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Evolving Role of PET in Detecting and Characterizing Atherosclerosis

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SYNOPSIS

Cardiovascular molecular imaging has for decades successfully focused on the assessment of myocardial perfusion and ventricular ejection fraction. However, as with almost all diagnostic cardiovascular procedures, proven abnormalities that are detectable by these modalities represent late downstream effects of the atherosclerotic disease process. This calls for a change of focus towards methods that can detect early arterial wall changes before macrocalcifications become visible on CT angiography and provide a better understanding of the disease process. Here, we summarize the current knowledge on the use of PET in atherosclerosis and highlight pertinent questions relating to the early detection of atherosclerosis. The interrelationship and chronology of inflammation and microcalcification remain obscure; it is unclear which process comes first and is the more important in initiating and maintaining plaque formation. Arterial wall inflammation and calcification rarely overlap in time and location, and only arterial microcalcification and not inflammation correlates consistently with 10-year Framingham risk scores. This points to NaF-PET as a future gold standard in the utilization of molecular imaging in diagnosis, prognosis, and treatment response assessment in atherosclerosis. The future of PET in atherosclerosis may be early individualized quantification of the arteriosclerotic disease burden rather than exploration of features of individual arterial plaques.

KEY POINTS

- The use of ^{18}F-FDG (FDG) and ^{18}F-sodium fluoride (NaF), depicting arterial wall inflammation and microcalcification, respectively, signifies a shift in focus of molecular imaging in cardiovascular disease, from imaging of late downstream effects of atherosclerosis to detection and characterization of active atherosclerosis in its early stages.
- Arterial wall inflammation and microcalcification are two dynamic processes that are not directly interconnected; they do not occur in parallel or in succession with a fixed time sequence; thus, their exact interrelationship is largely unknown.
- The frequency of arterial wall inflammation and microcalcification increases slightly with age, more so in patients with chest pain than in healthy controls, but only microcalcification and not arterial wall inflammation correlates positively with 10-year Framingham risk scores.
- The mainstay of PET imaging in atherosclerosis may shift toward early NaF PET grading of atherosclerotic disease burden, rather than characterizing features of single plaques.
- NaF PET imaging offers an individualized measurement of microcalcification in the heart, the aorta, carotids and other major arteries with a reproducibility allowing for monitoring of new anti-atherosclerotic interventions.
- Prospective studies are called for to elucidate the interrelationship between arterial wall inflammation and microcalcification and investigate to what degree NaF and/or FDG PET imaging alone or in combination with existing risk factors may replace or support traditional diagnostic procedures.

INTRODUCTION

Strategic PET imaging with ^{18}F-fluorodeoxyglucose (FDG) and/or ^{18}F-sodium fluoride (NaF) heralds a new era of molecular cardiovascular imaging. It will expand our understanding of atherosclerosis and allow us to shift our focus from the late to the early stages of atherosclerotic disease. If present promises hold true, it may even minimize or obviate most of the current actions we take against the disease.

Molecular imaging of cardiovascular disease (CVD) has been a success story from its beginnings in 1925, when Hermann Blumgart and Otto Yens used a modified Wilson cloud chamber to "image" the effects of α and β particles for the purpose of measuring delayed circulatory transit times in heart patients compared to normal controls.[1,2] The imaging milestones that followed included the visualization of the pulmonary circulation in the 1960s by George Taplin and by Henry Wagner Jr. by means of macroaggregated albumin,[3,4] the diagnosis of acute myocardial infarction in the 1970s by ^{99m}Tc stanneous pyrophosphate and ^{201}Tl ,[5,6] radionuclide ventriculography for measurement of ventricular function and not least myocardial perfusion scintigraphy with ^{201}Tl or with ^{99m}Tc-labeled compounds,[7-9] PET perfusion imaging using ^{15}O-water, the "gold standard" of perfusion measurement, as well as ^{82}Rb and $^{13}NH_3$ and in recent years ^{18}F-labelled PET probes targeting mitochondrial complex 1.[10,11] At this point, molecular imaging has been in use for decades in the assessment of cardiac viability, sarcoidosis, amyloidosis as for the diagnosis of cardiovascular infection, inflammation and neoplasm.[12]

Nonetheless, molecular imaging stands to lose ground in various clinical applications including the study of myocardial perfusion in angina pectoris patients and serial measurement of left ventricular ejection fraction during cancer chemotherapy. The task of ruling out significant coronary artery disease has successfully been taken over by cardiac CT,[13,14] leaving perfusion studies for

assessment of the clinical significance of CT-proven coronary artery disease.[15-17] Smart 3D echocardiographic measurements of left ventricular ejection fraction are much faster and cheaper, though less reliable, than multigated radioisotope determination, and in addition echocardiography provides significant information of diastolic function and regional contraction pattern that is not that easily obtained with radionuclide techniques.[18,19]

However, molecular imaging in CVD offers entirely new options in the study and management of atherosclerosis, the most common cause of death in the US[20] and, according to the WHO, the world's number one killer.[21] Most initiatives intended to alleviate the human and economic costs of this disease are aimed at controlling risk factors and improving primary care of CVD management. Modern PET molecular imaging plays a complementary and innovative role by focusing on early disease, when the chance of cure or effective control may be significantly greater. The basis for this shift was laid 17 years ago with the first reported use of FDG for assessment of arterial wall inflammation[22,23] followed almost a decade later by the introduction of NaF-PET for imaging of molecular arterial wall calcification.[24-31] More recent experience suggest that the potential value of PET imaging in atherosclerosis is not primarily a matter of diagnosing or characterizing the vulnerable plaque,[32,33] since the clinical significance of this approach may be less than anticipated. Rather, the main focus should be on measuring the atherosclerotic burden and its activity in the body,[34] preferably as early as possible in the course of disease.

