EDITORIAL COMMENT

18F-Sodium Fluoride Positron Emission Tomography
An In Vivo Window Into Coronary Atherosclerotic Plaque Biology*

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Coronary atherosclerosis is a progressive disease that involves vascular inflammation, development of cholesterol burdened atheroma, mechanisms of injury and repair, and subsequent calcification (1). Coronary artery calcification (CAC) detected with cardiac computed tomography has been shown to correlate well with overall plaque burden and is an independent predictor of cardiovascular events (2,3). It is well known that traditional cardiovascular risk factors contribute to the first incidence of CAC and CAC progression (4,5). Once present, CAC is diagnostic of the presence of coronary atherosclerosis, with increasing CAC burden correlating with increasing atherosclerosis burden and inferring different risks for cardiovascular events dependent on age, sex, race, and ethnicity (6). Once CAC is present, the atherosclerotic disease process is firmly established and therapies to induce plaque progression, although effective, are modest at best and inevitably leave a substantial residual risk of coronary events (7).

In this issue of the Journal, Dweck et al. (8) report an intriguing study that uses 18F sodium fluoride (18F-NaF) and 18F fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) in a study aimed to examine the feasibility of performing noninvasive imaging of active calcification and inflammation. The study highlights some of the difficulties in performing inflammation imaging with 18F-FDG in the coronary arteries, due to the avid uptake of 18F-FDG by the myocardium, but at the same time demonstrates a promising technique to measure active calcification of the coronary arteries in vivo. Several findings from this study are suggestive of the potential of 18F-NaF for studying atherosclerotic plaque biology in vivo. The authors demonstrated that patients with abnormal 18F-NaF imaging were more likely to have a history of coronary artery disease, revascularization, and angina. In addition, 18F-NaF uptake correlated with Framingham risk scores used for the prediction of coronary heart disease events. There was also a good correlation with CAC score, but CAC and 18F-NaF uptake were not always synonymous. Forty-one percent of patients with a CAC score >1,000 demonstrated no significant 18F-NaF uptake, and some patients with minimal calcium had increased 18F-NaF uptake. At the present time, the significance of severe calcification in the absence of 18F-NaF uptake is not known. One can hypothesize that 18F-NaF uptake in areas of noncalcified or minimally calcified plaque might represent areas of active calcification. This hypothesis, if true, has significant clinical implications, because there is evidence that coronary calcification is a result of plaque rupture and is part of the healing process (9), and patients with cardiac events are more likely to have CAC progression (10,11).

Coronary artery calcification is a dynamic process that resembles bone formation. It has been demonstrated that calcification involves osteoblast-like cells as well as some of the same cytokines, transcription factors, and bone morphogenetic proteins that are involved in bone formation and remodeling (12,13). Large epidemiologic studies suggest a strong association between factors that promote bone loss and atherosclerotic progression (14). 18F-NaF has been recognized as an excellent radiopharmaceutical for imaging pathological processes involving bone formation and remodeling, including primary bone malignancies, metastatic disease, and Paget’s disease. 18F-NaF is relatively easy to produce with beam currents achievable in today’s clinical cyclotrons. Hydroxyapatite, a constituent of bone and similarly calcified atherosclerotic plaque, is capable of exchanging hydroxyl groups with the fluoride ion (15). Although noncontrast computed tomography can detect the presence of coronary calcification, it cannot detect active calcification. 18F-NaF PET might provide this opportunity.

There are several limitations of the current study that require mentioning. First, this study is a substudy. The patient population was initially enrolled to study inflammation and active calcification in patients with aortic sclerosis or stenosis (16). Therefore, the population studied is not ideal for making final conclusions with regard to the efficacy of this technique in patients at risk of developing coronary atherosclerosis and cardiovascular events. Second, there is no histopathology confirmation of what 18F-NaF uptake indicates. Although the authors postulate 18F-NaF uptake or absence thereof differentiates between active and dormant calcification, this cannot be confirmed. This conclusion can only be derived from a study that includes histopathology or from a study that examines whether the presence of 18F-NaF uptake correlates with the appearance of new calcified

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plaque or progression of calcified plaque over time. The authors used noncontrast CAC scoring images to detect calcified plaque. It is unknown whether areas of tracer uptake in the absence of calcification were areas of noncalcified plaque or areas with spotty calcification, too small to be detected by CAC imaging alone. Although the study tries to make comparisons with Framingham Risk Scores, there is no follow-up of events, and the predictive ability of 18F-NaF PET cannot be confirmed.

The authors should be congratulated, regardless of these limitations, on taking the first step in demonstrating the feasibility of 18F-NaF PET imaging of the coronary arteries. This technique shows great promise in the noninvasive study of biological processes that contribute to coronary atherosclerosis. In addition, with further validation, it might be an early marker of plaque progression that could be used to guide clinical trials of novel therapeutics aimed at plaque regression and reducing cardiovascular events.

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REFERENCES


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