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Perspective Article

¹⁸F-Fluoride as a marker of unstable atheroma – A Perspective

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Abstract

The techniques currently available to detect myocardial and cerebral ischemia identify patients with advanced atherosclerosis. Localization and characterization of atheroma prior to a clinical event would allow a therapeutic intervention before any loss of function due to ischemia or infarction. To achieve a high level of specificity, the imaging technique should highlight lesions with a potential to cause a clinical event.

Several radiopharmaceuticals have been described to identify inflamed, thin-cap atheroma. Of these, ionic ¹⁸F- as fluoride ion, may be the most useful. Preliminary studies suggest that ¹⁸F- does not usually localize in areas of dense vascular calcification, but does localize in areas of microcalcification. Although the local pathophysiology required for fluoride localization is not fully understood, it appears that localization occurs in regions of severe inflammation. The lack of significant uptake in normal myocardium or normal brain, suggest that low levels of fluoride uptake should provide a sufficient

signal to detect small lesions. Although more work is needed to develop standard methods of quantitation and image mapping, ¹⁸F-PET-CT imaging may be useful to identify vulnerable atheroma.

Key words: ¹⁸F; atheroma; PET-CT; vulnerable plaque; microcalcification.

Vascular calcification is a marker of atherosclerosis [1]. To determine if atherosclerosis is a new disease, caused in part by sugary drinks and salty snacks, or is a disease that has afflicted humans for millennia, investigators performed CT scans on mummies from Egypt, Peru, Pueblo Indians from southwest United States and Unangan people from the Aleutian Islands. The CT scans demonstrated calcification of major vessels in 34% of specimens from each population [2]. The mummies were estimated to have lived from as long as several thousand years ago to as recently as several hundred years ago.

Current understanding of atherosclerosis suggests that atheroma begin with an endothelial injury, especially at sites of shear stress [3]. The damaged endothelial cell allows low density lipoprotein cholesterol to leak into the subendothelium. The injury elicits a repair response, where surrounding endothelial cells proliferate to replace the damaged cells, thus resulting in intimal thickening [4]. The lipid is trapped as the new endothelial cells replace the damaged cells. The presence of subendothelial lipid causes an inflammatory response of the overlying endothelium, resulting in expression of chemotactic peptides, recruiting monocytes to the site [5].

Monocytes traverse the endothelium, transform into macrophages and begin the job of removing the irritating lipid by ingesting and catabolizing the noxious material. The phagocytic macrophages increase their metabolic rate, both to allow the cells to migrate to the site of lipid deposition and to phagocytize/catabolize the lipoprotein cholesterol.

In the process of catabolizing the lipid, the macrophages oxidize the lipid [6]. Oxidized cholesterol is extremely toxic to the macrophages, causing the cells to die - either by initiating apoptosis, or a process that is a combination of apoptosis and oncosis [5,7]. Due to intense metabolic activity, the macrophages produce free radicals and release a variety of proteases in the lesion, resulting in further inflammation [8]. In the presence of persistent or recurring endothelial damage, more LDL cholesterol leaks into the subendothelium, increasing inflammation, resulting in a lesion that histologically looks like an abscess.

In the presence of persistent inflammation macrophages and adjacent smooth muscle cells produce proteases, digesting the fibrous barrier. As the separation between lesion and flowing blood decreases to <65 μ m, the lesion becomes vulnerable to rupture [9]. Only a small fraction of plaques that rupture (possibly 1 out of 100) result in clinical events (Fuster V, Mount Sinai Medical Center, New York, NY, personal communication). Identifying the presence and location of vulnerable plaques can direct

systemic, or, if sensitive and specific enough, identify the requirement for direct mechanical intervention.

Detection of metabolically active, vulnerable atheroma has been a major goal of nuclear cardiology since the birth of the field, over 60 years ago. Table 1 is a partial list of radiopharmaceuticals advocated for detecting and localizing atherosclerosis.

