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Assessment of calcification of the coronary arteries and long-term prognosis of cardiovascular disease

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ABSTRACT

Vascular calcification is a distinctive feature of cardiovascular diseases of atherosclerotic origin. Visualization of calcifications is carried out by invasive and non-invasive methods. Knowledge of the presence and degree of calcification can predict clinical outcomes in patients at high risk of coronary events, help in the prevention and treatment of coronary heart disease.

The article presents a brief description of the methods of visualization of vascular calcium and a review of studies on the relationship of calcification with the risk of long-term adverse cardiovascular events.

Key words: calcification, coronary atherosclerosis, methods of assessing vascular calcification, cardiovascular disease

List of abbreviations: IVUS - intravascular ultrasound, CHD – coronary heart disease, CAG – coronary angiography, MSCT – multispiral computed tomography, OCT – optical coherence tomography, CVD – cardiovascular disease.

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Оценка кальцификации коронарных артерий и отдаленный прогноз сердечно-сосудистых заболеваний

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РЕЗЮМЕ

Сосудистая кальцификация является отличительной чертой сердечно-сосудистых заболеваний атеросклеросклеротического генеза. Визуализация кальцификатов осуществляется инвазивными и неинвазивными методами. Знания о наличии и степени кальциноза могут предсказать клинические исходы у пациентов с высоким риском коронарных событий, помочь при проведении профилактики и лечении ишемической болезни сердца.

В статье представлены краткая характеристика методов визуализации сосудистого кальция и обзор исследований по изучению связи кальцификации с риском отдаленных неблагоприятных сердечно-сосудистых событий.

Ключевые слова: кальцификация, коронарный атеросклероз, методы оценки кальцификации, сердечно-сосудистые заболевания.

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

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INTRODUCTION

Coronary heart disease, which is based on atherosclerosis, remains one of the main causes of morbidity and mortality in all countries of the world. Vascular calcification is a hallmark of the atherosclerotic process. Despite the abundance of clinical data, the fundamental role of calcification in rupturing an unstable atherosclerotic plaque is still unclear. Visualization of the structural features of calcification in coronary arteries using invasive and non-invasive methods can be important for predicting plaque rupture, and knowledge of the presence / degree of calcification can provide an idea of the level of risk of cardiovascular disease and can help in the prevention and treatment of coronary heart disease (CHD) [1–3].

CALCIUM ASSESSMENT METHODS

The total indicator of coronary artery calcium, determined using invasive and non-invasive imaging methods, provides additional value compared with traditional risk indicators for identifying patients with a high risk of cardiovascular disease [4, 5]. Invasive methods include x-ray coronary angiography (CAG) and optical coherence tomography (OCT). Non-invasive methods include radiography, multispiral computed tomography (MSCT), single-photon emission tomography, positron emission tomography and others. These methods have their advantages and disadvantages.

INVASIVE METHODS

The main methods for assessing damage to the coronary arteries are endovascular methods. The advantages of these methods are the direct visualization of the lumen of the vessel, the installation of sensors near the atherosclerotic plaque, which allows the most reliable assessment of the severity of deposition of atherosclerotic masses and their calcination.

Coronary Angiography. Coronary angiography is still one of the leading methods for the diagnosis and treatment of coronary insufficiency. Coronary angiography allows for the obtainment of the most complete picture of the anatomy and degree of damage to the coronary artery bed. The disadvantages of this research method include the use of x-ray radiation and the introduction of contrast agents. In addition, coronary angiography can provide only a two-dimensional outline of the coronary lumen and cannot fully demonstrate the complex nature of atherosclerotic plaques, which are responsible for the relationship between angiographic data and clinical outcome [6]. To identify the morphological features of calcified plaques, 3D virtual intravascular endoscopy is used, which, as shown, provides additional information about the wall of the coronary arteries and plaques [7].

Recently, classical CAG has been replaced by intravascular ultrasound and optical coherence tomography.

