A New Tracer for Imaging Atherosclerosis

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Carotid artery disease accounts for ≈20% of strokes. Although the role of revascularization in reducing the incidence of stroke in symptomatic carotid stenosis is well established, the optimal treatment for asymptomatic disease remains controversial. In Asymptomatic Carotid Atherosclerosis Study (ACAS, published in 1995) and Asymptomatic Carotid Surgery Trial 1 (ACST-1, published in 2004), which enrolled patients with ≥60% carotid stenosis carotid endarterectomy (CEA) was found to be superior to medical therapy. Subsequent studies demonstrated that carotid stenting, the alternative revascularization procedure, is not inferior to CEA in these patients. However, recent advances in medical therapy have led to considerable reduction in stroke risk, such that the contemporary annual rate of ipsilateral stroke in medically managed patients with asymptomatic carotid stenosis (≤1%) is similar to the risks observed with revascularization in aforementioned trials. Accordingly, American Heart Association guidelines suggest that revascularization may be considered in a highly selected group of patients with asymptomatic carotid stenosis, acknowledging the effectiveness of this approach compared to medical therapy. Despite this, the excitement generated by the initial encouraging clinical trials and related technical and analytic pitfalls may result in a paucity of preclinical studies. Unfortunately, these are often overlooked in the face of the excitement generated by the initial encouraging clinical data and lack of interest of major journals and funding agencies to support this line of research. Neglecting these issues and related technical and analytic pitfalls may result in disappointment and questioning of the concept of molecular imaging in atherosclerosis as a whole.

18F-fluorodeoxyglucose (FDG) is the prototypical example of a tracer approved for imaging cancer or neurological disorders, for their potential in cardiovascular applications. Although the availability of these agents addresses a major barrier to clinical translation, it also leads to a paucity of preclinical studies. Such studies are often required to establish the specificity and significance of the signal in atherosclerosis (acknowledging the major differences that exist between preclinical models and human disease). A simple solution to this conundrum is follow-up studies and in-depth evaluation in preclinical models. Unfortunately, these are often overlooked in the face of the excitement generated by the initial encouraging clinical data and lack of interest of major journals and funding agencies to support this line of research. Neglecting these issues and related technical and analytic pitfalls may result in disappointment and questioning of the concept of molecular imaging in atherosclerosis as a whole. 18F-FDG targets highly metabolic cells, which include, but are not limited to macrophages. Although the value of 18F-FDG positron emission tomography (PET) as a clinical tool for carotid disease risk stratification remains to be determined, this technique is already incorporated in clinical trials to assess the effectiveness of therapeutic interventions. Acknowledging the nonspecificity of 18F-FDG, the search for more specific approved agents that target relevant processes in atherosclerosis continues. 18F-Sodium fluoride (NaF) is another regulatory agency-approved agent, which is rich in smooth muscle cells and proteoglycans with less inflammation. Recent data suggest that the frequency of plaque rupture, at least in coronaries arteries, is decreasing, whereas more events are triggered by superficial erosion. In parallel, the composition of CEA plaques is shifting toward a less inflammatory phenotype, independent of the patients’ symptom status.

To date, a large number of imaging agents have been developed to detect specific aspects of vessel wall biology in atherosclerosis using various imaging modalities. In the absence of suitable animal models and limited knowledge about superficial erosion, molecular imaging has focused primarily on plaque burden and propensity for rupture. Examples of clinically relevant targets evaluated in preclinical studies for imaging of atherosclerosis include αβ integrin, matrix metalloproteinases, and chemokine receptors. In this regard, it is worth emphasizing that although targeting specific aspects of atherosclerosis can be intellectually enticing, the costs associated with the development and clinical translation of new imaging agents (hundreds of millions of dollars) point to a different direction: focus on agents and techniques that target common biological processes involved in a broad range of human pathologies, eg, cell proliferation, inflammation, and remodeling.

Focal thrombosis triggered by plaque rupture, superficial erosion, or protruding calcified nodule in the setting of predisposing systemic factors can be asymptomatic or lead to myocardial infarction and stroke. Plaque rupture is the main cause of such thrombotic complications in both coronary and carotid artery disease. The nidus for rupture, a thin-cap, highly inflammatory fibroatheroma with a large necrotic core, contrasts sharply with that of superficial erosion, which occurs in plaques...
commonly used for bone imaging. The absence of myocardial uptake is a major advantage of \(^{18}\)F-NaF and facilitates its use for imaging coronary arteries. In a recent study in patients who presented with recent myocardial infarction and underwent \(^{18}\)F-NaF PET-CT imaging, the highest coronary signal was detected in culprit lesions, raising the possibility that this agent may detect recently ruptured plaques.\(^{14}\) The role of calcification in plaque vulnerability is complex and despite the link between calcium and inflammation, \(^{18}\)F-NaF does not seem to be a suitable agent for imaging inflammation in atherosclerosis.\(^{15}\) Clinical trials to evaluate \(^{18}\)F-NaF PET for predicting outcome in atherosclerotic diseases are underway.

