного чрескожного коронарного вмешательства. Фактором риска возникновения рестеноза стента у пациентов после чрескожного коронарного вмешательства является безболевая ишемия миокарда. Наличие безболевой ишемии миокарда само по себе может указывать на степень тяжести органических изменений в коронарных артериях. Следствием этого является необходимость выявления рестеноза, которое может осуществляться с помощью нагрузочных проб с визуализацией. Данные пробы также помогают выявить ишемию миокарда и скрытую коронарную недостаточность. Безболевая ишемия миокарда обнаруживается у четверти пациентов после чрескожного коронарного вмешательства. Безболевой инфаркт миокарда составляет 22-78 % от всех инфарктов после чрескожного коронарного вмешательства. Для определения наличия ишемии миокарда, в том числе скрытой коронарной недостаточности, а также с целью своевременной диагностики рестеноза и снижения частоты осложнений, могут быть использованы диагностические нагрузочные пробы, в частности, однофотонная эмиссионная компьютерная томография. Ее использование может быть целесообразно для выявления пациентов с высоким риском развития рестеноза, определения показаний к проведению повторного чрескожного коронарного вмешательства, а также для оценки прогноза после реваскуляризации. При отсутствии клинической симптоматики коронарной

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недостаточности после чрескожного коронарного вмешательства, пробы с физической нагрузкой рекомендуется проводить в первые два года после реваскуляризации. Пробы с физической нагрузкой необходимо проводить в более ранние сроки при следующих условиях: наличие высокого сердечно-сосудистого риска, неполная или субоптимальная реваскуляризация, стентирование коронарной артерии малого диаметра, бифуркационное или устьевое стентирование. Своевременная диагностика безболевой ишемии миокарда с помощью однофотонной эмиссионной компьютерной томографии у пациентов, перенесших чрескожное коронарное вмешательство, является важной задачей клинической практики.

Ключевые слова: *безболевая ишемия миокарда, чрезкожное коронарное вмешательство*

Конфликт интересов

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

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Abstract

Frequency and timing of appearance of myocardial ischemia, including silent ischemia, were analyzed in published scientific sources. Silent myocardial ischemia is risk factor for stent restenosis after percutaneous coronary interventions. Patients with silent ischemia lack clinical symptoms while perfusion, metabolic and electrical activity of their myocardium may be compromised. These patients do not have warning clinical symptoms during physical exercise and do not stop inappropriate activity. Silent myocardial ischemia itself can indicate severity of atherosclerosis in coronary arteries. High probability of stent restenosis can be assessed by exercise tests prior to coronary angiography. These tests also allow to reveal clinically silent myocardial ischemia. Quarter of patients after coronary intervention develop silent myocardial ischemia. Silent myocardial infarction comprises 22-78 % of all infarctions after coronary interventions. Exercise tests based on single-photon emitting computed tomography can be used in diagnosing stent restenosis, silent ischemia and assessment of cardiovascular risk in patients after coronary interventions. Its results can be used as indications for repeated coronary interventions and for prognosis after revascularization. Exercise tests are recommended in two years after revascularization in absence of ischemic symptoms. Early tests are recommended in cases of high cardiovascular risk, suboptimal revascularization, stenting of arteries with small diameter or at bifurcation. Diagnosis of silent myocardial ischemia by single-photon emitting computed tomography in patients after coronary revascularization is significant for clinical practice.

Key words: *silent myocardial ischemia, percutaneous coronary intervention*

Conflict of interests

The authors declare no conflict of interests

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24h ECG — 24h Holter ECG monitoring, CAG — coronary angiography, CHD — coronary heart disease, CKD — chronic kidney disease, DM — diabetes mellitus, ECG — electrocardiography, EchoCG — echocardiography, EF — ejection fraction, EL — exercise load, LV — left ventricle, MI — myocardial infarction, MRI — magnetic resonance imaging, PCI — percutaneous coronary intervention, PET — positron emission tomography, RF — radiopharmaceuticals, SCD — sudden cardiac death, SMI — silent myocardial ischemia, SPECT — single-photon emission computed tomography, stress echo — stress echocardiography

Introduction

Percutaneous coronary intervention (PCI) is widely used in the management of coronary heart disease (CHD). Its effectiveness is assessed by the elimination of episodes of myocardial ischemia, both painful and silent. Patients with silent myocardial ischemia (SMI) have no clinical manifestations, i.e. angina attacks or any equivalents, with underlying impaired perfusion, metabolism, function and electrical activity of the myocardium. In this regard, patients with SMI after PCI cannot control their level of physical activity because they have no pain as a limitation. Patients do not attempt to avoid factors that can lead to an angina attack or its equivalent. If patients have no clinical manifestations of disease progression, they may have no need to seek medical help. Therefore, the necessary treatment is not conducted on time. SMI leads to a worse prognosis in patients after PCI, with increased risk of myocardial infarction (MI) and sudden cardiac death (SCD) [1–4].