Intravascular ultrasound. One of the most informative and specific methods for determining atherocalcinosis is intracoronary ultrasound using high resolution sensors. This technique allows you to clarify the degree of the initial lesion of the coronary bed, to carry out effective control during x-ray endovascular interventions. In contrast to X-ray contrast angiography, intravascular ultrasound examination makes it possible to obtain a section of the vascular wall in several planes, allowing quantitative and qualitative assessment of the lumen of the vessel, the area of distribution of the plaque and its calcification, and the presence of a pronounced acoustic shadow. Factors limiting the use of IVUS include a feature of the coronary artery topic, impeding sensor advancement, and microvascular lesion nature. The possibilities of IVUS are significantly expanded by means of spectral analysis of the data obtained, in which the 4 main components of the atherosclerotic plaque are assigned the corresponding color coding. Such an analysis is called virtual histology. IVUS with virtual histology can detect the most dangerous type of atherosclerotic plaque [8]. Using IVUS with virtual histology Noto T. et al. (2015) observing patients with acute coronary syndrome, showed that with a calcium content of > 3.4% of the area of atherosclerotic plaques, the frequency of coronary events increased by 4.4 times [9].

Optical coherence tomography. Optical coherence tomography is an intravascular light-optical imaging technique that uses laser radiation with a wavelength of 1300 nm to obtain information about the three-dimensional structure of the vascular wall. Recently, OCT has become the leading technology of intracoronary imaging with a higher resolution (10–20 μm) than IVUS (100–200 μm) [10, 11].

In contrast to intravascular ultrasound, OCT is able to estimate the thickness of calcium and, consequently, the area and volume. This method has a number of advantages, such as high resolution sensors, short-term investigation, and the possibility of reconstructing visual and easy-to-interpret images in various planes. However, OCT has limitations on the depth of penetration through tissues, which is <2 mm, and this significantly affects the role of OCT in the evaluation of plaques [7, 12].

A study by Habara M. et al. (2018) aimed at assessing the characteristics of vascular calcification in vivo using OCT as compared with histological data, showed that OCT does not allow microcalcifications to be seen [13], but can show spotty or speckled calcification, which is smaller than macrocalcification, but larger than microcalcification [14]. Also, using the OCT method it is difficult to detect calcifications located behind the necrotic nucleus of an atherosclerotic plaque [15].

NON-INVASIVE METHODS

Since invasive interventions have a number of contraindications and a high risk of complications, high-tech methods of non-invasive imaging are increasingly used in medical practice.

Radiography. The detection of coronary calcification using x-ray was already used in the 30s of the twentieth century. The technique has some limitations in its application, when conducting an x-ray of the chest organs, only large calcifications can be detected and their extent can only be estimated indirectly. The X-ray method is the main method of radiation diagnostics at the first stage of medical care, and subsequently requires more high-tech methods, such as computed tomography, magnetic resonance imaging, positron emission tomography, etc. However, in recent years, the introduction of digital technologies has increased the capabilities of radiography. Sultanova M.D. (2017) studied the possibilities of digital radiography in the diagnosis of coronary calcifications on 90 patients and compared the results with multispiral computed tomography. The author noted that the detection of coronary calcifications during digital radiography is limited to certain values of the calcium index and this method can be recommended as a screening diagnosis of the risk strategy for cardiovascular diseases [16].

CT scan. The main method for quantifying coronary artery calcification is computed tomography. When synchronized with electrocardiography, computed tomography can detect and quantify even small deposits of coronary calcium and, accordingly, assess the presence and severity of coronary atherocalcenosis. According to a standardized quantitative system for measuring coronary calcification, the amount of coronary calcium is expressed in units of the calcium index. The calcium index is calculated according to the standard Agatston method [17] and is determined by multiplying the area of calcified lesion by the density factor. The density factor is calculated by the peak density in the calcification zone and is 1 for calcinates with a density of 130–199 HU, 2 for lesions with a density of 200–299 HU, 3 for 300–399 HU and 4 for calcinates with a density of more than 400 HU. The total calcium index is calculated as the sum of the indices on all slices [18].

Positron emission tomography. Positron emission tomography (PET)/CT using ^{18}F-sodium fluoride (^{18}F-NaF) has the potential of non-invasively identifying microcalcification [19–21]. Irkle et al. (2015) have shown that ^{18}F-NaF is adsorbed by calcified deposits inside a high atherosclerotic plaque affinity and is selective and specific. In addition, PET/CT using ^{18}F-NaF makes it possible to distinguish between macro- and microcalcification regions [22]. Molecular imaging can diagnose atherosclerosis at an earlier stage, including in pre-symptomatic patients, and may be another option for detecting vulnerable plaques and predicting future adverse cardiovascular events [23].

