

# From inflammation to calcification in atherosclerosis

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Selecting appropriate therapy for a specific patient with cardiovascular disease requires markers of both disease severity and location to identify the risk of a clinical event. Classic markers, such as the Framingham Risk Score, identify a population at risk, but do not perform well for an individual patient. To get patient specific information at a reasonable cost will likely require a two-step process. Step one would identify the presence of disease with an inexpensive laboratory assay; step two would be a non-invasive imaging technique to localize atheroma at risk of forming an occlusive thrombus. At this time we do not have a sensitive and specific screening blood test. There are, however, multiple imaging techniques that may provide information on the geographic distribution of lesions at moderate or high risk of rupture. PET/CT imaging can identify three markers that may be helpful for the imaging evaluation:

1. Vascular calcification (based on Agatston score of vessel calcification derived from CT);
2. Vascular inflammation (based on focal fluorodeoxyglucose vascular uptake); and
3. Vascular microcalcification (based on focal uptake of  $^{18}\text{F}^-$  sodium fluoride [1]).

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Microcalcification ( $^{18}\text{F}$ -fluoride localization in regions with either no CT detectable calcification or small foci of spotty calcification), appears to represent a specific phase in the evolution of an atheroma, when severe inflammation and necrosis begin to stabilize, and microcalcifications form in the necrotic core. This point in the life of the lesion may be a more specific indicator to identify risk for cardiovascular events than imaging inflammation, macrophage cell death [2], or dense calcification [3].

