^{18}F-sodium fluoride: An emerging tracer to assess active vascular microcalcification

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BACKGROUND

Visualizing vascular macrocalcification with computed tomography (CT) was the first noninvasive imaging technique to assess atherosclerosis as an alternative to conventional angiography. In 1990, Agatston *et al*. introduced a method of scoring coronary artery calcification using low-dose CT,[1] which subsequently became widely used clinically. Since then, many new modalities such as CT angiography, magnetic resonance image, magnetic resonance angiography, optical coherence tomography, and intravascular ultrasound have provided new insights into plaque morphology such as cap thickness, presence of intraplaque hemorrhage, and presence of a necrotic core. However, because these structural changes occur in later and often irreversible stages of disease, molecular imaging techniques are necessary to characterize early manifestations of atherosclerosis, allowing for timely diagnosis and intervention (Figure 1).

By portraying local glucose uptake, the utility of ^{18}F-fluorodeoxyglucose (FDG) as a positron emission tomography (PET) probe to image atherosclerotic disease activity was first suggested in a 2001 study by Yun *et al*., who showed a significant correlation between vascular FDG uptake and age.[2] Subsequent studies concluded that increased FDG uptake is associated with high-risk plaque morphology and adverse cardiovascular events.[3–5] However, recent literature has questioned the ability of FDG to differentiate morphologically unstable from stable atherosclerotic plaques[6] and the closeness of the association between arterial wall FDG uptake and risk factors.[7] Alternatively, uptake of ^{18}F-sodium fluoride (NaF), a PET tracer primarily used for skeletal imaging, has also been shown to be associated with high-risk plaques, and more consistently so with cardiovascular risk factors.[8]

In the current issue of the *Journal*, Takx *et al*. add to the growing body of evidence supporting the use of NaF-PET/CT to assess vascular microcalcification in patients at high risk for atherosclerosis. The target-to-background ratio (TBR) of NaF uptake in the superficial femoral arteries normalized to blood pool activity in the superior vena cava was calculated in 68 patients with type 2 diabetes and a history of cardiovascular disease. Of the 68 patients, 25 were on both insulin and a glucose-lowering agent, 35 were on a glucose-lowering agent alone, seven were on insulin alone, and one patient was on neither insulin nor a glucose-lowering agent.

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Additionally, 52 of 68 patients were treated with a statin. TBR was found to correlate with CT calcification, total cholesterol, and HbA1c, even after adjusting for age and sex. The authors concluded that NaF uptake is a useful marker for arterial disease burden in patients with diabetes and a history of cardiovascular disease. Limitations of this study included a relatively small sample size as well as reliance on the maximum standardized uptake value (SUVmax), which is less representative than metrics that include data from multiple voxels such as mean SUV (SUVmean). The femoral artery was chosen because a previous study showed significant correlations between femoral NaF uptake and cardiovascular risk factors as well as calcified plaque burden in 409 oncologic patients.[9] The use of global assessment by Takx *et al*. to assess the femoral artery was a strength of their study, and with the advent of total body imaging, we now have the ability to identify disease burden in more parts of the body with a single scan than we ever have had previously. As interest in PET to assess atherosclerosis continues to grow, the success of this technology will depend on the adoption of proper imaging techniques and reproducible and standardized methodologies that will most accurately reflect disease activity.

PET TRACERS

The reason for FDG uptake in atherosclerosis is likely due to macrophage-mediated inflammation within plaques.[10] While the use of FDG for assessing cardiovascular disease is becoming more popular, there are several limitations associated with this tracer. Because FDG uptake is involved in and influenced by many physiologic processes, it serves as a nonspecific marker of atherogenic activity. Therefore, plaque FDG uptake can be obscured by uptake from the vessel wall and surrounding structures. Evaluation of the coronary arteries in particular is limited by adjacent myocardial FDG uptake. In addition, a study by Blomberg *et al*. demonstrated a low correlation between thoracic aortic FDG uptake and cardiovascular risk factors, challenging the perceived utility of assessing arterial inflammation.[11] The authors found that calcification rather than inflammation was associated with CT calcification and 10-year Framingham Risk Score. Moreover, Meirelles *et al*.

