Commentary

Alavi–Carlsen Calcification Score (ACCS): A Simple Measure of Global Cardiac Atherosclerosis Burden

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Abstract: Multislice cardiac CT characterizes late stage macrocalcification in epicardial arteries as opposed to PET/CT, which mirrors early phase arterial wall changes in epicardial and transmural coronary arteries. With regard to tracer, there has been a shift from using mainly ^{18}F-fluorodeoxyglucose (FDG), indicating inflammation, to applying predominantly ^{18}F-sodium fluoride (NaF) due to its high affinity for arterial wall microcalcification and more consistent association with cardiovascular risk factors. To make NaF-PET/CT an indispensable adjunct to clinical assessment of cardiac atherosclerosis, the Alavi–Carlsen Calcification Score (ACCS) has been proposed. It constitutes a global assessment of cardiac atherosclerosis burden in the individual patient, supported by an artificial intelligence (AI)-based approach for fast observer-independent segmentation. Common measures for characterizing epicardial coronary atherosclerosis by NaF-PET/CT as the maximum standardized uptake value (SUV) or target-to-background ratio are more versatile, error prone, and less reproducible than the ACCS, which equals the average cardiac SUV. The AI-based approach ensures a quick and easy delineation of the entire heart in 3D to obtain the ACCS expressing ongoing global cardiac atherosclerosis, even before it gives rise to CT-detectable coronary calcification. The quantification of global cardiac atherosclerotic burden by the ACCS is suited for management triage and monitoring of disease progression with and without intervention.

Keywords: aorta; artificial intelligence; atherosclerosis; calcium; heart; imaging; microcalcification; PET/CT; score; sodium fluoride

1. Historical Background

Three major trends have dominated cardiac atherosclerosis imaging for the last 70 years. After World War II, invasive coronary angiography was developed to guide coronary artery bypass grafting and later percutaneous transluminal intervention. In the 1970s and 1980s, non-invasive myocardial perfusion imaging with [201]thallium and later ^{99m}Tc-labeled tracers was introduced, and this millennium has given rise to multislice cardiac CT, which has reduced perfusion imaging to assessment primarily of hemodynamic

consequences of CT-detected coronary stenosis. Additionally, quantification of coronary calcium deposits as a risk factor for future cardiac events was undertaken by electron beam CT in the 1980s, until it was largely replaced by ultra-fast multislice cardiac CT.

In general, these techniques characterize arterial wall macrocalcification, i.e., calcium deposits > 50 μm that occur late in the disease process [1], or its consequences, when curative treatment is no longer an option. Additionally, they cannot detect molecular calcium deposits ≤ 50 μm or their detrimental effects in early stage atherosclerosis, when the disease is still asymptomatic, but presumably more sensitive to intervention than later on when symptoms give rise to diagnostic work-up.

2. Molecular Imaging in Atherosclerosis

Therefore, there are compelling reasons to look for methods that can detect early stage atherosclerosis in an easy, rapid, and reliable way. Molecular imaging with ^{18}F-sodium fluoride (NaF) PET/CT is an obvious choice. Several tracers have been proposed for imaging atherosclerosis [2], but only two have achieved significant use, ^{18}F-fluorodeoxyglucose (FDG) and NaF. FDG was suggested for this purpose twenty years ago [3,4], whereas NaF was not applied until nearly 10 years later [5,6]. FDG was originally introduced for imaging of regional cerebral metabolism in healthy aging and neuro-psychiatric disorders [7,8] while NaF was initially used to demonstrate bone abnormalities [9].

With regard to atherosclerosis, the two tracers mirror arterial wall inflammation and microcalcification, respectively [2]. With time, focus has shifted from FDG towards NaF. Opposite to arterial NaF retention, arterial FDG accumulation does not correlate with CT calcium burden [10,11]. Arterial wall NaF uptake is more consistently related to cardiovascular risk factors than FDG accumulation [11–15], which tends to come and go with time [16], whereas arterial NaF deposits are more consistently present, at least in patients with angina compared to healthy control subjects [17]. Moreover, it has been demonstrated in the Ossabaw swine model of metabolic syndrome that (a) coronary NaF uptake precedes macroscopic calcification on intravascular ultrasound and CT scans and (b) NaF does not accumulate in the myocardium [18], opposite to the high physiologic myocardial uptake of FDG, hampering FDG-PET imaging of coronary atherosclerosis [2,19]. Finally, arterial uptake and blood background clearance of NaF occur much faster than with FDG [12]. Thus, NaF appears to be the more promising PET tracer for imaging cardiac atherosclerosis [2,20].

What remains to make NaF-PET an indispensable adjunct to clinical assessment of atherosclerosis? There are two obstacles preventing clinical implementation of NaF-PET imaging: (1) demonstration in humans of a time-dependent close association between NaF-detectable arterial microcalcification in early stage atherosclerosis and later CT-detectable macrocalcification and (2) rapid and reliable methods providing within minutes a valid assessment of the extent and activity of ongoing cardiac atherosclerosis. The former requires repeat NaF-PET imaging on the same scanner in longitudinal studies, which have still not been conducted [21,22], whereas, for the latter, we propose using artificial intelligence (AI)-based determination of what we have termed the Alavi–Carlsen Calcification Score [18,23–26].