AGENT/MODALITY	TARGET
X-ray [10]	Large vessel calcification; identify the presence of atherosclerosis
Autologous LDL [11]	Localize lipid-laden plaques
Antibodies recognizing oxidized LDL [12]	Localize inflamed lesions
Chemoattractant peptides [13]	Localize vascular inflammation
[¹⁸ F]FDG [14,15]	Lesions with inflammation, high macrophage content and hypoxia
[¹⁸ F]-Fluoride [16]	Lesions with active calcification
Annexin V [17]	Apoptosis

Table 1. An incomplete list of agents to localize atheroma.

Vascular calcification, as detected on current generation CT scans, designates areas of inflammation that have been walled off. These calcific lesions are more of a tombstone than a site of ongoing inflammation, as indicated by the very low concordance between sites of FDG vascular uptake (as a marker of inflammation) and calcification [18]. In a multicenter trial [19], the highest quartile of patients with >130 Hounsfield units of coronary vascular calcium predicted cardiac events over the next 3 years in ~ 1% of the population. As a result, while the presence of calcium means the presence of atherosclerosis, it does not provide sufficient information on the likelihood of a clinical event within the next few years.

Similarly, the use of radiolabeled LDL in patients with documented carotid disease provides important information about the striking permeability of these highly inflamed lesions to large molecules, such as autologous LDL cholesterol [11]. However, preparation of autologous cholesterol is complex, requiring experienced staff to perform the separation and purification of the LDL and label the protein.

Antibodies recognizing oxidized LDL [12] radiolabeled with iodine-125 (¹²⁵I-MDA2) and with ^{99m}Tc demonstrated co-localization of oxidized LDL antibody with regions demonstrating lipid deposition in the aorta of LDLR^{-/-} mice. In mice treated with a reduced cholesterol diet or antioxidant intervention, there was a marked decrease of antibody uptake in regions that contained lipid. Although this technique is useful to identify areas of intense inflammation, it is complex for a screening study.

Radiolabeled chemoattractant peptides [13] localize in regions of re-endothelializing vascular injury in cholesterol fed rabbits. This observation is consistent with the known pathophysiology of atheroma, but occurs very early in the process, and may be too sensitive for clinical use.

Localizing areas of vascular inflammation with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) [14] has been useful to demonstrate the relative effectiveness of dietary and pharmacologic therapy on inflammation in the carotid arteries [20]. While this technique is straightforward to use in large vessels, it is problematic to apply in the coronary arteries, due to physiologic uptake in the myocardium of ~ 50% of patients. Joshi *et al.* [21] compared the coronary uptake of ^{18}F as ionic fluoride to localization of ^{18}F -FDG in patients myocardial infarction (n=40) and stable angina (n=40). The authors demonstrated the most intense localization of fluoride in the culprit lesion, while ^{18}F -FDG localization was ‘often obscured by myocardial uptake, and where discernible, there was no differences between culprit and non-culprit plaques.’

Apoptosis is an integral step in the pathophysiology of vulnerable plaque [22]. Unfortunately, studies comparing $^{99\text{m}}\text{Tc}$ - annexin to carbon-14 labeled 2-deoxyglucose in apo $e^{-/-}$ mice, demonstrated 6.3 fold greater uptake of deoxyglucose to annexin V in regions of atheroma. The low uptake of annexin in experimental atheroma makes it difficult to detect small lesions by external imaging *in vivo*.

The pathophysiology demonstrated by fluoride imaging of atheroma is not fully elucidated. A review the history of this imaging agent may shed some light on this complex subject. In 1954 a study of the biodistribution of ^{18}F -fluoride in 25 week old rats by Wallace-Durbin [23] reported that at 1 (n=10), 4 (n=10) and 9 (n=12) hours after intravenous injection ~50% of the dose was in the skeleton and ~30% in the urine. At 1 hour there was 5.6% of the injected dose in skeletal muscle and 1.4% of the injected dose in the blood volume (most in plasma); by 4 hours skeletal muscle decreased to 0.88%/organ and blood to 0.15%. An autoradiograph of the distal femur demonstrated striking uptake in the epiphysis. Wallace-Durbin concluded that there was ‘no significant deposition of ^{18}F in the soft tissues...’

