# $^{18}$F-FDG Imaging of Carotid Arteries for Identifying the Vulnerable Patient: Are We at the Beginning of the End?

During the past decade, there have been several landmark clinical studies demonstrating the use of $^{18}$F-FDG PET imaging of arterial inflammation and atherosclerosis for identification of vulnerable plaque and for cardiovascular risk stratification of asymptomatic patients with no previous history of coronary artery disease (CAD). In this issue of *The Journal of Nuclear Medicine*, Noh et al. (*1*) report a strong association between carotid artery $^{18}$F-FDG uptake and Framingham risk scores (FRS) in addition to conventional risk factors for CAD in a cohort of asymptomatic patients who underwent whole-body $^{18}$F-FDG PET for malignancy screening. These findings add more support for the value of vascular $^{18}$F-FDG PET imaging for risk stratification and identification of the vulnerable patient, especially among those in whom the primary reason for $^{18}$F-FDG imaging may be evaluation of other disease processes. It still remains to be seen if identification of the vulnerable patient is in turn followed by appropriate treatment and if this is associated with improved clinical outcomes.

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Atherosclerosis-associated cardiovascular disease is a major cause of morbidity, mortality, and healthcare costs in the United States and in most industrialized nations. Atherosclerosis is induced by vascular injury and inflammation caused by the interaction between genetic and environmental factors. Myocardial infarction or cerebrovascular accidents are the most common clinical manifestations of vascular inflammation, plaque formation, vascular remodeling, and plaque rupture. Patients with traditional risk factors for atherosclerotic cardiovascular disease often undergo noninvasive imaging using radiolabeled tracers (rest–stress SPECT or PET myocardial perfusion imaging), ultrasound (stress echocardiography or vascular ultrasound), and, to a lesser extent, CT angiography. Invasive risk assessment of patients for CAD is performed with invasive coronary angiography. Although luminal narrowing of coronary and carotid arteries has been a major focus of angiographic studies, it is increasingly appreciated that plaque instability and remodeling are crucial determinants of thrombus formation, luminal obstruction, and distal embolization (*2,3*).

During the past 2 decades, numerous investigators have sought to develop imaging tools to identify the vulnerable plaque; however, their efforts have been met with limited success. As a result, the search for molecular and noninvasive imaging probes that selectively bind to unstable plaque has continued to remain a vital area of investigation (*4*). Rupture-prone plaque is characterized by accelerated angiogenesis, inflammation, and apoptosis; these biologic processes have become targets for the design of noninvasive imaging probes for early detection of vulnerable plaque (*5–8*). One of the most popular agents used for detection of plaque in the peripheral vasculature is $^{18}$F-FDG, a well-known PET tracer traditionally used for oncologic imaging. $^{18}$F-FDG was found to be useful for detecting inflammation because of its selective uptake by metabolically active leukocytes. In one of the early studies describing the use of $^{18}$F-FDG for inflammation imaging in an experimental model of soft-tissue injury, the highest $^{18}$F-FDG uptake was detected in the injury zone containing fibroblasts, macrophages, and neovascular endothelium (*9*). Preclinical studies of vascular injury in the iliac arteries of atherosclerotic rabbits showed enhanced $^{18}$F-FDG uptake in the vessel wall and an associated increase in macrophage activity at the site of injury (*10*). The first clinical study demonstrating preferential $^{18}$F-FDG uptake by atherosclerotic and presumably vulnerable plaque was performed by Rudd et al. who showed that in 8 patients with symptomatic carotid artery atherosclerosis, there was increased $^{18}$F-FDG uptake in the carotid artery responsible for the cerebrovascular accidents, compared with the contralateral carotid artery (*11*). Rudd et al. also demonstrated that in a smaller subset of these patients, $^{18}$F-FDG uptake was more prominent in areas of the carotid plaque containing increased macrophage density. A more recent and larger study of 21 patients has confirmed these findings with the demonstration that $^{18}$F-FDG uptake, expressed as the maximal standardized uptake value (SUV), in carotid plaque was strongly associated with macrophage density and enhanced tissue expression of vascular endothelial growth factor (*12*). Although there has been controversy regarding the exact cell types responsible for the observed increase in $^{18}$F-FDG uptake by atherosclerotic plaque, studies performed in vitro have demonstrated that $^{18}$F-FDG uptake is mediated primarily by hypoxic macrophages and cytokine stimulation of smooth muscle cells (*13*). In addition to its application for detection of carotid artery atherosclerosis, $^{18}$F-FDG imaging has also been used to visualize rupture-prone plaque in the coronary artery (*14*). However, the difficulties in suppressing endogenous myocardial glucose uptake and the combined respiratory and motion artifacts that are associated with cardiac imaging have imposed additional obstacles in terms of cardiac plaque imaging. In terms of overall cardiovascular risk assessment, there has been an increased appreciation for the potential application of $^{18}$F-FDG PET for detection of not only the vulnerable plaque but also the vulnerable patient. The idea was that an assessment of whole-body atherosclerotic burden using $^{18}$F-FDG PET might provide a better gauge of those patients who would most benefit from therapeutic intervention. Data

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For correspondence or reprints contact: Rory Hachamovitch, Division of Cardiovascular Imaging, Cleveland Clinic, J1-5, 9500 Euclid Ave., Cleveland, OH 44195.
E-mail: hachmr@ccf.org