MOLECULAR IMAGING OF ATHEROSCLEROSIS

Traditionally, the atherosclerotic process has been considered a product of inflammation mobilizing monocytes, which differentiate into macrophages and become foam cells by phagocytizing lipids, particularly low density lipoproteins (LDLs).[35,36] Along with cellular debris, these foam cells form

the main part of the atherosclerotic plaque. At the center of these plaques is a necrotic core that holds minute vesicles giving rise to micro-calcification, which can contribute to plaque rupture (**Fig. 1**), but can also stabilize the plaque once inflammation subsides and overt macro-calcification takes over.[37,38] This complicated line of processes with multiple modifying and contributing factors has given rise to a number of gamma camera and PET tracers targeting features of the atherosclerotic plaque, including inflammatory cells, lipids and fatty acids, hypoxia, angiogenesis, proteases, thrombosis, apoptosis, and microcalcification, as recently summarized by Nakahara et al.[36] To these might be added matrix metalloproteinases tagged with ^{111}In, ^{99m}Tc, ^{123}I, and ^{18}F[39] and more recently ^{18}F-fluorinated matrix metalloproteinase inhibitors[40] and ^{89}Zr-labeled high density lipoprotein forming natural nanoparticles, which have been shown to accumulate in advanced atherosclerotic lesions of established animal atherosclerosis models.[41] However, practically none of the potentially more specific radiopharmaceuticals have attained extensive human use, with the notable exceptions of FDG and NaF, whose full potential in this application is not yet known.

FDG-PET/CT IN ATHEROSCLEROSIS

Vulnerable Plaque

Multiple efforts with multiple modalities including PET have been made to identify features of the vulnerable plaque with the purpose of predicting risk of future cardiovascular events.[36] Clinical studies in patients with stable cancer have shown that increased FDG uptake in plaques in major arteries and the carotid arteries is associated with a higher risk of cardiovascular and cerebrovascular events, respectively.[42,43] However, as pointed out by Dilsizian & Jadvar, FDG uptake may not be able to differentiate morphologically unstable (inflammatory) from stable (noninflammatory) atherosclerotic plaque, and there are other vascular diseases in which macrophages and inflammation

play an important role in the absence of atherosclerosis (e.g., Takayasu arteritis, chemotherapy- or radiation-induced vascular inflammation, and foreign-body reactions such as synthetic arterial graft), meaning that "the nonspecific nature of FDG uptake by any cell (upregulated under hypoxic conditions or other microenvironmental factors)" calls for caution "when interpreting vascular FDG uptake as indicative of inflammatory atherosclerosis in the clinical setting".[44] This and results obtained recently by our group challenge some of the preliminary conclusions that we drew in a prior review, including that by targeting macrophages and hypoxia FDG PET can "potentially detect atherosclerosis, evaluate response to treatment, and prognosticate risk for acute cardiovascular events," and further that arterial FDG uptake is "helpful in risk stratification of patients at risk for cardiovascular disease, beyond standard tools, such as the Framingham risk score (FRS) and coronary calcium score".[45] As argued in a review by Arbab-Zadeh & Fuster, multiple pathologic and clinical studies suggest that the vulnerable plaque is more a myth than a reality of clinical significance and that the quest to identify vulnerable atherosclerotic plaques may be quixotic.[34] Their more cogent arguments include (a) numerous investigations have demonstrated that many (if not most) plaques rupture without clinical symptoms, (b) the percentage of patients with subclinical plaque ruptures varies vastly depending on risk profile and assessment methods, (c) plaque rupture and healing are frequently clinically silent, (d) millions of individuals most likely unknowingly experience plaque rupture each year, (e) plaque morphology changes in the span of months, gaining or losing their vulnerable characteristics, and (f) in patients with acute coronary syndrome, plaque rupture is frequently found in non-culprit lesions. The authors propose that a state of generalized vulnerability is more important than the individual sites of vulnerability in a patient. Very few plaque ruptures will trigger symptomatic events, and therefore, the prediction of adverse outcome based on characteristics of particular lesions is "unlikely to be of incremental benefit for risk prediction over established risk factors (e.g., extent and distribution of atherosclerotic plaque burden).[34]

We agree with this assertion from a molecular imaging perspective. PET can measure the extent and severity of atherosclerotic burden in an organ or the entire body and provide a "global disease score (GDS)", which we consider a conceptually more correct expression of the disease and its activity than sequential examinations of a few selected lesions.[28,46,47] With FDG-PET it is possible to demonstrate the presence of inflammation with a reproducibility that appears to be sufficient to allow demonstration of spontaneous or disease-inflicted changes. However, the question of whether this inflammation precedes or follows the formation of atherosclerotic calcification remains unanswered.[48]