Myocardial ischemia after PCI and risk factors for restenosis

Restenosis is one of the complications after PCI. In patients without SMI, it is accompanied by the recurrence of angina pain or other clinical signs. Several factors that have an effect on the increase in the incidence of restenosis have been identified. They include: age, female sex, history of several diseases (diabetes mellitus (DM), chronic kidney disease (CKD), etc.), allergic reactions to metals, polymers and drugs, structural features of coronary vessels (stenting of small-diameter arteries), zones of atherosclerotic lesions (bifurcation or ostial stenting), etc. [5, 6].

A number of studies included the follow-up of patients who underwent PCI. Within two years, recurrences of myocardial ischemia were observed, which manifested as exertional angina, isolated SMI, or their combination. SMI was detected in 22.2 % of all patients with recurrent ischemia during exercise tolerance tests (EL). In rare cases, MI developed. In addition, recurrences of myocardial ischemia occurred more often during 3–8 months after PCI. If this process was due to stent restenosis, the recurrence developed earlier, within 3–6 months after PCI [7]. During 24h Holter monitoring (24h ECG), ischemic episodes were detected in 72 % of cases: 17 % of patients had only episodes of ischemia with classical signs of angina; 15 % had only silent episodes of ischemia (SMI type I). 40 % of patients had a combination of silent and painful ischemia (SMI type II) [8, 9].

After successful PCI, 14 % of patients showed signs of MI in the area of blood supply to the target vessel during exercise tolerance tests after six months of follow-up. Patients with SMI had a lower threshold of exercise load, which led to ischemia, compared to patients with angina without SMI episodes. The time of the onset of symptoms associated with stent restenosis after its placement ranged from 3 to 12 months; the average period of the development of stent restenosis after PCI was six months [10, 11]. Restenosis rates were found to range from 3 % to 20 % for drug-eluting stents and from 16 % to 44 % for non-drug-eluting stents. These data were obtained over a follow-up period of 3 to 20 months after stent placement [12].

The incidence of restenosis was 8–12 % in the period of 6 to 9 months after angioplasty, while three variants of ischemia recurrence were revealed: a pain attack, or SMI, or their combination [13]. Even after effective myocardial revascularization with a significant increase and stabilization of exercise tolerance, one year later, 54 % of the followed-up patients demonstrated an increase in the number of episodes, duration, and total index of painful ischemia and SMI compared with the results of examination one month after PCI with stenting [14].

Results of the 24h ECG in ten days and in three months after PCI were of prognostic value. Episodes of ischemia during these periods correlate with the increased incidence of CHD complications during one year of follow-up [15–17]. In a quarter of patients after PCI, restenosis may not be diagnosed in a timely manner due to the development of SMI [18].

According to 24h ECG results, in the group of patients with CHD who underwent stenting, SMI was detected in 6.6 % of cases after six months. According to the results of coronary angiography (CAG) in these patients, stent restenosis was found, which led to repeated stenting (stent-in-stent placement) [19].

The prevalence of silent MI after PCI is not fully understood. According to one study, silent MI (SMI) occurs in 3.7 % of patients [16]. A multicenter study was conducted, which included 15,991 patients who underwent PCI. Within two years after PCI, Q-wave MI was confirmed in 186 (1.16 %) patients; most cases (78 %) were classified as SMI due to the absence of clinical signs [20]. The actual incidence of SMI in this study was 0.9 %, which is four times lower than in the previous study. This difference is probably related to the follow-up period, which was limited to two years after PCI. Over time, the frequency of detection of MI, including silent MI, in patients increases [21, 22].

Patients with SMI found before PCI belong to a separate group. Clinical predictors of delayed adverse cardiovascular events in these patients remain unclear. The most common late events in this group of patients are acute coronary syndromes with and without ST elevation, revascularization, thrombosis of a previously placed stent, hospitalization for heart failure, and all-cause mortality. In their 2019 study that included follow-up for one and a half years, Doi S. et al. found late cardiovascular events in 10–15 % of cases; more than 60 % of them were due to repeated revascularization [23].

