¹⁸F-sodium fluoride and vascular calcification: Some like it hot

Valeria Gaudieri, MD, PhD,^a Emilia Zampella, MD, PhD,^a Adriana D'Antonio, MD,^a and Alberto Cuocolo, MD^a

^a Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy

Received Mar 27, 2020; accepted Mar 27, 2020

doi:10.1007/s12350-020-02125-0

See related article, pp. 2244–2254

Atherosclerosis is still the leading cause of morbidity and death worldwide. Therapeutic interventions in the most advanced stages of the disease do not change its course and, in the last few years, innumerable efforts are aimed at early diagnosis and grading of the disease when it may still be susceptible to therapy. Vascular calcifications are accepted as a hallmark of atherosclerotic burden, and several biological mechanisms, including the release of calcifying extracellular vesicles, alterations in local microenvironment and increased mineralization, are involved in their pathogenesis.¹ In particular, these factors seem to promote osteogenic and chondrogenic differentiation of vascular smooth muscle cells and pericytes, encouraging cellular death. In an early stage, microcalcifications can be only histologically observed and are more frequently observed in regions of plaques with significant macrophage infiltration, suggesting a relationship between calcification and inflammation. On the contrary, macrocalcifications, well assessed with computed tomography (CT), are mainly detected in non-inflamed regions of plaques and are the expression of a more advanced stage of disease.^{2,3} It is now accepted that microcalcification is a dynamic process and plays an active role in plaque evolution, intensifying the incident stresses and leading to microfractures and plaque rupture. On the other hand, large calcifications may provide biomechanical stability and are more prevalent in patients with stable coronary artery disease⁴ and diffuse coronary atherosclerosis has been associated to severe vascular dysfunction also in absence of macroscopic disease.^{5,6} Hence, early detection of calcification could allow to identify the subjects at higher risk and to improve the risk stratification of

patients. Coronary artery calcium (CAC) score by CT, or its derivatives, including vascular age,⁷ seems to provide incremental information in addition to traditional risk factors in the prediction of all-cause mortality.^{8–10} However, the additional risk of CAC is still uncertain, maybe because CAC score assesses CAC density which seems to be inversely related with cardiovascular risk. Currently attention is being focused more on the CAC volume of calcium as a predictor of events than on CAC density.¹¹ Current-generation CT scanners are unable to detect microcalcifications, instead molecular imaging techniques provides a new method for studying early stage atherosclerosis by positron emission tomography (PET) with ¹⁸F-sodium fluoride (NaF). ¹⁸F-NaF is a highly sensitive bone-seeking PET tracer commonly used for skeletal diseases imaging; in particular, it finds its main application in the oncological field.¹² Recently, ¹⁸F-NaF has been studied in plaque imaging as a biomarker of active calcification in coronary atherosclerosis.^{13,14} The ¹⁸F ions bind to the surface of nanocrystalline hydroxyapatite in areas far from macrocalcifications, and the intensity of NaF uptake is higher for the smaller sized crystals.¹⁵ Thus, ¹⁸F-NaF is able to bind microcalcifications too small to be detected by CT. Over the years, there have been several studies on the use of fluoride to obtain functional information on calcified plaque, demonstrating that this technique is a reliable method for imaging active microcalcification. PET-derived information allows the early detection of disease before structural changes have established. Remarkably, ¹⁸F-NaF uptake appears to be higher in patients with greater cardiovascular risk factor burden and able to identify microcalcification in patients with unstable manifestations of atherosclerosis.¹³ ¹⁸F-NaF PET has been already used for in vivo quantification of microcalcification in the carotid and coronary arteries, and in the aorta, as a marker of culprit plaques. It has been observed that patients with ¹⁸F-NaF uptake are more likely to have angina, established coronary artery

Reprint requests: Alberto Cuocolo, MD, Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy; cuocolo@unina.it

J Nucl Cardiol 2021;28:2255–7.