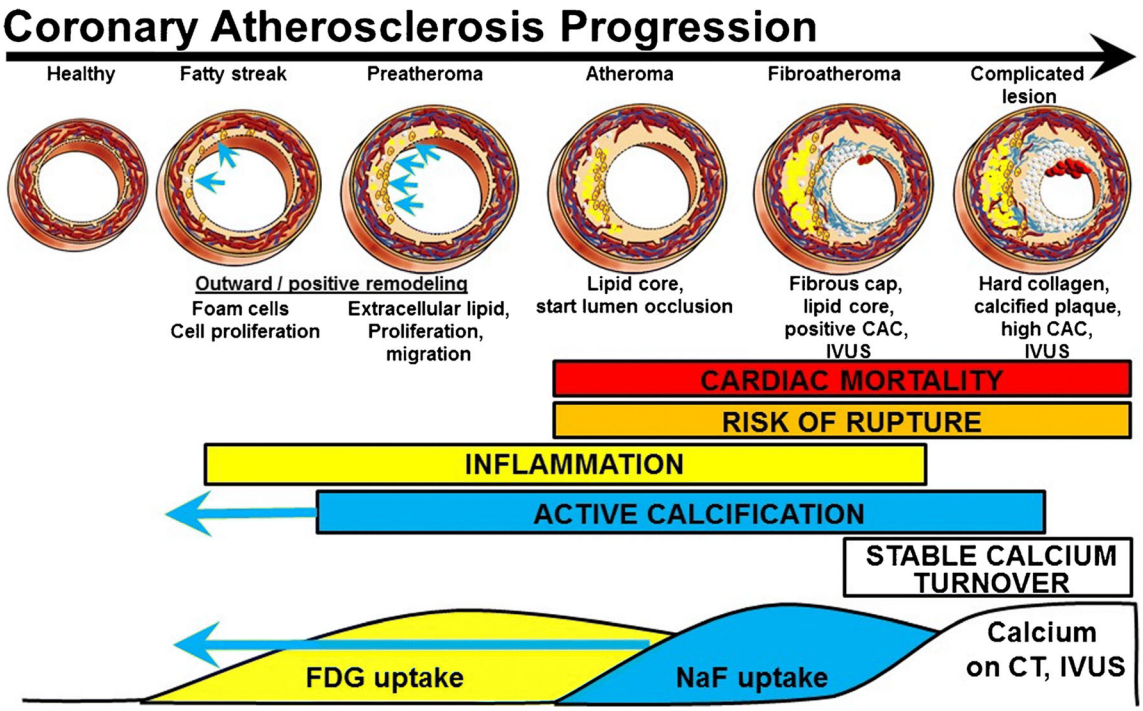


Figure 1. The progression of a complicated atherosclerotic lesion. Although it has been established that evidence of disease progression is apparent on PET imaging prior to coronary artery calcium (CAC) detected by CT and intravascular ultrasonography (IVUS), there is a paradigm shift suggesting active microcalcification assessed by NaF uptake may be present earlier than previously believed, occurring in coronary fatty streaks and preatheromas (arrows). Image reprinted without changes from McKenney-Drake *et al*.[21] under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

found in cancer patients with at least two FDG-PET/CT scans performed a mean of seven months apart that thoracic aortic FDG uptake had changed (and often disappeared) on the second scan in 55% of cases, which caused the authors to conclude that inflammation in atheromas is a ''waxing and waning inflammatory process.''[12]

More recently, a study by Arani *et al*. showed a similar association between abdominal aortic NaF uptake and the factors age and 10-year Framingham Risk Score, where there was no such association with FDG uptake.[13] NaF is highly specific for ongoing microcalcification and therefore avoids some of the limitations of FDG, except that in some locations cross-talk from the high uptake in nearby bone may be a challenge.[8] As such, NaF-PET/CT imaging can portray microcalcification in the coronary arteries as early evidence of coronary artery disease.[14,15] Although studies have shown the utility of assessing both arterial inflammation and microcalcification, their relative roles remain to be determined. In particular, an in-depth analysis of the surprisingly large topographic and temporal differences between the presence of the two tracers in the arterial system is needed.[7]

