# Clinical Molecular Imaging for Atherosclerotic Plaque

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Contributor: Anton Kondakov

Atherosclerosis is a well-known disease leading to cardiovascular events, including myocardial infarction and ischemic stroke. These conditions lead to a high mortality rate, which explains the interest in their prevention, early detection, and treatment. Molecular imaging is able to shed light on the basic pathophysiological processes, such as inflammation, that cause the progression and instability of plaque.

Keywords: atherosclerosis ; plaque ; molecular imaging ; PET/CT ; FDG ; radiotracers ; 18F sodium fluoride ; vulnerable plaque

## 1. Introduction

The concept of “vulnerable plaque” was first proposed by J. Muller et al. in 1989 to designate atherosclerotic plaques that do not affect hemodynamics, but at the same time are dangerous from the point of view of thrombosis [1]. Histopathologically vulnerable plaques are usually described as thin-capsule fibroatheromas [2]. The concept of unstable plaque is more often used for symptomatic plaques that have realized their potential by giving rise to a vascular event (ischemic stroke, acute coronary syndrome, etc.). It is proposed that this term is used to refer to the clinical syndrome as a whole but not to individual examples of damage [3], and in general, that its use is a less common practice.

In 2003, M. Naghavi et al. proposed the introduction of the term “vulnerable patient” to refer to those people who have a high risk of developing cardiovascular accidents in the near future [4]. It was assumed that plaque destruction and subsequent thrombosis in these individuals were more likely to manifest as a coronary event in the simultaneous presence of three circumstances: a vulnerable plaque, a tendency to thrombosis due to corresponding blood changes, and an electrically unstable myocardium.

However, calcification of vascular walls and plaques themselves occurs at a later stage, and the mechanisms by which vulnerability develops are triggered much earlier. In this regard, the search for various technologies and techniques that allow timely objectification of the risk criteria for atherosclerotic lesions in asymptomatic individuals, with a view to preventive correction and prevention of vascular events, is relevant for practice. Great hopes for detecting plaque instability are pinned on the technologies of diagnostic nuclear medicine and the specific tracers that target certain biomarkers and pathophysiological processes that accompany the process of plaque transition to an unstable state [5]. In this review, we analyze only those tracers that are readily available for clinical implementation and have been investigated on the human population.

## 2. Molecular Imaging of the Atherosclerotic Plaques

Quantification of the PET/CT data can be performed either in the form of the aforementioned target-to-background ratio, which is calculated as the ratio of SUV in the arterial wall to that in the venous blood pool or in the form of the metabolic volumetric product (MVP), which is calculated as the product of the average SUV and the volume of the area of interest in which it was calculated [6]. It is worth noting that inflammation is usually measured in the aortic wall, but not in the plaque itself, reflecting the vulnerability of the patient’s state.

Inflammation is a common pathophysiological process that occurs as a response to any injury, so its visualization in the case of atherosclerosis, especially in its early stages, is a cornerstone of molecular imaging. Macrophages in atherosclerotic plaque use glucose as an energy source (including those in areas of hypoxia, where they compensate for the inefficiency of glucose utilization) and have increased expression of the glucose transporter proteins GLUT-1 and -3 [7]. Thus, FDG (fluorodeoxyglucose) uptake reflects macrophage density, the degree of their activation, and consequently the “activity” of plaques. It is assumed that FDG can detect foam cells at the stage of their formation, while formed foam cells, according to M. Ogawa et al., do not show increased uptake of this radiopharmaceutical (RP) [8]. FDG is widely used in a clinical setting nowadays, mostly in cases of different types of cancer.

The meta-analysis by M. M. Chowdhury et al. [9], which included 14 studies, compared the uptake of FDG in the carotid arteries in symptomatic and asymptomatic cases. A significantly higher accumulation of the indicator was shown in symptomatic individuals. Although PET/CT (positron emission tomography-computed tomography) imaging for atheromas is primarily a research tool and is currently used only sparsely in the clinic, the results of the method can provide valuable information about the biological characteristics of plaques and thus the risk of complications, including those associated with the development of stroke in atherosclerotic lesions of the carotid arteries.