In this issue of *Circulation: Cardiovascular Imaging*, Vöö et al\(^{16}\) report the results of a pilot study of \(^{18}\)F-fluorocholine (\(^{18}\)F-FCH) PET imaging in carotid atherosclerosis: Ten patients with recent cerebrovascular accidents underwent \(^{18}\)F-FCH PET-CT imaging a few days before surgical CEA. The \(^{18}\)F-FCH signal expressed as maximum target:background ratio was higher in symptomatic carotids than in asymptomatic, contralateral arteries (median maximum target:background ratio: 2.0 versus 1.2; \(P<0.05\)), but no correlation existed between carotid signal and the degree of luminal stenosis. In addition, the \(^{18}\)F-FCH signal on PET images correlated with macrophage infiltration assessed by immunostaining in CEA samples. Acknowledging the necessity of larger prospective studies, the authors conclude that \(^{18}\)F-FCH PET-CT can be a valuable technique to identify vulnerable carotid plaques.

The study by Vöö et al\(^{16}\) adds another clinically available tracer, \(^{18}\)F-FCH, to the list of imaging agents proposed for the detection of inflammation in atherosclerosis. The high uptake of this agent in proliferating cells and the role of macrophage proliferation in plaque vulnerability motivated the selection of \(^{18}\)F-FCH. Choline is a precursor for cell membrane lipids: phosphatidylcholine and sphingomyelin.\(^{17}\) Cellular uptake of choline is mediated by several transporters, combinations of which are present in different cells to accommodate specific functions.\(^{17}\) A major component of intracellular choline undergoes phosphorylation by choline kinase to yield phosphocholine and ultimately, phosphatidylcholine.\(^{17}\) Given the role of choline in cell membrane biosynthesis and upregulation of transporters in neoplastic cells, choline-based agents have been used for imaging cell proliferation in cancer. As stated by Vöö et al, \(^{18}\)F-FCH has several characteristics that are favorable for imaging of atherosclerosis, including low uptake in the myocardium and an early imaging time because of rapid hepatic and renal transport.\(^{18}\)

The difference in \(^{18}\)F-FCH signal observed by Vöö et al\(^{16}\) between the symptomatic and the contralateral carotid artery is reminiscent of early \(^{18}\)F-FDG data in carotid disease and \(^{18}\)F-NaF data in CAD. Although promising, existing data do not necessarily indicate that this agent has a role in carotid disease risk stratification, as plaque rupture and thrombosis may have enhanced \(^{18}\)F-FCH uptake by enhancing nonspecific binding to surrounding structures. Almost half of the contralateral arteries in this study had mild stenosis (potentially reflecting smaller plaques with less nonspecific tracer uptake) and 1 had complete occlusion (which may reduce tracer delivery to the plaque). Although the numbers are small, it would have been interesting to investigate whether \(^{18}\)F-FCH signal correlates with plaque burden independent of symptoms. As indicated by the authors, this issue needs further evaluation in prospective studies. About the origins of the choline signal, macrophages constitute nearly three quarter of proliferating cells in the aortic wall of atherosclerotic mice, where the disease is developed within a period of months.\(^{19}\) Histological analysis of CEA samples (two thirds of them from symptomatic patients) has shown a proliferation index of 0.49±1.05% (mean±SD) in human carotid plaque.\(^{20}\) Accordingly, the small rate of cell proliferation in most plaques is unlikely to account fully for choline uptake observed in this study. As specified by the authors, beside cell proliferation, changes in choline transport and choline kinase activity under inflammatory conditions may have contributed to \(^{18}\)F-FCH signal in vivo. The reduction in membrane expression of choline transporter-like protein-1 and reduction of choline uptake upon macrophage differentiation, observed in at least one monocytic cell line, further complicates this picture.\(^{21}\) Given the importance of choline in cell membrane, choline receptors are widely expressed. It would have been informative to stain the CEA samples for various choline transporters in combination with cell-specific markers. In this regard, it is important to note that although CD68 is routinely used as a macrophage marker, up to 40% of CD68-positive cells in advanced human atherosclerotic lesions are of smooth muscle cell origin.\(^{22}\)

Vöö et al\(^{16}\) should be congratulated for their important contribution to the field. Although many unresolved technical and analytic issues (eg, spatial resolution, scatter and partial volume effect, quantification methodology) persist,\(^{15}\) molecular imaging of the vessel wall has become a reality in recent years. With the introduction of new tracers and advances in technology, which should ultimately address the remaining technical and analytic issues, it will be possible to detect and quantify various aspects of plaque biology in humans. The promise of molecular imaging is in addressing existing diagnostic gaps, advancing pathobiology research, and helping drug development to transform cardiovascular care. The key to realizing this potential is innovation, while remaining reasonably critical to identify gaps in knowledge and ascertain they are addressed. With any advance in the field, it is critical to take a step back and make sure that the data are sound and relevant in light of recent progress in cardiovascular medicine and biology.

**Disclosures**

None.

**References**


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