Factors of the development of late cardiovascular events in patients with SMI are CKD and DM, which increase the risk by more than eight times. CKD or DM can be an indicator of late adverse cardiovascular events in silent myocardial ischemia, even after a successful PCI [10, 23]. In patients who initially had SMI, even after a successful PCI and with complete or partial revascularization, there is a risk of SMI recurrence. It was found that after PCI, ischemia was found in one in every five patients with DM, and in half of the cases, it was silent [24].

Imaging methods used for the diagnosis of myocardial ischemia after PCI

When the myocardium is damaged due to its ischemia, the following pathological processes develop: perfusion heterogeneity, metabolic disorders, diastolic and systolic dysfunction of the left ventricle (LV), pathological changes according to electrocardiography (ECG) results. Then, the clinical presentation of angina or its equivalents develops.

In patients who underwent PCI, myocardial imaging should be performed with exercise tolerance tests. Non-invasive exercise tolerance tests help identify transient myocardial ischemia in a patient based on ECG changes, LV wall motion abnormalities on stress echo (stress echocardiography) or magnetic resonance imaging (MRI), or based on the occurrence/deterioration of myocardial perfusion, which can be detected during single-photon emission computed tomography (SPECT), positron emission tomography (PET), EchoCG with contrast enhancement, or MRI with contrast enhancement [25, 26].

Stress echo helps detect local contractility disorders associated with myocardial ischemia [27], while the location of the area of cardiac muscle contractility disorders most often corresponds to the areas of blood supply of the affected coronary artery. This method is helpful due to the detection of emerging impairments of regional contractility in short-term ischemia [28]. The following are key benefits of stress echo: imaging of each LV segment; assessment of changes during the test; multiple Echo-CG parameters of regional and global contractility; mobility of advanced ultrasonic devices; non-invasiveness; safety; good tolerance by patients; absence of ionizing radiation; the possibility of conducting repeated examination; relatively low cost. Sensitivity of stress echo with exercise load is 80–85 %, and its specificity is 80–88 % [27]. Shortcomings of stress echo include the poor quality of imaging heart structures in a number of patients; the human factor when processing the results; the quality of ultrasound imaging during the test; possible insufficient skills of the person conducting the test. To improve the quality of the visualization of the endocardium, special contrast agents are used ("microbubbles" coated with albumin, lipids or other polymers) [28]. The problem of the human factor in analyzing the results of stress echo can be solved with the help of tissue Doppler sonography [29, 30]; its results depend on the scanning angle, movement of neighboring myocardial regions, as well as movement of the entire heart. The possibility of analyzing myocardial deformation based on the speckle-tracking technique, which does not have the disadvantages of tissue Doppler sonography, for the quantitative assessment of myocardial kinetics during stress echo has been studied in recent years [31–33]. A description of stress echo is given in Figure 1.

Cardiac MRI is the method that allows determining the volume of heart cavities, the amplitude of movement of sections of the heart muscle, and ejection fraction. The resolution of this imaging method increases during exercise tolerance tests. The myocardial inotropic reserve is assessed via MRI and dobutamine test. The accuracy of examination increases with contrast enhancement. The sensitivity of stress perfusion MRI is 89 %, specificity — 80 %. New impairments of LV wall contractility (in three of 17 segments) or perfusion defect >10 % (more than two segments) may indicate a high risk of complications. The benefits of stress MRI include high spatial resolution and good reproducibility. Stress MRI is used in individuals with poor cardiac imaging on Echo-CG. MRI has contraindications, such as claustrophobia in a patient or foreign metal objects in the patient's body [34]. A description of MRI is given in Figure 2.

SPECT and PET help visualize the entire spectrum of myocardial viability: irreversible changes (postinfarction cardiosclerosis, fibrosis), transient ischemia, hibernation and myocardial stunning processes. CT absorption correction and the most advanced software improve image quality, allowing the visualization of increasingly small perfusion impairments [34].

The great significance of SPECT in the comprehensive analysis of the state of the heart muscle has been proven [35–37]. It helps find the first signs of impaired metabolism, perfusion, myocardial viability in the absence of angina attacks or their equivalents in a patient. Ischemia or damage to the myocardium leads to areas of reduced accumulation — perfusion defects. Synchronization with the patient's ECG allows using SPECT to observe the movement of myocardial walls depending on the phases of the heart cycle and assess the functional state of the LV myocardium, obtain additional information about the presence of reversible myocardial dysfunction