1071-3581/\$34.00

Copyright © 2020 American Society of Nuclear Cardiology.

disease, previous major adverse cardiac events and revascularization procedures. In subjects with myocardial infarction, ¹⁸F-NaF was able to localize to recent plaque rupture, whereas, in patients with stable coronary artery disease, ¹⁸F-NaF uptake appears to recognize coronary plaques with high-risk characteristics on intravascular ultrasound.¹⁶ PET systems are usually integrated with CT and may identify both microcalcification and macrocalcifications, providing a more complete evaluation of vascular beds. The combined assessment could change the clinical utility of calcification imaging from a global risk stratification tool to a tool for improved plaque characterization. In support of this, in vivo clinical studies have found that among plaques with ¹⁸F-NaF uptake among these 88% showed concordant calcification by CT, but, in the remaining 12% of plaques, ¹⁸F-NaF uptake does not match with CT-detectable calcifications.¹⁷ Only few studies examined the relationship between ¹⁸F-NaF uptake and calcification progression. Li et al.¹⁸ investigated the arterial uptake of ¹⁸F-NaF and ¹⁸F-FDG and considered the association between tracer uptake and calcium density at different stages of atherosclerosis. They enrolled 34 multiple myeloma patients, who underwent both ¹⁸F-FDG and ¹⁸F-NaF imaging, 19 of these had a follow-up scan at an interval of 15 ± 4 months without in between important change in medication. A total of 221 atherosclerotic lesions were detected and divided in three groups: non-calcified (< 130 Hounsfield units, HU), mildly calcified (130-399 HU), and severely calcified (≥ 400 HU). ¹⁸F-NaF and ¹⁸F-FDG uptake was not correlated in non-calcified lesions, but in mildly calcified ($r = .7$) and highly calcified lesions ($r = .4$). Both ¹⁸F-NaF and ¹⁸F-FDG uptake was higher in non-calcified than calcified lesions; ¹⁸F-NaF uptake was higher with increasing plaque density, whereas ¹⁸F-FDG uptake decreased. Ishiwata et al.¹⁹ evaluated ¹⁸F-NaF uptake in the thoracic and abdominal aorta and in the common iliac artery of 34 patients, underwent to PET/CT for malignancy or orthopedic disease, with a 1-year follow-up data, to understand if ¹⁸F-NaF uptake could predict progression of calcification on CT. They compared 182 sites with > 130 HU on CT and 96 hot spots with < 130 HU and high uptake of ¹⁸F-NaF at baseline with CT at follow-up and found that baseline ¹⁸F-NaF uptake correlated with change in calcification volume and change in HU score, but not with calcification in HU or volume. New detectable macrocalcification was observed in 19/96 of original NaF hot spots without macrocalcification.

In this issue of the Journal, den Harder et al.²⁰ evaluated if ¹⁸F-NaF could assess the presence of calcification and the prognostic value of this radiotracer in predicting vascular calcification progression. They