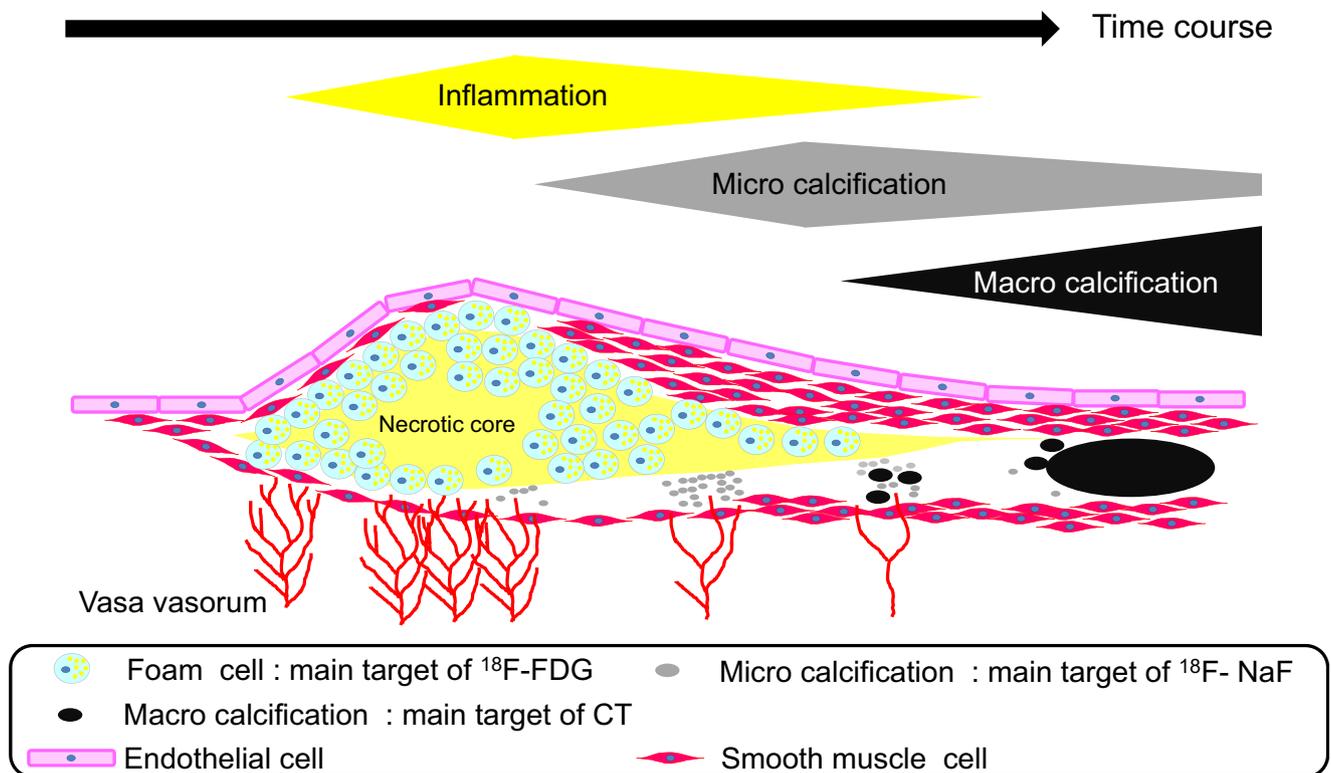
In a recently published manuscript Blomberg et al. [4], challenge the role of  $^{18}\text{F}$ -FDG uptake as a cardiovascular disease risk marker, compared to  $^{18}\text{F}$ -NaF and calcium burden. Their challenge is based on data derived from the CAMONA Study (a multi-institutional study to assess ‘Cardiovascular Molecular Calcification Assessed by  $^{18}\text{F}$ -NaF PET/CT’). The authors performed a retrospective analysis evaluating several findings in the thoracic aorta of these patients in relation to their Framingham Risk Score (FRS). The parameters included: focal uptake of  $^{18}\text{F}$ -FDG, focal uptake of  $^{18}\text{F}$ -NaF – fluoride and focal calcification on CT. CAMONA enrolled 89 healthy volunteers (as the control group) and 50 patients with chest pain syndromes.  $^{18}\text{F}$ -FDG PET/CT images were recorded 180 min after intravenous injection of 4.0 MBq/kg  $^{18}\text{F}$ -FDG.  $^{18}\text{F}$ -NaF PET/CT imaging was performed at 90 min after intravenous injection of 2.2 MBq/kg of  $^{18}\text{F}$ -NaF. The interval between FDG and Fluoride imaging was less than 2 weeks. Uptake of  $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -NaF and the presence of focal calcifications in the thoracic aorta were quantified by manually delineating regions of interest (ROI). The investigators calculated the maximum decay and background-corrected  $^{18}\text{F}$ -FDG and  $^{18}\text{F}$ -NaF activity concentration (kBq/ml) per slice. Maximum values obtained per ROI were summed and divided by the number of ROIs resulting in a single average maximum value (FDGmax or NaFmax). Calcification was measured in the thoracic aorta on low-dose CT images recorded for