The use of ^{18}F -fluoride for imaging the skeleton in human subjects was initially described by Blau and colleagues in 1962 [24]. In 1972 the authors describe their experience with this tracer [25] over a decade of clinical use. The authors suggest that the major mechanism of uptake is ion exchange in hydroxyapatite crystals - most likely with hydroxyl (OH^-) ions. Individual hydroxyapatite crystals are $20 \times 5 \times 5 \mu\text{m}$, providing ‘an enormous surface area’ ($\sim 300 \text{ m}^2/\text{g}$) for localization. Blau described the passage of a fluoride ion from the blood to the bone crystal as follows:

The fluoride ion ‘must pass (1) from the plasma, (2) through the extracellular fluid, (3) into the shell of bound water surrounding the crystal, (4) onto the surface and (5) into the interior of the crystal. The first 3 steps have half times in minutes. Step 4 is probably measured in hours and step 5 takes days or weeks. *However, once ions have entered the bound water shell they are essentially part of the bone...*’

‘Areas of high uptake...result from any processes that increase exposed bone crystal and/or the blood flow.’

In the seminal publication the authors include a table, listing soft tissue abnormalities that had been detected with fluoride imaging, including *dystrophic* calcification in: calcific tendinitis, healing postoperative sites, soft tissue metaplasia and dental abscess. Vascular calcification often occurs as a result of focal inflammation. In a longitudinal study of 137 patients, Abeldaky *et al.* [26] used the metabolic marker, [¹⁸F]FDG, to perform [¹⁸F]FDG PET/CT scans on two occasions, 1-5 years apart. Focal uptake of [¹⁸F]FDG in specific regions of the thoracic aorta were identified on the initial scan. The CT scans of the initial and follow-up studies were sent to a separate group of investigators, who evaluated these same aortic segments for the presence of calcium at baseline (>130 HU) and identified any change at follow-up: 9% of aortic segments (n=67) demonstrated increased calcification.

The sites of new calcification occurred in areas that had increased [¹⁸F]FDG uptake on the baseline scan. Similarly, Derlin and colleagues [27] demonstrated ionic ¹⁸F⁻ fluoride deposition in the vasculature (carotid, iliac and femoral arteries as well as the aorta) in 57 of 75 patients referred for ¹⁸F-fluoride bone scans as part of an oncologic evaluation. However, there was co-localization with arterial calcification in only 12% of patients, suggesting that ¹⁸F-fluoride uptake and dense calcium likely represent different phases of an atheroma.

This was confirmed in a study of 45 patients who had both [¹⁸F]FDG and ¹⁸F-fluoride bone scans, where only 6.5% of lesions had colocalization of both tracers in regions without gross calcification, and 14.5% demonstrated colocalization in regions of calcification [28].

The lack of ¹⁸F-fluoride localization in regions of dense calcium suggests that these regions have a much smaller surface area for rapid exchange than regions of microcalcification. Regions of early dystrophic vascular calcification, on the other hand, occur in regions recovering from acute inflammation. These areas have a rich vascular network of ‘immature endothelial tubes with leaky imperfect linings [29].

These regions would have rapid delivery of fluoride ion to the developing calcium-organic material complex that forms the basis of vascular microcalcification [30], and would localize at a time in the evolution of the plaque when the lesion is vulnerable. Microcalcifications range from 5 to 60 μm, too small to be defined on conventional CT. However, when atheromas are subjected to high resolution micro-CT these lesions are readily visible [31]. Based on the kinetics of fluoride localization in dystrophic calcification, it is likely that focal ¹⁸F-fluoride uptake in atheroma occurs in lesions in this critical phase.

Clinical studies are required to validate this hypothesis. However, based on PET/CT studies to date [21] the future of ¹⁸F-fluoride imaging for the localization of vulnerable atheroma looks promising. Due to significant lesion uptake and high target to background ratios, it may be possible to develop a

score based on a combination of lesion SUV (in spite of the partial volume effects) and the number of lesions in a vascular territory. This score may determine if pharmacologic therapy will be sufficient or revascularization is necessary.

Conflict of interest

The authors have no conflicts of interest.

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Key Article References: 2, 9, 13, 14, 18, 21, 26, 28, 30 & 31

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