In particular, according to A. L. Figueroa et al., the uptake of FDG in the walls of arteries, as measured by routine PET/CT, significantly improved the prediction of cardiovascular events in individuals under investigation for cancer diseases, and also indicated the possible timing of such events since the target-to-background ratio appeared to be inversely related to the time before the onset of the cardiovascular event [10]. These results are supported by the study by R. Iwatsuka et al., where it was found that the target-to-background ratio (TBR) was associated with a significantly higher coronary heart disease events rate, with a hazard ratio of 1.19 per 0.1 increase in TBR [11]. With the use of FDG, a number of “vulnerable” patients, particularly those suffering from rheumatoid arthritis, showed a vulnerable plaque phenotype and more frequent aortic damage than patients without rheumatoid arthritis [12]. This demonstrates that PET with FDG can be used to identify the most high-risk groups of patients. In a recent study by B. Koa et al., it was demonstrated that lung cancer patients have higher FDG uptake in different parts of the thoracic aorta compared to patients with extrapulmonary cancer, and it was suggested that the former group of patients has a higher risk of atherosclerosis and subsequent adverse cardiovascular events [13].

A recent review by R. Sriranjan et al. [14] presented the results of some risk-prediction studies showing that an increase in arterial FDG uptake leads to a higher risk of adverse cardiovascular events. One of the papers mentioned in the review was the prospective trial by A. Rominger et al. [15], which showed that a maximal TBR of over 1.7 is a good predictor of a subsequent vascular event in cancer patients and that this predictor is stronger than a calcified plaque sum of more than 15. Therefore, it seems valuable to report these metabolically active plaques in the radiological report.

In a preclinical setting, C. M. Matter et al. used 18F-choline as an indicator for detecting atherosclerotic plaques in ApoE-deficient mice and reported results superior to those with FDG [16]. I. E. K. Laitinen et al. reported a high uptake of 11C-choline in aortic plaques in mice with atherosclerosis deficient in both LDLR and apolipoprotein B48 [17]. There are also contradictory data: L. Sarda-Mantel et al., in an experimental study on rats, showed that the accumulation of choline in atherosclerotic vessels is lower than the accumulation of FDG [18].

High choline uptake and the degree of plaque calcification is shown by PET/CT rarely coincide, which led to the conclusion that labeled choline can provide information about atherosclerotic plaques regardless of the degree of their calcification [19].

A potential target for molecular imaging is calcification of the vascular wall associated with the activation of osteoblasts in its structure, which has long been considered a hallmark of atherosclerosis. It has been shown that atherosclerosis is associated with the phenotypic transformation of vascular myofibroblasts into osteoblastic cells, which contributes to calcification [20]. Calcification of the elastic surface (vascular lining) can cause discrepancies in the extensibility of different layers of the wall, which can lead to a rupture at the interface of tissues with calcium [21][22]. Since the fluoride ion in 18F-NaF is exchanged with hydroxyl ions in hydroxyapatite crystals, osteoblastic calcification in atherosclerotic plaques can be detected using this radiopharmaceutical [23].

In the work of A. Irkle et al., it was shown that the accumulation of labeled sodium fluoride occurs in unstable plaques with a significant number of microcalcifications, which was confirmed by the results of electron microscopy and autoradiography in preclinical studies [24].

In a prospective study by N. V. Joshi et al., it was found that high uptake of sodium fluoride occurred in all unstable atherosclerotic plaques, and active calcification, macrophage infiltration, and the presence of apoptosis and necrosis zones were also histologically confirmed in these plaques [25]. At the same time, the uptake of FDG in progressive plaques in coronary vessels was masked by the high metabolic activity of the myocardium, while labeled sodium fluoride was readily visualized.

Somewhat later, in the CAMONA study (Cardiovascular Molecular Calcification Assessed by 18F-NaF PET CT), which included 139 patients, B. A. Blomberg et al. showed that sodium fluoride accumulation and calcification in the thoracic aorta are a more significant predictor of an unfavorable cerebrovascular prognosis than PET/CT with labeled fluorodeoxyglucose [26]. Based on the results of their own preclinical studies and a limited sample from the same data set (78 patients—40 asymptomatic and 38 with angina pectoris), McKenney-Drake et al. showed that sodium fluoride is a

more promising tracer for assessing plaque activity and concomitant vascular risk than FDG [27]. Similar results were achieved in a prospective study by J. M. Lee et al., who examined 51 patients with sodium fluoride before the intravascular ultrasound [28].

Y. Ishiwata et al., who examined 34 patients, showed that the accumulation of sodium fluoride can predict the progression of vascular calcification, which in turn is a predictor of vascular catastrophes during the year after the PET/CT investigation [29]. A study of 293 patients, using PET with fluoride, showed not only its prognostic significance but also the possibility of using machine learning systems to predict the risk of cardiovascular events [30].