Relation to Risk Factors

In their 2001 study of 137 patients undergoing either whole-body or lower-extremity FDG-PET scans, Yun et al. demonstrated that half of all subjects had abnormal FDG uptake in at least one of the following studied arteries: abdominal aorta, iliac, proximal femoral, and popliteal arteries (34% of patients aged 20-40 years, 50% of patients aged 41-60 years and 61% of patients aged 61-80 years).[22] Since then, a number of studies of various designs applying different imaging techinques and vastly differing image analyses have demonstrated similar findings,[23-27,50-56] often showing "strong" or "highly significant" correlations between age and with risk factors. Dependency on age is also what we see with extended analyses[56-59] of the CAMONA (Cardiovascular Molecular Calcification Assessed by ^{18}F-NaF PET/CT) study in Odense, Denmark, in which a total of 139 subjects aged 21-75 years, 52% men, (89 healthy controls + 50 angina pectoris patients) were examined with both FDG and NaF PET/CT.[56] However, with modern imaging acquisition and analysis techniques, we and others could not demonstrate a significant correlation of thoracic aortic FDG uptake and the 10-year FRS, whereas this was clearly present between NaF uptake and the FRS (**Fig. 2**).[60,61] The

many analyses we have performed on our CAMONA material, or part of it, have without gender differences shown frequent and higher FDG uptake in the thoracic aorta and its three segments in angina pectoris patients than in healthy controls and weak but positive correlation with age, which is also more pronounced in patients.[56,57] We found the same tendencies in the abdominal aorta,[58] but not in the carotid arteries.[59]

It is difficult to compare the many reports on FDG uptake in the arterial system due to vast differences in design and materials, frequent use of retrospective data and post hoc analyzes, and above all a lack of standardization with regard to image acquisition, analysis, and interpretation. In reviewing 49 articles, Huet et al. found 53 different acquisition protocols, 51 reconstruction protocols, and 46 quantification methods to characterize atherosclerotic lesions on FDG PET scans.[62]

Despite the variability in the methodology, the evidence suggests that foci of increased FDG uptake are frequently present in major arteries of the body and that this tendency increases slightly with age, albeit with large inter-individual differences, and that there seems to be only a vague association between arterial FDG uptake and cardiovascular risk factors.

Monitoring of Treatment

Preclinical studies in hyperlipidimic rabbits have demonstrated a decrease in aortic FDG uptake and macrophage infiltration of the aorta following antioxidant therapy[63] and an increase in aortic FDG uptake in rats on a sustained atherogenic diet.[64] In the few human studies on the role of FDG PET in monitoring the effects of statins, Tahara et al. demonstrated a decline in FDG uptakes in the thoracic aorta and/or carotid arteries following 3 months therapy,[65] while Ishii et al. reported a reduction in FDG target-to-background ratio (TBR) in the ascending aorta and femoral arteries after atorvastatin 20 mg for 6 months.[66] Finally, in a randomized trial including 76 patients with known

atherosclerosis, Tawakol et al. found reductions in arterial FDG activity after 4 and 12 weeks treatment with both 10 mg and 80 mg atorvastatin, and a further reduction in the 80 mg group only after 12 weeks.[67] Other anti-atherosclerotic drugs have been evaluated by FDG PET imaging, however, without showing significant effects.[45]

Disease Progression

Of great scientific interest and potential clinical significance is the existence of a causal and/or temporal association between arterial wall inflammation and calcification. It remains unclear which of these processes precedes the other, to what extent they overlap or succeed each other in time and location, and whether or not they stimulate or inhibit each other and/or other elements of the atherosclerotic process. Relatively few studies have reported findings from two or more succeeding scans and none of them were designed to study disease progression.

Meirelles et al. reviewed retrospectively the records of 100 consecutive cancer patients (51 male, 49 female; aged 20-80 y) with at least two FDG-PET/CT scans performed a mean of 7 months apart (range 21 d to 3 y) and found aortic uptake in 70%, which had changed on the second scan in 55% of patients.[53] Calcifications were often seen in patients with FDG-uptake but were present at the same site in only two cases, a finding that has been documented in several prior studies.[68-70] Calcification and FDG-uptake correlated with age, and patients with diabetes, hypertension, hyperlipidemia, or a history of CVD had significantly more calcification. Calcifications were stable, but the fact that FDG uptake changed in more than half of patients led the authors to conclude that "inflammation in atheroma is a waxing and waning inflammatory process".[53]