GLOBAL QUANTIFICATION

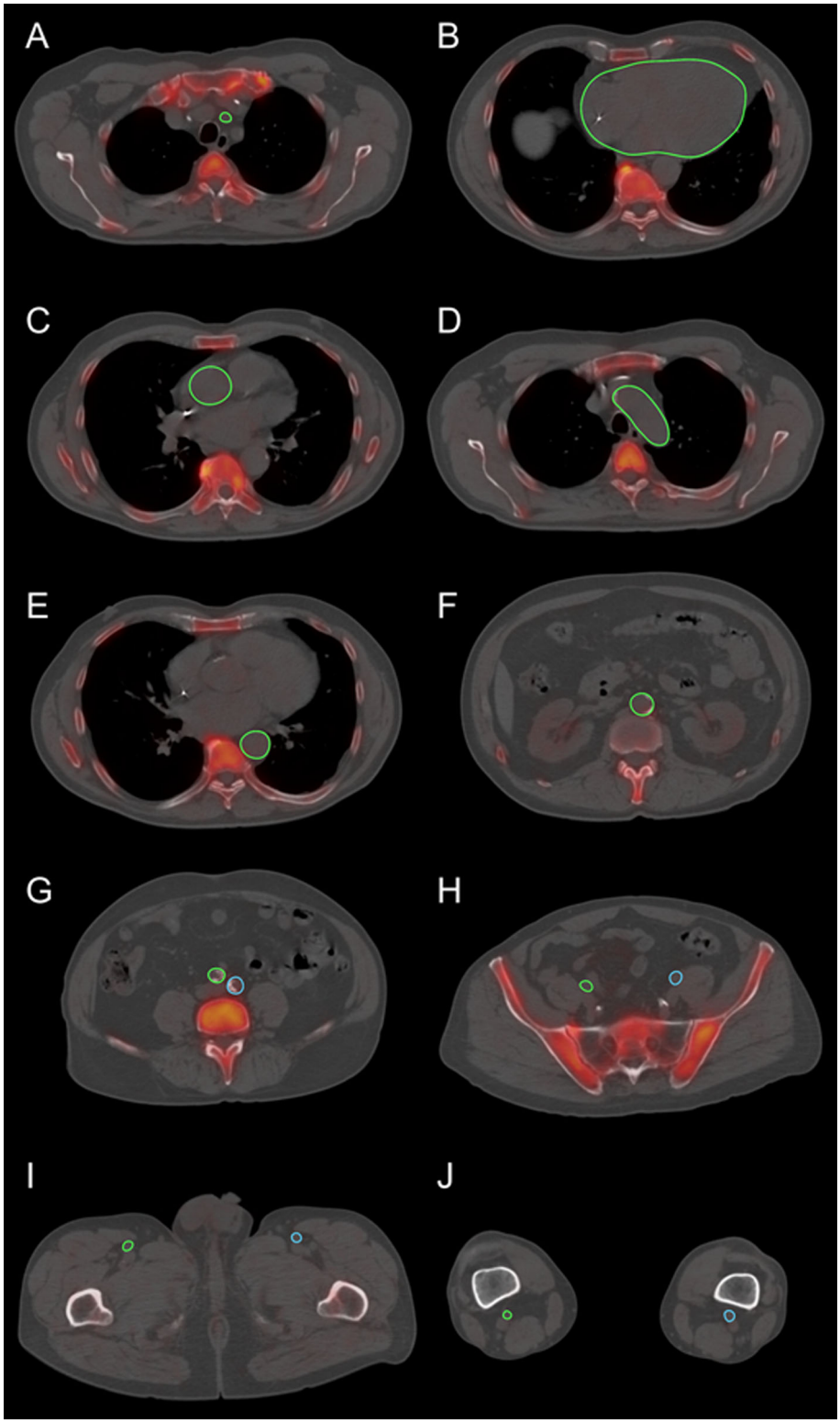
Innovations in PET technology have led to improvements in spatial resolution, achieving resolutions of 8-10 mm in human studies through greater numbers of detectors and new reconstruction algorithms.[10] Nevertheless, visualization of structures smaller than one cm^3 such as atherosclerotic plaques will be impacted by the partial volume effect, causing underestimation of tracer uptake.[16] Partial volume correction in the aorta has been proposed by measuring wall thickness,[17] but this method is not feasible for smaller vessels. Coronary artery assessment is further complicated by respiratory and cardiac motion, which has been addressed by the development of combined respiratory and cardiac gating with mixed success.[18]