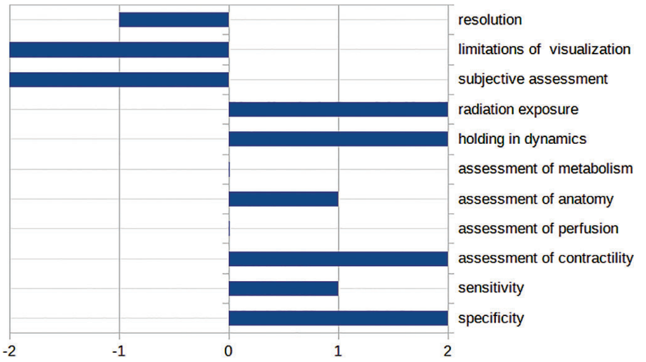

Figure 1. *Characterization of Stress-EchoCG*
Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

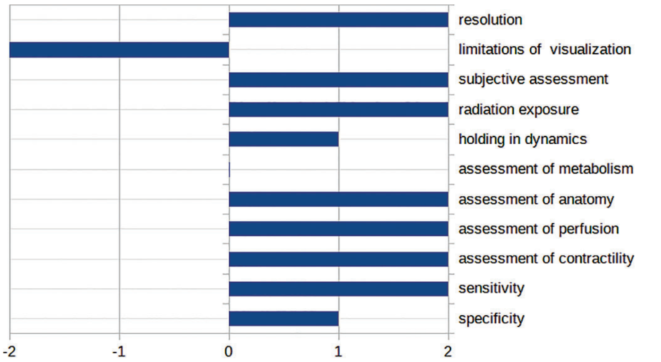

Figure 2. *Characterization of MRI*
Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

and its severity. In addition, global and local LV contractility is assessed, a quantitative analysis of LV systolic and diastolic functions is performed, and the diagnostic value of the examination increases. According to the literature, the sensitivity and specificity of SPECT are 87 % and 76 %, respectively. Synchronization with ECG increases the specificity of this method to 96 % [38–42]. SPECT results, primarily myocardial perfusion parameters, help define prognosis by suggesting the level and grade of coronary artery disease. However, data obtained during stress tests are more informative. The sensitivity and specificity of exercise tolerance tests are on average 85–90 % and 70–75 %, respectively [43]. Mortality in patients depends on the area of transient ischemia. It was found that with values of more than 20 % of the total LV area, it reaches 6.5 % per year. In addition, it was found that the development of ischemia in patients after MI around the scar area increases the risk of cardiac death compared with the identification of ischemic areas that are not associated with the scar. SPECT helps identify patients with the risk of restenosis, considering the presence, grade and area of ischemia that developed after an exercise tolerance test, its localization, transient LV dysfunction, and a decrease in LV ejection fraction. The advantage of SPECT, according to the "rest/stress" protocol, is the ease of use. At the same time, radiation exposure should be considered during repeated procedures [44–46]. A description of SPECT is given in Figure 3.

The advantage of PET is using radiopharmaceuticals (RF) to determine viable myocardium; one of such agents (13NH3, 82Rb-chloride, H215O) shows the state of cell perfusion, and another (18F-FDG) represents the level of glucose consumption by the myocardium, which, in the case of reversible ischemia, can be preserved or even increased. PET includes a range of metabolic radiopharmaceuticals, both for assessing fatty acid oxidation and for evaluating the functioning of the Krebs cycle and glycolysis. The technical advantage of PET over SPECT is its higher resolution and adjustment of the attenuation of photon radiation by soft tissues [27]. However, PET is not used often in clinical practice due to its high cost. The use of ultra-short-lived radioisotopes also limits the widespread use of PET [34]. A description of PET is given in Figure 4.

Table 1 presents the advantages and disadvantages of certain methods of non-invasive diagnosis of myocardial ischemia that can be used in patients after PCI (adapted [47]).

Management of patients after PCI

Based on the results of studies performed, recommendations were developed for the follow-up of patients after PCI. The ADORE study (Aggressive Diagnosis Of REstenosis) showed that there was no need to screen patients for SMI using ECG with exercise tolerance tests in six weeks and stress test with SPECT in six months after PCI compared with performing stress tests in patients with previously diagnosed painful myocardial ischemia. There was no significant difference between the groups of patients with painful myocardial ischemia and ischemia without clinical signs in predicting the likelihood of myocardial infarction, survival, functional state, quality of life, and frequency of invasive cardiac procedures after nine months of follow-up after PCI. The choice of the individual management approach for patients after PCI is of great importance; it depends on clinical and angiographic risk factors for the development of restenosis [6, 48, 49]. To confirm the preserved results of the resolution of coronary artery lesions in the absence ischemia signs in patients who underwent PCI, an exercise tolerance test should be performed after incomplete or suboptimal revascularization, as well as for patients who had silent myocardial ischemia before PCI [50].