Abdelbaky et al. retrospectively studied 137 patients (aged 61 ± 13 years, 48.1% men) with inactive cancer, who underwent ≥2 FDG-PET/CT examinations spaced 1-5 years apart.[71] Using "square root-transformed difference of calcium volume score, with a cutoff value of 2.5" to determine whether vascular segments showed evidence of calcification, 67 (9%) of aortic segments were deemed to have developed calcification. Baseline FDG uptake proved predictive of which patient would go on to develop calcification. In univariate analysis, segment SUV, segment TBR, age, hyperlipidemia, statin therapy, systolic blood pressure, baseline CVD, and follow-up duration were all associated with subsequent calcium deposition, which led to the conclusion that "arterial inflammation precedes subsequent Ca deposition, a marker of plaque progression, within the underlying location in the artery wall".[71] Hetterich et al. retrospectively studied scans of 94 patients, aged 62.5 ± 8.7 years, 35% men, who underwent FDG-PET/CT at baseline and at follow-up 14.5 ± 3.5 months later because of various known or suspected cancers.[72] Annualized calcified plaque volume, judged by the Agatston score, increased by 10% in the carotid arteries, by 23%, 16%, and 18% in the thoracic, abdominal, and entire aorta, respectively, and by 9% in the iliac arteries. The lumen area measured in the carotids and the aorta decreased by 10% and 2%, respectively. Interestingly, FDG uptake, quantified by the TBR, did not change at all in any of these locations, and hypertension and not FGD uptake was the only independent predictor of calcification. In a post-hoc analysis of 130 patients in the del-PLAQUE trial, Joshi et al. found no effect of dalcetrapib on vessel wall inflammation.[73] This analysis revealed that patients with a zero calcium score at baseline had almost no new calcification at follow-up, while patients with a non-zero baseline calcium score had a higher rate of calcification, a tendency which was most pronounced in the aortic arch. However, no relationship was noted between baseline calcification and change in inflammation.[73] Cho et al. analyzed data from 96 asymptomatic middle-aged subjects (84% men) without a history of cardiac disease, who underwent FDG-PET/CT and CT calcium scoring on the same day and had follow-up scans ≥ 1

year later (mean 4.3 years) without having suffered interim cardiac events or received statin therapy in between.[74] Their aim was to investigate whether FDG uptake in the carotid arteries, ascending aorta, and abdominal aorta can predict coronary artery calcification (CAC) progression in asymptomatic individuals. At baseline, 21 subjects (22%) had CAC by CT, while 75 (78%) did not, and 59 (79%) of these had no CAC at follow-up. CAC progression was observed in 31 subjects (32%), in 15 of 21 (76%) with CAC at baseline and in 16 of 75 (21%) without. FDG uptake was significantly higher in CAC-progressors, and significant positive correlations were observed between several FDG uptake parameters and CAC progression, but all of them far too weak to all to allow relevant prediction. Interestingly, in multivariate analysis, only peak TBR for FDG uptake in the abdominal aorta was significantly associated with CAC progression.[74]

None of these studies showed a close association in time and place between arterial wall FDG uptake and arterial wall (macro)calcification, only a vague relationship that is moderately more pronounced with age but lacks striking coincidence or covariation. A picture emerges of CT-visible macrocalcification which changes little over time, whereas FDG uptake changes rapidly ("waxing and waning") with regard to location, size, and intensity. On the whole, the aforementioned sequential studies are difficult to interpret, since they were not planned as prospective trials with a primary focus on changes in FDG uptake and calcification and because they lack sufficient follow-up.

In conclusion, FDG uptake in the arterial system is a frequent finding, which unlike CT-visible macrocalcification, varies rapidly over time. It is positively, but vaguely, associated with age, it overlaps with arterial wall macrocalcifications only to a limited degree, and it cannot with any reasonable certainty predict progression of arterial macrocalcifications. It remains unknown if it is always a predecessor of arterial wall microcalcification and/or macrocalcification.

NaF-PET/CT IN ATHEROSCLEROSIS

Vulnerable Plaque

Molecular mechanisms of NaF deposition in bone have been summarized by Czernin et al.[75] In short, NaF is taken up by bone after a single pass of blood, so that initial NaF distribution reflects blood flow that varies among different bones. Otherwise, NaF is rapidly cleared from plasma and excreted by the kidneys, leaving less than 10% in plasma after one hour and less than 3% after five hours. After chemisorption onto hydroxyapatite ^{18}F exchanges rapidly for OH on the surface of a hydroxyapatite matrix to form fluoroapatite, the first part of this process being rapid (seconds, minutes), the last part slow (days, weeks).[76-78] If the uptake of NaF by the arterial wall can be explained by a similar mechanism, NaF would presumably be taken up rapidly by microcalcification in the necrotic core of focal arterial injuries irrespective of whether this process is preceded by focal inflammation. NaF PET does not suffer from the same disadvantage as FDG PET in atherosclerosis imaging, namely that physiological myocardial glucose metabolism precludes imaging of coronary artery inflammation. On the other hand, quantification of arterial wall uptake of NaF PET is challenged by spillover from nearby bones, which makes it difficult to determine blood background activity.[79]

Few studies have examined the potential significance of NaF uptake for characterizing vulnerable plaques. Joshi et al. found that 93% of post myocardial infarction patients had higher NaF uptake in culprit vs non-culprit coronary lesions, that marked NaF uptake was present at the site of all carotid plaque ruptures, and that nearly half of stable angina patients had plaques with focal NaF uptake that was associated with more high risk features on intravascular ultrasound than those without NaF uptake.[32] Irkle et al. used electron microscopy, autoradiography, histology, and PET/CT to show that NaF adsorbs to calcified deposits within plaque with high affinity and is selective and

specific in a way that NaF PET/CT imaging can distinguish between areas of macro- and microcalcification.[80] Finally, Marchesseau et al. reported increased NaF uptake in coronary culprit lesions in a small cohort of post myocardial infarction patients and noted that NaF was taken up by scarred myocardial tissue[81], a finding that is reminiscent of the earlier work of Bonte and Parkey, who visualized acute myocardial infarction using ^{99m}Tc-pyrophosphate scintigraphy.[5] However, the characterization of vulnerable plaques may prove less clinically useful than imagined; as argued by Arbab-Zadeh and Fuster,[34] the question remains of what should be the preferred measure of atherosclerosis: the atherosclerotic burden, its location, extent and activity, or something else?