included patients, participating in two different longitudinal studies, who underwent ¹⁸F-NaF PET/CT at baseline and after six months or one-year follow-up. Since the populations under examination had very specific pathologies, they analyzed the findings of the two patient groups separately. The first group included 72 patients with a clinical diagnosis of pseudoxanthoma elasticum and evidence of arterial calcification on a CT of the lower limbs. One half of the patients received 1-year treatment with a bisphosphonate the other half was assigned to placebo. The second group included 56 patients with diabetes mellitus type 2 and presence of arterial disease. 30 patients received vitamin K for 6 months and 26 patients had placebo. The target to background ratio (TBR) was measured on PET at baseline and CT calcification was quantified in the femoral arteries at baseline and follow-up. For the first group 6294 slices were evaluated, for the second group 4642. They found that for both patient groups a higher TBR at baseline was related with higher calcification mass at baseline and calcification progression at follow-up, moreover, in the slices without calcification at baseline, in which calcium develop at follow-up, TBR at baseline was slight but significantly higher compared to slices in which no calcium formation occurred. The authors also evaluated the evolution of the slices with higher uptake and without calcification in the placebo groups. In patients with pseudoxanthoma elasticum the 148 hottest slices showed a mean calcium mass score at follow-up of 3.204 vs 1.064 in the 1525 other slices ($P < .001$); calcium developed at follow-up in 20% (30/148) of the hottest slices and only in 8% (129/1525) of the remaining slices. Different results were observed in diabetic patients: the 32 hottest slices presented a mean calcium mass score at follow-up of .304 vs .345 in the 1321 other slices; calcium developed at follow-up in 3/32 (9%) of the hottest slices and in 130/1321 (10%) of the remaining slices. Maybe the length of follow-up of diabetic patients (6 months) was relatively short, since progression of calcification is a slow process, this could be affected in some way the findings. The results of this investigation are of note, demonstrating that ¹⁸F-NaF activity in the femoral arteries is related to the amount of calcification and calcification progression. Therefore, evaluation of femoral arteries by ¹⁸F-NaF could be used as a method in different populations. However, the differences between vessels that present progressive calcification and those without is minimal and in the absence of a clear cut-off, the clinical relevance might be limited.

¹⁸F-NaF PET is arousing great interest in the non-invasively evaluation of the early beginning of vascular calcification. In addition, numerous studies are proceeding on potential drugs to combat microcalcification,

such as statins, bisphosphonates, phosphate binders and vitamin K.²¹ There is the need for more extensive clinical trials using these possible therapies to stimulate vascular health and maybe ¹⁸F-NaF PET could be useful for monitoring active microcalcifications and response to therapy. Future research should have a longer follow-up time, document transformation of ¹⁸F-NaF-avid microcalcification into CT-detectable macrocalcification, and evaluate to what extent and when anti-atherosclerotic intervention can slow down or stop the arteriosclerotic disease progression.

Conflict of interest

Valeria Gaudieri, Emilia Zampella, Adriana D'Antonio, and Alberto Cuocolo declare that they have no conflict of interest.