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supporting the hypothesis that vascular $^{18}$F-FDG uptake may be of prognostic value comes primarily from retrospective studies performed in asymptomatic patients undergoing whole-body PET imaging for oncologic monitoring. The first large clinical study of $^{18}$F-FDG PET in asymptomatic patients was published in 2009 in *The Journal of Nuclear of Nuclear Medicine* by Rominger et al. (*15*). It was a retrospective single-center study of patients who underwent whole-body PET for detection of primary and metastatic malignancies. Vascular $^{18}$F-FDG uptake of the carotids and the great vessels including the abdominal aorta was quantified by measuring the SUV in the vascular structures of interest. Increased $^{18}$F-FDG uptake was shown to have incremental value in predicting overall mortality in addition to traditional risk factors. Studies have also shown that the treatment of patients with statins—which are known to cause regression of atherosclerosis—is associated with an interval decrease in vascular $^{18}$F-FDG uptake (*16*). $^{18}$F-FDG PET has also been used to assess treatment effects of antiatherosclerosis therapy; treatment with dalcetrapib, a cholesterol ester transfer protein inhibitor, was associated with reduced vascular $^{18}$F-FDG uptake (*17*). In the current study by Noh et al. the key observation is the positive association between FRS and vascular $^{18}$F-FDG uptake in a group of asymptomatic patients. This observation supports the hypothesis that vascular $^{18}$F-FDG uptake may be used as a surrogate marker of the overall cardiovascular risk among a population of patients without a known history of cardiovascular disease.

Noh et al. measured carotid artery $^{18}$F-FDG uptake in 1,181 asymptomatic patients who underwent whole-body PET imaging for detection of malignancies. Patients underwent $^{18}$F-FDG imaging 45 min after the injection of the radiotracer. Mean and maximum SUV of the entire carotid artery was measured, and $^{18}$F-FDG uptake was expressed as the target-to-background ratio (mean and maximum SUV divided by the mean SUV of the blood pool measured in the inferior vena cava). They further classified a target-to-background ratio greater than 1.7 as high uptake. The investigators present data that suggest a positive association between patients with high $^{18}$F-FDG uptake and both FRS and intimal medial thickness. They also observed an association between carotid artery $^{18}$F-FDG uptake and traditional risk factors for CAD including increasing age, waist circumference, abdominal fat, body mass index, high-density lipoprotein, and low-density lipoprotein levels. A similar relationship was also observed between high-sensitivity C-reactive protein (hsCRP), FRS, intimal medial thickness and traditional cardiovascular risk factors in this cohort of patients. However, the authors were unable to find a strong association between hsCRP and carotid $^{18}$F-FDG uptake in their patient cohort. This observation is in contrast to a study published by Tahara et al. In their retrospective study of 216 patients, Tahara et al. reported a positive association between hsCRP and the average of maximum SUV measured in the carotid arteries bilaterally (*18*). The lack of association between hsCRP and carotid $^{18}$F-FDG uptake may suggest that hsCRP levels and $^{18}$F-FDG uptake are controlled by independent signaling mechanisms in patients with cardiovascular disease or it may be related to possible differences in the methodology used by these investigators with respect to quantification of $^{18}$F-FDG uptake in the carotid artery. With respect to methodologic approaches to this question, it is important to point out that a 2-h time after injection has been accepted as a more optimal imaging window best suited for monitoring vascular $^{18}$F-FDG uptake and is considered to result in a higher target-to-background ratio; however, $^{18}$F-FDG uptake in the current study by Noh et al. was measured at 1 h after tracer injection (*19,20*). Additionally, it is important to consider that the current study only measured carotid artery $^{18}$F-FDG uptake. It is likely that by quantifying only carotid $^{18}$F-FDG uptake, the investigators may have overlooked additional information that could have been gained by measuring $^{18}$F-FDG uptake in the thoracic and abdominal aorta. Regardless, this study illustrates the independent value of $^{18}$F-FDG uptake in addition to traditional risk factors as a noninvasive imaging marker of overall cardiovascular risk.

In reviewing the studies that have used $^{18}$F-FDG uptake as a marker of cardiovascular disease burden and as a means of monitoring the effect of therapy, it becomes clear that there is a need for identification of specific molecular imaging targets that are most enriched in vulnerable atherosclerotic plaque. Although $^{18}$F-FDG may be a useful marker for measuring vascular inflammation for reasons mentioned previously, it may not be practical to use $^{18}$F-FDG as a tracer for monitoring plaque vulnerability in the coronary arteries. Furthermore, $^{18}$F-FDG may be used by multiple cell types found in atherosclerotic plaque in response to different stimuli; although, this may improve its ability to detect inflamed plaque it may prove to be less specific in serving as a surrogate marker for specific biologic pathways that might play an active role in plaque rupture. It is therefore understandable that there is a need for the development of more specific tracers that can be used for identification of vulnerable plaque and thereby risk-stratify patients who are at greatest risk for adverse cardiac events.

Although this study does not introduce ground-breaking concepts in terms of noninvasive imaging of atherosclerosis, it adds to the body of evidence demonstrating the association between vascular disease burden as measured by $^{18}$F-FDG uptake and cardiovascular risk. It also supports the need for a more careful examination of peripheral vascular $^{18}$F-FDG uptake in patients not known to have CAD to detect and quantify atherosclerotic disease burden. The logical next step will be to examine whether patients with differences in vascular $^{18}$F-FDG uptake experience different outcomes based on different therapeutic strategies used to treat them. This further examination will enable us to evaluate whether the detection of total-body atherosclerosis and quantification of the overall vascular atherosclerotic disease burden will yield actionable information in the form of specific treatment strategies associated with enhanced patient outcomes.

**Balaji Tamarappoo**
**Rory Hachamovitch**
*Cleveland Clinic*
*Cleveland, Ohio*

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