Relation to Risk Factors and Treatment

As described, arterial wall uptake of NaF correlates not only with age, but contrary to FDG, consistently also with risk factors for atherosclerosis and cardiovascular disease.[25,29,56-60] From the information collected thus far, it appears that NaF PET reflects key elements of initiation and development of the atherosclerotic process in a way that makes it worthwhile to explore its potential for studying the effects of anti-atherosclerotic treatment.

Disease progression

NaF-PET may be a better indicator of atherosclerotic disease progression than FDG-PET. Studies of the latter have been heterogeneous and often difficult to interpret, but have generally portrayed arterial FDG uptake as “waxing and waning” and only rarely overlapping with NaF uptake. This observation raises questions about the ability of FDG to predict or indicate more than local waxing and waning arterial inflammation, especially since it appears that there is no direct link between focal

inflammation and microcalcification. It seems more likely that such a link exists between micro- and macrocalcification. This relationship has not been reported yet. What we have seen so far from data of the CAMONA study is a more tight relationship between NaF uptake and risk factors than between FDF uptake and risk factors,[56-59,82-88] a finding which supports the assumption that NaF uptake may be a more faithful real-time representative of early active calcification. However, only carefully conducted longitudinal studies will reveal if this notion is correct.

Animal studies

Studies applying an Ossabaw miniature swine model of metabolic syndrome (MetS) have demonstrated that NaF uptake in the coronary arteries precedes the emergence of macroscopic calcification on IVUS and CT scans.[89-91] When fed a high-calorie atherogenic diet and forced to live a sedentary lifestyle, the Ossabaw swine develops progressive CAD from the stages of clinically insignificant fatty streaks through necrotic, flow-limiting lesions with macrocalcification detectable by intravascular ultrasound (IVUS).[92] Comparing lean and MetS pigs without evidence of CAC by CT, quantitative PET imaging showed almost a 2.5 higher NaF uptake in the hearts of MetS pigs compared to lean.[91] Another preclinical PET/CT study demonstrated that increased ^{18}F-NaF uptake in coronary arteries is a biomarker for early CAC in pigs with CAD that lack frank evidence of calcification by IVUS and CT imaging. [93] These findings imply that ^{18}F-NaF binds to microcalcifications too small to be detected using anatomic or morphologic imaging modalities, an interpretation that is strengthened by histopathology data revealing sparse calcifications within the proximal region of the coronary artery. These data do not significantly correlate with ^{18}F-NaF uptake in the coronaries, suggesting histological assessment detects macroaggregates of hydroxyapatite, but not the microcalcifications visualized by ^{18}F-NaF-PET/CT.[94] Several findings in this type of preclinical swine

model of CAD have hinted at a role for ^{18}F-NaF-PET/CT in the early detection of atherosclerosis.[59,60,93,94] With regard to treatment, Lee at al. have in diabetic dyslipidemic swine demonstrated almost complete attenuation by atorvastatin of coronary disease, a finding which has thus far not been verified in humans.[95]

PET/MRI IN ATHEROSCLEROSIS

Hybrid PET/MR imaging has been applied in experimental animal studies of atherosclerotic plaques that have utilized FDG and other tracers, including nanoparticles.[96-98] PET/MRI studies of atherosclerosis in humans are still sparse and are largely limited to first-in-human or feasibility studies.[99-102] Of particular interest is an observational, longitudinal, and prospective cohort study by Fernández-Ortiz et al. comprising a target population of 4000 healthy subjects (40-54 years old, 35% women) based in Madrid, Spain.[103] In a subgroup of 1300 subjects with evidence of atherosclerosis on 2D/3D ultrasound or cardiac CT, FDG PET/MR imaging of the carotid and iliofemoral arteries was performed at baseline and repeated at 3 and 6 years. At the 3-year mark, the authors found that subclinical atherosclerosis—classified as focal (1 site affected), intermediate (2-3 sites), or generalized (4-6 sites)—was present in 63% of participants (71% of men, 48% of women) and that 41% had intermediate and generalized atherosclerosis. Plaques were most common in the iliofemorals (44%), carotids (31%) and aorta (25%). Coronary artery calcification was present in only 18% of cases. Among participants with low 10-year FRS, subclinical disease was present in 58%.[104] It will be highly interesting to learn the result of the baseline FDG PET/MRI scans and to what degree these may have changed after 6 years.

LIMITATIONS AND CAVEATS

Despite the many unique advantages of PET, many of which have been mentioned above, it is appropriate to summarize the main caveats and limitations, which need to be considered to get the best out of this technology. The spatial resolution of PET is limited to a few millimeters under optimized conditions, but is actually closer to 5-10 millimeters in practice. This is due to blurring of imaging from patient, cardiac, and respiratory motion, some of which is irregular and non-episodic in nature and cannot be accurately corrected for by current techniques. Therefore, the higher sensitivity of PET may not be fully utilized without being paired with the much better spatial solution of CT and MR. The latter two methods can determine with very high precision the location of an abnormal weak signal that only PET can capture. CT and MR suffer from insufficient sensitivity, which means that they may ignore weak signals, even if abnormal. Moreover, they detect mostly anatomical, morphological, or structural changes in tissues and organs that typically occur late in the disease process. This principle applies to metastatic cancer[105] and most likely to atherosclerosis as well. Other considerations include motion artifacts and partial volume effects, have been the focus of prior studies.[46,47,106] Finally, the choice of parameter—TBR, SUV, metabolic tumor volume, or another local or global metrics[28,47,82,85,94]—can greatly affect the interpretation of a PET study. Ideally, PET parameters should be standardized and automated for ease of clinical use.