References

- Pugliese G, Iacobini C, Blasetti Fantauzzi C, Menini S. The dark and bright side of atherosclerotic calcification. *Atherosclerosis* 2015;238:220-30.
- McEvoy JW, Blaha MJ, Defilippis AP, Budoff MJ, Nasir K, Blumenthal RS, et al. Coronary artery calcium progression: An important clinical measurement? A review of published reports. *J Am Coll Cardiol* 2010;56:1613-22.
- Aikawa E, Nahrendorf M, Figueiredo JL, Swirski FK, Shtatland T, Kohler RH, et al. Osteogenesis associates with inflammation in early-stage atherosclerosis evaluated by molecular imaging in vivo. *Circulation* 2007;116:2841-50.
- Zampella E, Acampa W, Assante R, Nappi C, Gaudieri V, Mainolfi CG, et al. Combined evaluation of regional coronary artery calcium and myocardial perfusion by (82)Rb PET/CT in the identification of obstructive coronary artery disease. *Eur J Nucl Med Mol Imaging* 2018;45:521-9.
- Assante R, Acampa W, Zampella E, Arumugam P, Nappi C, Gaudieri V, et al. Coronary atherosclerotic burden vs coronary vascular function in diabetic and nondiabetic patients with normal myocardial perfusion: A propensity score analysis. *Eur J Nucl Med Mol Imaging* 2017;44:1129-35.
- Gaudieri V, Acampa W, Rozza F, Nappi C, Zampella E, Assante R, et al. Coronary vascular function in patients with resistant hypertension and normal myocardial perfusion: A propensity score analysis. *Eur Heart J Cardiovasc Imaging* 2019;20:949-58.
- Nappi C, Gaudieri V, Acampa W, Arumugam P, Assante R, Zampella E, et al. Coronary vascular age: An alternate means for predicting stress-induced myocardial ischemia in patients with suspected coronary artery disease. *J Nucl Cardiol* 2019;26:1348-55.
- Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. *J Am Coll Cardiol* 2007;49:1860-70.
- Assante R, Acampa W, Zampella E, Arumugam P, Nappi C, Gaudieri V, Mainolfi CG, et al. Prognostic value of atherosclerotic burden and coronary vascular function in patients with suspected coronary artery disease. *Eur J Nucl Med Mol Imaging* 2017;44:2290-8.
- Zampella E, Acampa W, Assante R, Gaudieri V, Nappi C, Mannarino T, et al. Combined evaluation of regional coronary artery calcium and myocardial perfusion by (82)Rb PET/CT in predicting lesion-related outcome. *Eur J Nucl Med Mol Imaging* 2019. <https://doi.org/10.1007/s00259-019-04534-x>.
- Criqui MH, Knox JB, Denenberg JO, Forbang NI, McClelland RL, Novotny TE, et al. Coronary artery calcium volume and density: Potential interactions and overall predictive value: The Multi-Ethnic Study of Atherosclerosis. *JACC Cardiovasc Imaging* 2017;10:845-54.
- Segall G, Delbeke D, Stabin MG, Even-Sapir E, Fair J, Sajdak R, et al. SNM. SNM practice guideline for sodium 18F-fluoride PET/CT bone scans 10. *J Nucl Med* 2010;51:1813-20.
- Dweck MR, Chow MW, Joshi NV, Williams MC, Jones C, Fletcher AM, et al. Coronary arterial 18F-sodium fluoride uptake: A novel marker of plaque biology. *J Am Coll Cardiol* 2012;59:1539-48.
- Fiz F, Morbelli S, Piccardo A, Bauckneht M, Ferrarazzo G, Pestarino E, et al. ¹⁸F-NaF uptake by atherosclerotic plaque on PET/CT imaging: Inverse correlation between calcification density and mineral metabolic activity. *J Nucl Med* 2015;56:1019-23.
- Creager MD, Hohl T, Hutcheson JD, Moss AJ, Schlotter F, Blaser MC, et al. (18)F-fluoride signal amplification identifies microcalcifications associated with atherosclerotic plaque instability in positron emission tomography/computed tomography images. *Circ Cardiovasc Imaging* 2019;12:e007835.
- Joshi NV, Vesey AT, Williams MC, Shah AS, Calvert PA, Craighead FH, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: A prospective clinical trial. *Lancet* 2014;383:705-13.
- Derlin T, Richter U, Bannas P, Begemann P, Buchert R, Mester J, et al. Feasibility of 18F-sodium fluoride PET/CT for imaging of atherosclerotic plaque. *J Nucl Med* 2010;51:862-5.
- Li X, Heber D, Cal-Gonzalez J, Karanikas G, Mayerhoefer ME, Rasul S, Beitzke D, et al. Association between osteogenesis and inflammation during the progression of calcified plaque evaluated by (18)F-fluoride and (18)F-FDG. *J Nucl Med* 2017;58:968-74.
- Ishiwata Y, Kaneta T, Nawata S, Hino-Shishikura A, Yoshida K, Inoue T. Quantification of temporal changes in calcium score in active atherosclerotic plaque in major vessels by (18)F-sodium fluoride PET/CT. *Eur J Nucl Med Mol Imaging* 2017;44:1529-37.
- den Harder AM, Wolterink JM, Bartstra JW, Spiering W, Zwakenberg SR, Beulens JW, et al. Vascular uptake on (18)F-sodium fluoride positron emission tomography: Precursor of vascular calcification? *J Nucl Cardiol* 2020. <https://doi.org/10.1007/s12350-020-02031-5>.
- Wu M, Rementer C, Giachelli CM. Vascular calcification: An update on mechanisms and challenges in treatment. *Calcif Tissue Int* 2013;93:365-73.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.