ASSESSMENT OF CORONARY CALCIFICATION AND PROGNOSIS OF RISK OF LONG-TERM ADVERSE CARDIOVASCULAR EVENTS

Evaluation of coronary calcification is important for predicting the risk of long-term adverse cardiovascular events in patients with various forms of coronary atherosclerosis, including subclinical. Shaw L.J. et al. (2015) using electron beam computed tomography, determined the coronary calcification index in 9715 patients of different sexes and ages without the clinical manifestations of coronary artery disease, followed up for 15 years. High coronary calcification indices were associated with males, old age, and diabetes mellitus dyslipidemia and smoking. The authors noted that in patients with even a low level of arterial calcium, the overall risk of mortality is almost 70% higher than in those who did not have any calcium deposits, and in patients with the largest calcium deposits, this risk is six times higher. Researchers noted that the degree of calcification of the coronary arteries predicts 15 year mortality in asymptomatic patients [24].

Genereux P. et al. (2014) included in the study about 7000 patients with acute coronary syndrome who underwent coronary angiography. In 32% of patients, severe and moderate calcification of the infarction-associated artery was noted. It was these patients who had recurrent adverse cardiovascular events more often during the year after acute coronary syndrome. The authors noted that moderate / severe calcification was more common in older people, patients with hypertension and myocardial infarction with ST-segment elevation. The authors also noted gender differences; more pronounced calcification was in men [25].

Blaha M.J. et al. (2016) studied more than three thousand patients with an initial coronary calcification coefficient> 0. Observation was conducted for about 10 years. During this time, 368 cases of CHD and 493 cases of CVD were identified. The authors showed that taking into account the number of calcified vessels together with the determination of the overall calcification index can improve the prognosis of adverse cardiovascular events [26].

Based on the results of the CARDIA study, which included more than 5,000 young participants observed over 30 years, in which coronary calcium was measured 15, 20, and 25 years from the start of the study, Carr J.J. et al. (2017) concluded that the presence of coronary calcification among individuals aged 32 to 46 years is associated with an increased risk of fatal and non-fatal coronary artery disease during 12.5 years of follow-up. The authors noted that a coronary calcification coefficient of 100 or more is associated with early death, and study participants younger than 50 years old with any level of coronary calcium, even with very low rates detected by computed tomography, have an increased risk of clinical coronary artery disease, CVD and death [27].

Lutai M.I. and Golikova I.P. (2017) studied 142 people with coronary artery disease or suspected coronary artery disease. In order to detect coronary calcification, all patients underwent MSCT; the diagnosis was verified by coronary angiography. The authors also evaluated the degree of calcification of the aorta. The authors concluded that calcification of the coronary arteries and aorta significantly increases with age, higher in the presence of diabetes mellitus, arterial hypertension, and hypercholesterolemia. Patients with a high coronary calcium index were more likely to have had myocardial infarction and had a family history of CHD aggravated than patients with low calcium index [28].

The severity of calcification of the aorta and coronary arteries is an independent predictor of cardiovascular mortality. Hoffmann U. et al. (2016) studied coronary artery calcium, thoracic and abdominal aorta, mitral and aortic valve using computed tomography of the heart in people without cardiovascular disease at the time of observation. The study included 3217 participants, the average age of which was 50 years, half of which were women. Participants were observed for an average of 8 years. The authors evaluated the possibilities of predicting coronary heart disease, CVD, and mortality from all causes by the level of vascular calcification and compared with the data obtained using the Framingham scale. According to the authors, calcification of the abdominal aorta and coronary artery was most common, while calcification of the thoracic aorta and valves was less common. Coronary artery calcium was most strongly associated with CHD, CVD, and all-cause mortality, regardless of the risk factors of the Framingham scale. Moreover, with an increase in the initial level of calcium, the risk of adverse events increased. The modified

Agatston index 101 and higher indicated a significant risk of developing coronary heart disease and CVD. The degree of non-coronary calcification also identifies individuals with a higher risk of developing coronary heart disease and CVD, regardless of risk factors [29].