CONSIDERATIONS ABOUT ATHEROSCLEROTIC DISEASE

Most of what we know about atherosclerosis is based on histologic examination and experimental animal models of atherosclerosis rather than in vivo human studies. The results of FDG and NaF PET imaging of atherosclerosis are often in conflict and make it difficult to spot the more important underlying mechanisms and establish a unifying concept that can provide the basis for research into and improved management of this condition. From FDG PET imaging it appears that focal arterial

wall inflammation arises in response to minor injuries, most of which are harmless and heal quickly without any long-term damage. However, a subset of injuries, whether by virtue of their location, severity, or other characteristics, cause lasting damage to the arterial wall. Whether this process begins with an inflammatory cascade that culminates in apoptosis, necrosis, and calcification, or rather that calcifications arise at areas of stress (e.g., aortic arch or bifurcation) and induce chronic calcification and plaque formation, is not yet clear. To best apply PET imaging in atherosclerosis, it will be important to determine whether arterial wall microcalcification by NaF PET imaging is (i) always a forerunner to CT-visible macro-calcification, (ii) always an indicator of active, ongoing arterial wall calcification, (iii) comparable or superior to other known risk factors, and (iv) able to reliably monitor response to anti-atherosclerotic therapy. If NaF PET imaging possesses most of these key features, it may replace other modalities in current use for patients with CVD in spite of being more costly and less accessible.

WHERE TO GO FROM HERE

NaF PET imaging may cause a shift from the management of late-occurring symptomatic effects of atherosclerosis to the early detection and quantification of arterial wall microcalcification in asymptomatic subjects long before macrocalcification have developed and become CT-detectable. Traditionally, it may have been viewed as unorthodox to search for disease before the onset of symptoms and functional impairment. However, with modern technology, this outdated viewpoint need no longer apply. In cardiology, we have been testing for hypercholesterolemia and hypertension in asymptomatic patients on a massive scale for decades, ever since cheap testing became easily accessible. The downside has been enormous drug expenditures and side effects as a result of millions of people being put on lifelong treatment on the basis of a few cheap measurements and statistical

evidence that did not necessarily apply to each individual patient. Molecular imaging, including NaF PET/CT, offers more individualized disease assessment than what we are used to, particularly in the early stages of disease. From analyses of the CAMONA data, we know now that there is a positive correlation between age and the uptake of NaF in the heart (i.e., coronary arteries), thoracic and abdominal aorta, carotids, and choroid plexus in the brain. We also note that the slope of the regression line in all locations is modest, though greater in patients than controls.[82-88] Furthermore, the individual differences are huge, meaning for that some healthy volunteers and some angina pectoris patients above the age of 70 may still have a very low atherosclerotic burden, whereas some symptomless young individuals already have significant arterial wall microcalcification (**Fig. 3**). In these parts of the arterial system, the Alavi-Carlsen global molecular calcium score (GMCS), which is a measure of the total NaF uptake in part of the arterial system,[82,85] was a stronger predictor of the 10-year FRS than the commonly used parameters of average SUVmax and average SUVmean. FDG uptake in these segments were positively correlated with age in patients only, but not with the 10-year FRS.[82-88] All positive correlations had a wide scatter (**Fig. 3**), illustrating the need to characterize each individual subject by NaF PET imaging. Similarly, the scatter around the regression line when looking at the association with age was also so large that it questions the often postulated close association of atherosclerosis with age.

CONCLUSION

What has been published thus far in the literature on the use of PET in atherosclerosis portends great clinical utility but leaves ambiguous as to how the modality will be applied. A case can be made for NaF PET emerging as the key technique for the early detection and grading of atherosclerosis when it is still symptomless and devoid of CT-detectable macrocalcification. Intervening at

this early stage should produce a more efficacious response to therapy than later in the disease course when symptoms have appeared and organ damage has occurred. If this holds true, NaF PET imaging can be expected to play an increasingly central role in the diagnosis and management of atherosclerotic disease in the years to come.

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Figure 1.