Global disease assessment, which was first introduced in the context of brain imaging by Alavi *et al*.,[19] is a method of quantification designed to overcome limitations associated with visualizing small structures such as plaques. By measuring uptake in entire structures such as the heart and major vessels, we can obtain more robust PET parameters and avoid problems posed by insufficient image resolution.[20] The Alavi-Carlsen global molecular calcium score represents the application of global assessment to characterize arterial microcalcification using NaF-PET/CT,[21] first being implemented in a 2011 study by Beheshti *et al*.[15] Global assessment has since been successfully employed in the assessment of both arterial inflammation and calcification in healthy subjects and high-risk patients.[13,22–28] Based on these data, we strongly believe that global assessment is critical for a robust and reproducible measure of disease burden. Further, we argue that SUVmax is an oversimplified measure of disease severity. Methods utilizing SUVmax are easily influenced by noise and do not accurately represent the total pathologic uptake in a vessel of interest. By contrast, we believe that global assessment with SUVmean is a much more sensitive and specific methodology to measure disease activity,[16] recognizing that for this approach to become clinically useful, fast and automated, and probably artificial intelligence-based, methods will be necessary.[29]

Table 1. Global NaF SUVmean representing microcalcification in multiple arteries of one healthy subject and one high-risk subject

Vessel	Healthy subject (NaF SUVmean)	High-risk subject (NaF SUVmean)
Carotid artery	0.75	0.96
Coronary arteries	0.79	0.71
Ascending aorta	1.12	1.28
Aortic arch	1.24	1.31
Descending aorta	1.29	1.42
Abdominal aorta	1.16	1.46
Common iliac artery	1.73	2.75
External iliac artery	1.64	1.96
Femoral artery	1.84	2.22
Popliteal artery	1.61	2.01
Total body arterial uptake	13.15	16.08

NaF, ^{18}F-sodium fluoride; *SUVmean*, mean standardized uptake value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◀**Figure 2.** Axial fused NaF-PET/CT images with regions of interest in a 67-year-old subject. The manually delineated regions of interest were used to quantify NaF uptake in the left carotid artery (**A**), global coronary arteries (**B**), ascending aorta (**C**), aortic arch (**D**), descending aorta (**E**), abdominal aorta (**F**), bilateral common iliac arteries (**G**), external iliac arteries (**H**), femoral arteries (**I**), and popliteal arteries (**J**). The SUVmean from each region was summed to calculated the Alavi-Carlsen global molecular calcium score and presented in Table 1 as the high-risk subject.

TOTAL BODY IMAGING

Over the last several years, advancements in PET imaging instrumentation have allowed us to measure the radiotracer distribution of the entire body concurrently.[30–32] Preliminary data from our group indicated that NaF uptake measured by SUVmean in high-risk patients was correlated with age in the common iliac artery, external iliac artery, femoral artery, and popliteal artery.[33] In our ongoing research, we correlated age and total body arterial uptake of NaF in 80 individuals (40 healthy and 40 high-risk for cardiovascular disease). Our regression analysis revealed a robust association between the two parameters in both subgroups. Each segmental SUVmean of vessels analyzed in one healthy subject and one high-risk subject is presented in Table 1, with total body arterial uptake calculated as the summation of the SUVmean of all the arteries examined (Figure 2). The clinical significance of the total body arterial NaF uptake, yet to be validated with further studies, may prove to be of great value in providing a better understanding of disease burden. As atherosclerosis is a systemic disease, total body imaging enables a more accurate assessment of true disease activity with greater precision and accuracy as compared to current conventional PET imaging techniques. Total body imaging may also allow for superior monitoring of the distribution and progression of the disease in the body as well as assessment of the response to appropriate interventions.

CONCLUSION

PET imaging with FDG and in particular NaF has shown great promise regarding the early detection of atherosclerotic activity, which will be crucial for interventions in presymptomatic individuals. Greater adoption of PET-based methods must also be accompanied by knowledge of limitations associated with this technology and the proper means of overcoming these obstacles, namely by global assessment. Takx *et al*. have adequately demonstrated the application of these methods to the assessment of the femoral artery, and we are eager to see these techniques applied to vessels throughout the body as total body imaging becomes a reality.

Disclosure

The authors declare that they have no conflict of interest.

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