Lehmann N. et al. (2018) studied risk factors and performed CT at the beginning of the study and after five years in 3281 people, without cardiovascular events at the beginning and within 5 years of observation. Severe coronary and cardiovascular events, as well as general cardiovascular events, including revascularization, were recorded after a second CT scan for 10 years. The authors established a high prognostic value of coronary calcium in relation to coronary and cardiovascular events, as well as mortality from all causes. A particularly pronounced relationship was shown in patients with coronary calcium levels in the first stage of the study> 400. These patients had high rates of severe coronary and severe / general cardiovascular events (10-year risk: 12.0%, 13.5%, and 30.9%, respectively). An increase in coronary calcium> 400 at the second stage of the study led to an almost twofold increase in the risk of coronary and general cardiovascular events compared with individuals whose level of this indicator during repeated CT did not exceed 400. In patients with zero calcium level at two stages of CT 10- summer risk was 1.4%, 2.0% and 2.8% [30].

Paixao A.R. et al. (2015) in their study evaluated the effect of coronary artery calcification on predicting the risk of coronary heart disease in a younger population (44.4 ± 9.0 years). The study included 2084 patients without diabetes and cardiovascular disease. In a young multinational cohort, according to the authors, adding the definition of coronary calcium to a model consisting of traditional risk factors for coronary heart disease significantly improved discrimination and risk classification [31].

Criqui M.H. et al. (2017) having examined 6814 men and women who at the time of registration did not have clinical manifestations of cardiovascular diseases, concluded that the volume of calcification of the coronary artery is positively and independently associated with the risk of coronary artery disease and CVD, while the density of calcification for any volume is inversely proportional and reliably associated with the risk of coronary heart disease and CVD [32]. Forbang N.I. et al. (2016) using computed tomography in a multinational cohort of 997 participants with an Agatston index> 0 determined the volume and density of calcification of the abdominal aorta and coronary arteries. The observation was carried out for 9 years. They studied the association of the volume and density of calcification with CHD, CVD, and death from all causes. In models adjusted for factors of cardiovascular disease, an increase in the volume of calcification of the abdominal aorta was associated with an increase in mortality from all causes, and in coronary arteries, with coronary artery disease and CVD. Unlike previous researchers, Forbang's calcification density was not significantly associated with CVD [33].

Puchner S.B. et al. (2018) investigated using computed tomography of patients with and without acute coronary syndrome. The authors noted that a low level of local calcium indicates plaque instability, while a high level of high density calcium may be a marker of plaque stability, despite the fact that a higher overall score of the coronary calcification index is a marker of increased cardiovascular risk [34].

In addition to the volume and density of calcium in the coronary arteries, data on the structural characteristics of calcifications have predictive value. Studies show that microcalcification is more common in unstable plaques, while stable plaques are characterized by larger deposits [35, 36]. Kataoka Y. et al. (2014) by studying OCT patients with stable coronary artery disease who have clinical indications for percutaneous coronary intervention showed that spotted calcification indicates a greater vulnerability of plaques [37]. Later Sakaguchi M. et al. (2016) examined patients with acute coronary syndrome, with and without rupture of a plaque. The authors showed that more often spotted calcification tends to be located near the site of plaque rupture, while analysis of spotted calcification is an independent prognostic factor for plaque rupture [2].

CONCLUSION

Assessing coronary calcium, in addition to traditional risk factors, provides valuable, long-term prognostic information for assessing the risk of coronary heart disease and cardiovascular disease of atherosclerotic origin. In the future, the determination of calcium density indicators, regional and extra-coronary calcification, which are prognostic for the risk of coronary heart disease and CVD, regardless of the Agatston indicator, can further improve the risk assessment, which will allow the clinician to prescribe preventive pharmacotherapy taking into account the assessment of the 10-year risk of coronary heart disease in their patients. Knowledge of the morphological features of the plaque can affect treatment strategies for the prevention of acute coronary syndrome and may be useful in understanding the pathophysiological mechanisms of plaque rupture.

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