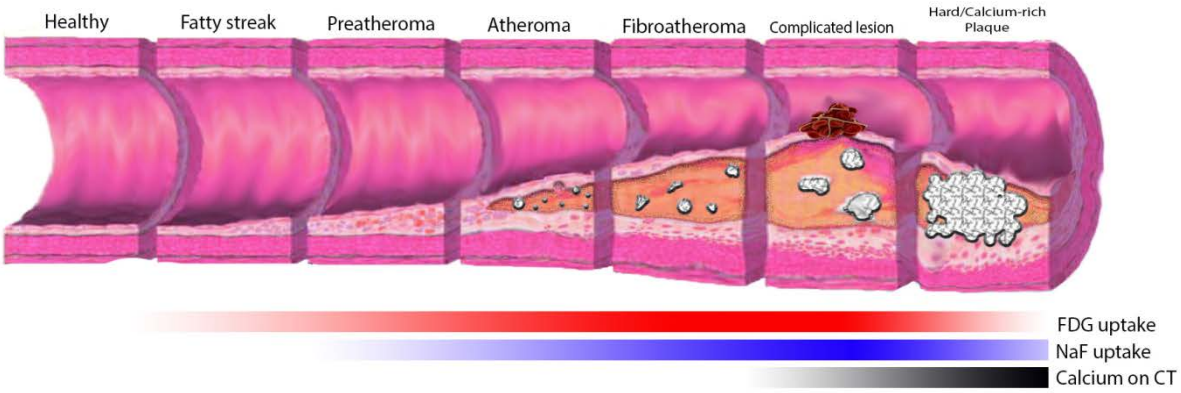
Healthy
Fatty streak
Preatheroma
Atheroma
Fibroatheroma
Complicated lesion
Hard/Calcium-rich Plaque
FDG uptake
NaF uptake
Calcium on CT

Figure 2.

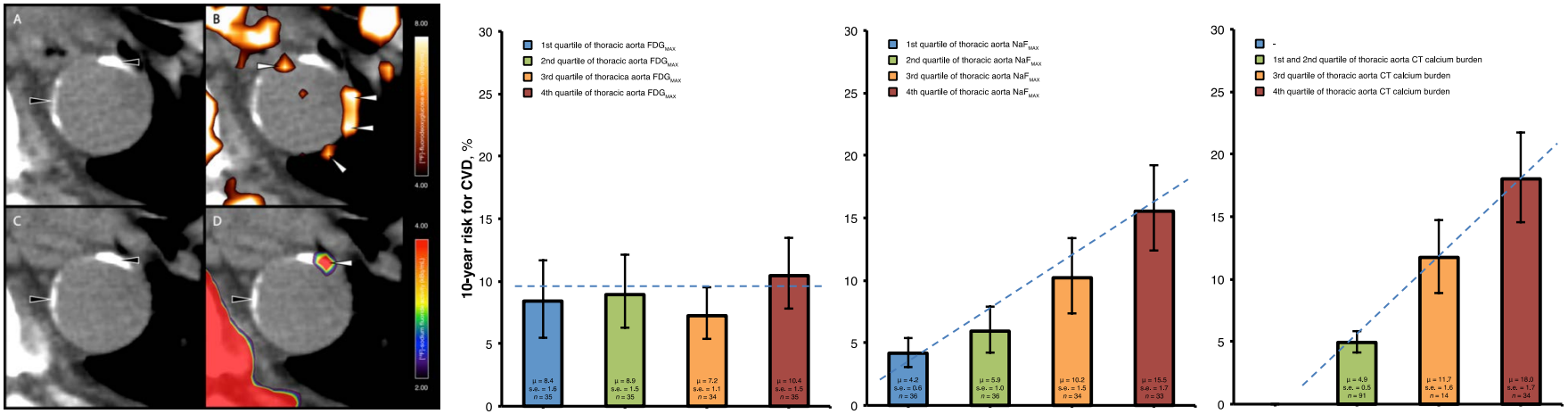
A
B
C
D
8.00
4.00
4.00
2.00
10-year risk for CVD, %
1st quartile of thoracic aorta FDG$_{MAX}$
2nd quartile of thoracic aorta FDG$_{MAX}$
3rd quartile of thoracica aorta FDG$_{MAX}$
4th quartile of thoracic aorta FDG$_{MAX}$
μ = 8.4 s.e. = 1.6 n = 35
μ = 8.9 s.e. = 1.5 n = 35
μ = 7.2 s.e. = 1.7 n = 34
μ = 10.4 s.e. = 1.5 n = 35
1st quartile of thoracic aorta NaF$_{MAX}$
2nd quartile of thoracic aorta NaF$_{MAX}$
3rd quartile of thoracic aorta NaF$_{MAX}$
4th quartile of thoracic aorta NaF$_{MAX}$
μ = 4.2 s.e. = 0.5 n = 36
μ = 5.9 s.e. = 1.0 n = 36
μ = 10.2 s.e. = 1.5 n = 34
μ = 15.5 s.e. = 1.7 n = 33
-
1st and 2nd quartile of thoracic aorta CT calcium burden
3rd quartile of thoracic aorta CT calcium burden
4th quartile of thoracic aorta CT calcium burden
μ = 4.9 s.e. = 0.5 n = 91
μ = 11.7 s.e. = 1.6 n = 14
μ = 18.0 s.e. = 1.7 n = 34

Figure 3.