measuring attenuation at the time of NaF PET/CT (using an attenuation threshold of 130 Hounsfield units). The calcium volume from all slices was summed and divided by the number of slices resulting in a single mean CT calcium volume (mm<sup>3</sup>).

The investigators report three major observations from this study:

1. Thoracic aorta <sup>18</sup>F-FDG uptake did not correlate with thoracic aorta <sup>18</sup>F-NaF uptake or with thoracic aorta CT calcium burden. On the other hand, thoracic aorta <sup>18</sup>F-NaF correlated with thoracic aorta CT calcium burden;
2. FRS increased linearly with quartiles of thoracic aorta <sup>18</sup>F-NaF uptake or thoracic aorta CT calcium burden, although FRS remained similar across quartiles of thoracic aorta <sup>18</sup>F-FDG uptake;
3. Multivariate linear regression established that thoracic aorta <sup>18</sup>F-NaF uptake and thoracic aorta CT calcium burden, but not thoracic aorta <sup>18</sup>F-FDG uptake, were independent determinants of FRS. From these findings, the investigators concluded that thoracic aorta calcification, but not inflammation, is associated with increased cardiovascular disease risk.

The lack of correlation of vascular FDG uptake and FRS is surprising, and differs from the results of other investigators. Moon et al. [5] found a correlation of carotid FDG uptake and FRS, but not of carotid intima/media ratio, as a predictor of events during an average follow-up of 4.2 years. Similarly, Hetterich et al. [6] found a correlation of FDG vascular uptake with traditional risk factors. The discordance of findings by Blomberg et al. in the CAMONA study population and those of Moon and Hetterich primarily in cancer patients may be due to the difference in the study populations, or other factors. Atherosclerosis is a dynamic, ongoing process. Lesions evolve. Rudd et al. suggest the FDG uptake is stable during a 2 week interval [7]. Lesions evolve, however, from a low risk for causing a clinical event such as a fatty streak, to high risk when the lesion develops a large necrotic core, neovascularization and a thin cap. A high risk lesion may evolve to low risk, with development of a thick cap and a decrease in size of the necrotic core, usually associated with increased calcification within the lesion. Obtaining a ‘snapshot’ of the status of a dynamic lesion in a small population of patients can lead to erroneous conclusions. The evolution of an atheroma from low risk to high risk and back to low risk is summarized in Fig. 1.



**Fig. 1** Time course of “inflammation” and “calcification” in atherosclerosis. (overview). Macrophage ingests lipoproteins and become cholesterol-laden foam cells (main target of <sup>18</sup>F-FDG). Initially, apoptotic foam cells are phagocytized by adjacent smooth muscle cells. However, as the number of apoptotic cells increase, apoptotic cell debris

is not cleared, resulting in the necrotic core. Vesicles in the necrotic core serve as nucleation sites for calcium phosphate microcalcification (main target of <sup>18</sup>F- NaF). Microcalcifications gather into a large mass or a calcification cascade like bone formation and result in macrocalcification (main target of CT)

The potential role of  $^{18}\text{F}$ -FDG to detect vascular inflammation in atherosclerosis was proposed over 20 years ago [8] and has been well investigated compared to the relatively recent (~6 year [1]) literature on vascular  $^{18}\text{F}$ -NaF uptake.  $^{18}\text{F}$ -FDG imaging has been applied to demonstrate a decrease in carotid inflammation due to therapy with simvastatin [9]. Confounding these changes in FDG uptake is the waxing and waning course of inflammation in atheroma.

In spite of the short-term reproducibility of vascular FDG uptake, both Menezes LJ et al. [10]. and Meirelles et al. [11] confirmed that  $^{18}\text{F}$ -FDG uptake changes over time, either increasing or decreasing in intensity and extent, reflecting the waxing and waning course of atheroma. On the other hand, calcification had only minimal changes over time, often increasing slightly over the interval between imaging. These changes are in keeping with the intravascular ultrasound findings described by Kubo et al. [12] and eloquently discussed by Arbab-Zadeh and Fuster in their landmark editorial in JACC [13]. The Kubo study determined that of 20 lesions classified as thin cap fibroatheroma on virtual histology intravascular ultrasound (VH-IVUS), 15 healed and five remained unchanged 1 year later.

Although  $^{18}\text{F}$ -NaF was introduced by Blau et al. in 1962 [14] for detection of osseous metastasis, it was only recently proposed for the detection of vascular microcalcification by Derlin et al. [1]. Derlin et al. showed  $^{18}\text{F}$ -NaF uptake is a surrogate marker of calcifying carotid plaque and only 6.5% of arterial lesions seen on the  $^{18}\text{F}$ -fluoride images co-localized with  $^{18}\text{F}$ -FDG, suggesting that  $^{18}\text{F}$ -NaF and  $^{18}\text{F}$ -FDG provide different information about atheroma [15, 16]. Aortic calcium is a known risk marker of CVD. Fiz F et al. investigated the relationship between the aortic calcium and  $^{18}\text{F}$ -NaF uptake on atherosclerotic plaque on PET CT imaging and found greater  $^{18}\text{F}$ -NaF uptake in the lowest density calcifications (<210 HU) than in medium calcifications (211–510 HU) and dense calcification (>510 HU). They suggested  $^{18}\text{F}$ -NaF uptake reflects calcium deposition in the early stages of plaque formation [17].

The surprising lack of correlation of FDG uptake and Framingham Risk Score in the Blomberg study needs to be confirmed in a follow-up study with more patients, evaluated at multiple time points, over several years. When we have that data, we will know whether FDG imaging, fluoride imaging or calcium score (or a combination of measurements) provide the most sensitive and specific prognostic information about cardiovascular events.

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