## 3. Discussion

According to the reviewed studies, it is seen that molecular imaging can have an impact on patients' treatment and health status monitoring, reflecting different aspects of pathophysiologic processes involved in plaque progression and vulnerability.

In the modern scientific literature, there is some criticism of the theory of unstable plaques, indicating that the discovery of one or more vulnerable atheromas may indicate a higher stage of development of atherosclerotic lesions in general [31]. However, it is emphasized that the condition necessary for the development of a vascular catastrophe is not only the presence of a vulnerable plaque but also the simultaneous presence of a tendency of the blood to thrombosis, without which the plaque can recover from the damage that has occurred. Thus, a significant number of metabolically active plaques, detected by the methods of molecular imaging, reflects the high probability that episodes of capsule tears will coincide with periods of susceptibility to thrombosis, leading to poor circulation, but not necessarily in the vascular bed of the artery where the specific plaque was identified by PET or SPECT [32].

Fluorodeoxyglucose remains the leading radiopharmaceutical for assessing the activity of inflammation in plaques and consequently their vulnerability. Other radiotracers cannot yet replace FDG for this purpose. The advantage of FDG over other tracers is that it accumulates indiscriminately in a variety of cells expressing GLUT-type transporters, which makes it possible to obtain a high signal in the zone of active inflammation due to the high uptake of FDG by macrophages, leukocytes, and activated smooth muscle cells. The most important problem with regard to more specific tracers is their concentration in a small area of the vascular wall surrounding the lipid core of the plaque, the fibrous capsule, and the adjacent adventitia—an area much smaller than, for example, the area of injury in vasculitis, where inflammatory cells infiltrate the entire thickness of the vessel wall for a significant length.

The issue of quantifying accumulation is still a subject of debate. Direct PET scanner measurements are expressed as the tracer activity in becquerels per milliliter of tissue volume. In oncological practice, the most commonly used standardized uptake value (SUV) is defined as the ratio of tracer accumulation in the analyzed lesion to the expected accumulation with a uniform distribution of the administered dose in the human body volume. However, the direct transfer of this indicator to atherosclerosis research showed the impossibility of reliable differentiation of plaques with and without signs of inflammation, which necessitated the introduction of an alternative estimated value: the ratio of target and background accumulation [33]. In this approach, an unchanged ipsilateral or contralateral artery wall or blood pool can be selected as the background.

The research results published so far are characterized by a pronounced heterogeneity of measurement methods, a limited number of included groups, insufficiently strict selection criteria, or their relativity (in works studying vascular problems simultaneously with tests for verification and staging of oncological diseases); special preparation of the included individuals does not allow for a full analysis and comparison of the results, which in turn significantly limits the information regarding reproducibility. Therefore, in the future, to ensure comparability of the results of the RP tests designed to detect atherosclerotic lesions, it is likely that attempts will be made to unify the relevant protocols. Otherwise, the generalizing judgments will remain equally uncertain, and the possibilities of using the described methods in practice will be doubtful.

## 4. Conclusions

The instability of atherosclerotic lesions is recognized as the most important cause of significant events that develop in atherosclerosis–acute coronary syndrome and myocardial infarction, as well as in ischemic brain infarction.

An analysis of the available literature suggests that one of the main processes forming a part of atherosclerosis and mediating its activity and the vulnerability of atheroma is inflammation, which can be reasonably visualized through molecular imaging

Fluorodeoxyglucose is the main accessible tracer for assessing inflammatory changes in atherosclerotic lesions. Its use in PET/CT or full-body PET/MRI allows the severity of atherosclerotic artery damage, in general, to be analyzed, and the risk of future vascular events to be predicted, with several assumptions and limitations. Valuable additional information can also be provided by widespread fluoro-18-based tracers such as choline and sodium fluoride, the accumulation of which reflects the proliferative activity of pro-inflammatory cells presented in plaque and the formation of microcalcinates on the surface of the plaque, respectively. These data can be used for individual prediction of vascular events and are of great clinical significance and relevance. In the case of FDG PET, a target-to-background ratio higher than 1.7 was found to be a predictor of adverse vascular events in the future. Somatostatin receptor imaging, being a highly specific imaging method, faced some problems in its implementation and needs additional research in order to draw conclusions regarding its applicability in atherosclerotic lesion detection, vulnerability estimation, and cardiovascular events prediction.

All clinical trials on atherosclerosis molecular imaging should follow a strict protocol, which is still to be developed.

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