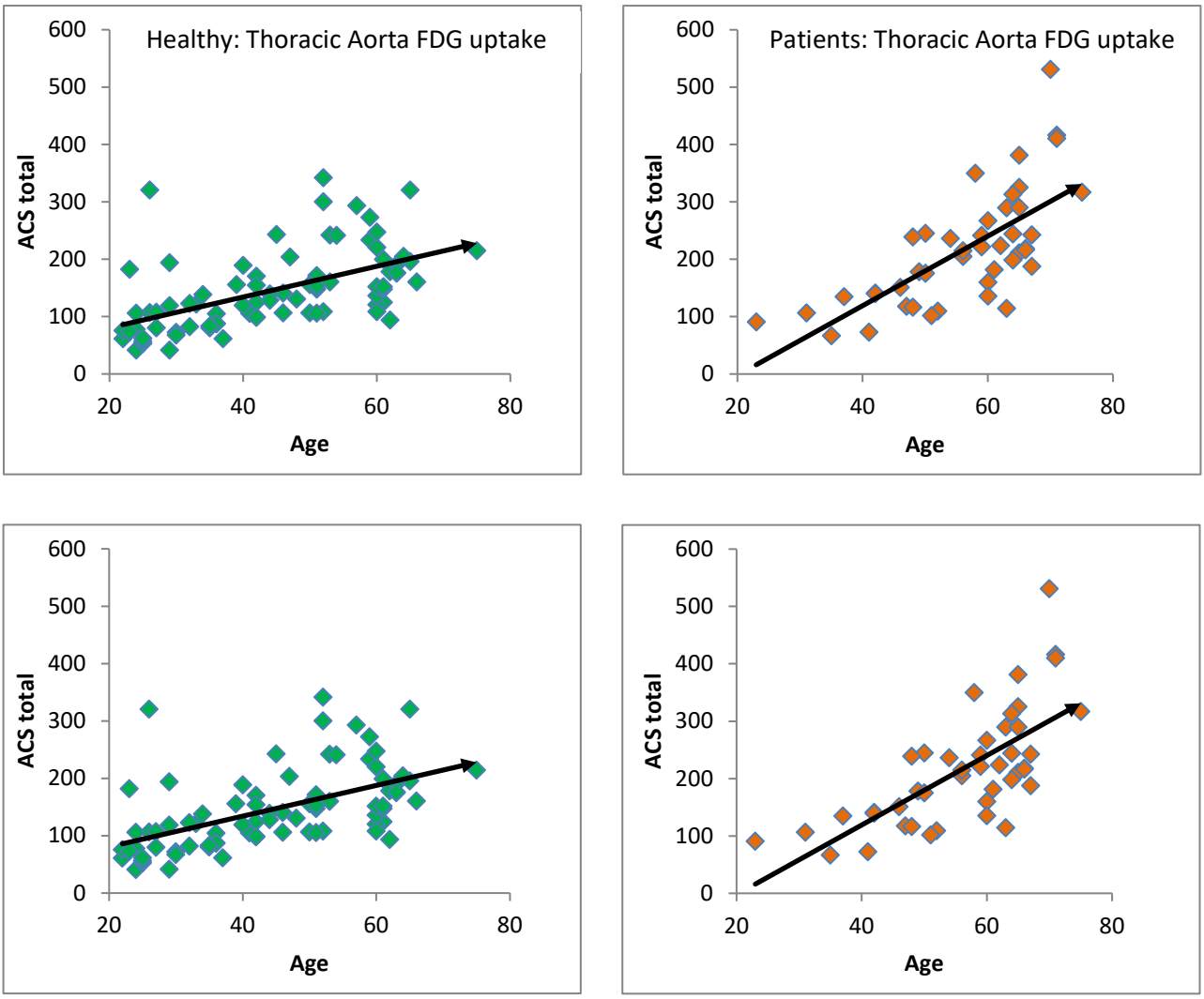
Healthy: Thoracic Aorta FDG uptake
Patients: Thoracic Aorta FDG uptake
ACS total
Age
0
100
200
300
400
500
600
20
40
60
80

Figure legends

Figure 1.

Progression from healthy to hard calcium-rich arterial wall lesion. FDG and NaF uptakes precede vascular calcification evident on CT. The stronger predictive power of NaF uptake and the identification of active calcification by NaF PET herald a paradigm shift in atherosclerosis imaging. Illustration by Reza Piri, MD.

Figure 2.

Left panel: Axial CT (**a**, **c**), FDG PET/CT (**b**), and NaF PET/CT (**d**) images obtained at the same location in 69-year-old man with hypertension, a body mass index of 28 kg/m^2, and a Framingham risk score of 26%. FDG accumulation is seen in the descending thoracic aorta (**b** *white arrowheads*), but not at sites with structural calcium deposits (**a**, **c** *black arrowheads*). In the NaF PET/CT image (**d**) active (*white arrowhead*) and indolent (*black arrowhead*) vascular calcifications are distinguished.

Three panels to the right: The estimated 10-year Framingham risk score in relation to quartiles of (**a**) thoracic aorta FDG activity, (**b**) thoracic aorta NaF activity, and (**c**) thoracic aorta CT calcium burden. CVD risk is similar in all quartiles of thoracic aorta FDG activity, but increases linearly with each increasing quartile of thoracic aorta NaF uptake ($P < 0.001$ for a linear trend) and with each increasing quartile of thoracic aorta CT calcium burden ($P < 0.001$ for a linear trend). *s.e.* standard error, μ mean.

Figure 3.

Significant correlation of FDG uptake and age (upper panels) and NaF uptake (lower panels) in the thoracic aorta of healthy subjects (left) and angina pectoris patients (right). Note the large scatter meaning that for instance a young and healthy control subject may have as high or higher uptake of both tracers than an old patient and vice versa.