Patients in a stable condition after PCI should undergo prophylactic medical examination once every six months [51]. If there are no clinical signs after PCI, it is recommended to conduct exercise tolerance tests no earlier than two years after revascularization [52].

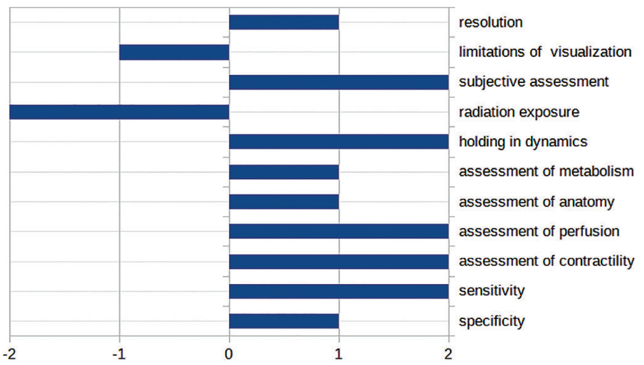

Figure 3. *Characterization of SPECT*

Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

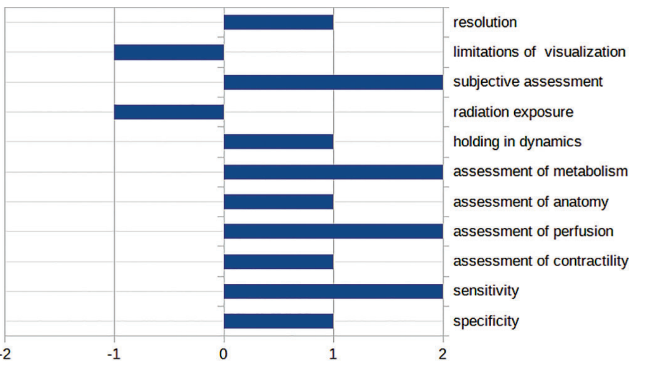

Figure 4. *Characterization of PET.*

Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

Table 1. Advantages and disadvantages of methods for non-invasive diagnosis of myocardial ischemia

Methods	Advantages	Disadvantages
Stress-EchoCG	• higher specificity than in radionuclide methods and MRI • multiple indicators of contractility • mobility of devices • non-invasive technic • good tolerance by patient • no ionizing radiation • safe for repeated use • high availability in clinics	• lower sensitivity than in radionuclide methods and MRI • poor visualization in some cases • technical difficulties during stress test • subjective assessment • depends on experience of operator
SPECT	• higher sensitivity compared to Echo-CG • combined study of perfusion and contractility	• radiation exposure • limited spatial resolution • low temporal resolution • lower specificity in Echo-CG • low availability • duration of procedure • uncertain data for basal inferior wall and apical septum • lower sensitivity for multiple coronary artery lesions • side reactions to RFP • limitations for patient's weight
MRI	• detection of scar tissue • possibly combined with perfusion assessment	• unsafe for pacemakers and cardioverters-defibrillators • lower risk for patients with renal insufficiency • arrhythmia/tachycardia impair image quality • claustrophobia and motionless issues • low availability • foreign metal objects
PET	• assessment of metabolism and perfusion • quantitative measurements • high resolution • correction of attenuation by soft tissues	• lower spatial resolution • exposure to radiation • limited availability

Note: MRI — magnetic resonance imaging, SPECT — single photon emission computed tomography, PET — positron emission tomography, RFP — radiopharmaceuticals, Stress-EchoCG — stress-echocardiography, EchoCG — echocardiography

A number of researchers recommend using radionuclide research methods after revascularization in patients with no signs of ischemia during the first two years after PCI [46].

Active clinical examination and follow-up of all patients after coronary artery stenting, especially women, is recommended, with exercise tolerance tests within nine months after intervention in the absence of pain syndrome or at any time in case of angina recurrence [25, 53, 54].

Summary

SMI is a risk factor for stent restenosis in patients after PCI. The presence of SMI itself may indicate the severity of organic changes in coronary arteries. Therefore, restenosis diagnosis is required, which can be carried out using stress tests with imaging, which helps determine myocardial ischemia and latent coronary insufficiency. Using SPECT to monitor the condition of patients after PCI with stenting is required to identify patients with a high risk of developing restenosis, determine indications for repeated PCI, and evaluate the prognosis after revascularization. Timely diagnosis and management of SMI in patients who underwent PCI are critical issues in clinical practice.

Conclusion

Timely diagnosis and management of SMI in patients who underwent PCI are critical issues in clinical practice.

Вклад авторов:

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

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