3. Alavi–Carlsen Calcification Score (ACCS)

The ACCS is based on the concept of global disease assessment [23], inspired by a milestone review by Arbab-Zadeh and Fuster [27] arguing for "a transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment". The concept of global disease assessment was introduced in 1993 for FDG uptake imaging of the brain [28]. It can be used for the entire body, tumor tissue, or specific organs such as the heart [19,29,30], assuming that total tracer uptake, i.e., the weighted average uptake in all diseased lesions, is a truer indicator of the extent and aggressiveness of the disease than simple measures like diameter on an X-ray or the maximal SUV in a single voxel of the affected tissues [23]. The aforementioned review concludes that a state of generalized vulnerability is more important than characterizing the individual sites of

vulnerability in the individual patient, since plaque rupture often occurs without clinical symptoms, plaque morphology changes over a few months, and plaque rupture frequently occurs away from the culprit lesions [27]. In addition to coronary plaque burden, the activity of atherosclerosis, assessed by plaque progression over time, is strongly associated with acute coronary event risk [31]. In line with this, the ACCS represents a shift in nuclear cardiology from diagnosing late stage coronary artery stenosis and its consequences to providing a measure of early atherosclerosis burden and its activity in the entire coronary arterial tree, including transmural and minor arteries subtending the most ischemia-prone parts of the myocardium.

The ACCS represents early phase global cardiac atherosclerosis burden rather than characterizing late-phase atherosclerotic calcification in vulnerable coronary plaques in proximal coronary arteries by measures like the target-to-background ratio (TBR) [32–37]. In contrast, the ACCS is the mean standardized uptake NaF value within the entire cardiac silhouette in 3D, i.e., average cardiac standardized uptake value (SUV), excluding the aortic offspring of the coronary arteries and including cardiac blood pool activity (Figure 1), which is why we have chosen the designation "cardiac" instead of "coronary" calcification burden.
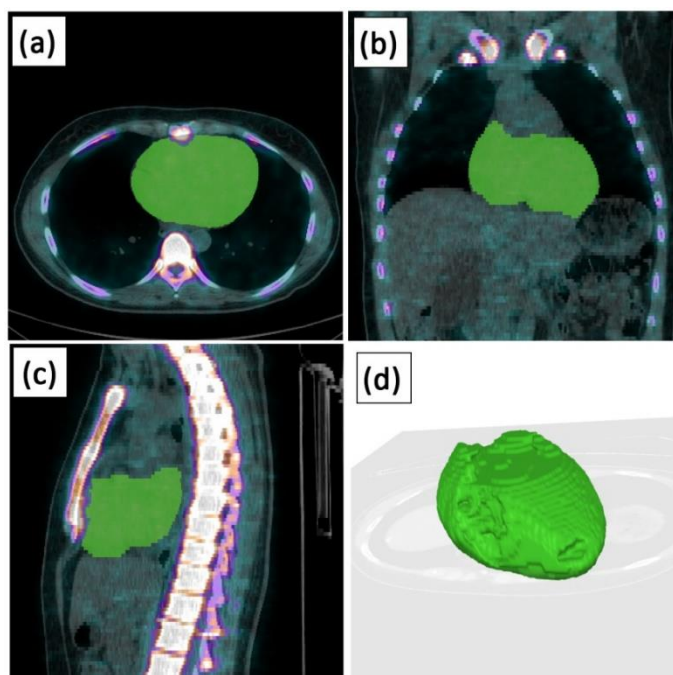
Figure 1. Axial (**a**), coronal (**b**), and sagittal (**c**) reconstruction of AI-based cardiac segmentation in the same patient and 2D representation of the 3D reconstructed heart using AI (**d**).

The ACCS is equal to the average cardiac SUVmean and can be measured by segmenting the entire heart from the surrounding tissues to obtain the average cardiac SUV. Manual segmentation typically lasts half an hour per patient and is associated with some variability, whereas the AI-based approach yields the same measure in less than a minute and with a reproducibility of 100% at reanalysis of the same PET/CT scan. The principle of the AI-based method is organ segmentation using multiple labels in the CT images in two so-called convoluted neural networks trained beforehand in a separate set of scans. One of these networks handles bone segmentation and the other deals with other, non-bone labels, as described in detail elsewhere [38]. The main challenge with both approaches when it comes to heart segmentation is the cranial delineation of the heart in non-contrast CT scans [39]. However, with continued learning, it is foreseeable that this and other challenges will diminish and almost disappear. An inevitable limitation is the inclusion of cardiac blood activity, as delineation of the endocardial surface is impossible with manual segmentation

and not accounted for with AI-based segmentation to date due to the complicated structure of the trabeculae carneae. However, with the rapid blood clearance of NaF [40], this is a minor problem if the same acquisition time following tracer administration is used at repeat scanning.

4. Current Measures of Late Stage Coronary Atherosclerosis

Present common semi-automated measures of late stage coronary atherosclerosis are the Agatston score obtained by non-contrast CT and the SUVmax and the TBR calculated from NaF-PET/CT scans. The Agatston score is a useful tool to calculate coronary artery calcification from a low-dose CT scan. It is the product of the maximum attenuation value in Hounsfield units (HU) multiplied by the area of a calcification [41,42]. It has an arbitrary lower cut-off of typically 130 HU, meaning that early state calcification on the molecular level is not considered. Being a fairly reproducible measure, it allows for long-term monitoring of coronary calcification development, and is sensitive enough to record an unexpected 2-year decrease in coronary calcification in healthy control subjects in concert with a similarly unexpected 2-year decrease in global NaF uptake [17].

Common measures of NaF uptake, such as the SUVmax or TBR, are more versatile, error prone, and less reproducible. Nonetheless, SUVmax appears in a multitude of PET studies of many diseases, although it is, in principle, an extreme stand-alone outlier, which cannot serve as reliable indicator of the extent and activity of disease. When it comes to coronary uptake of PET tracers, there is no standardization. Thus, in 2015, when reviewing 49 articles, Huet et al. [43] counted 53 different acquisition protocols, 51 reconstruction protocols, and 46 quantification methods to characterize atherosclerotic lesions on FDG PET scans. The picture has hardly changed since then, and conditions are no different with respect to quantifying NaF uptake. The often-applied TBR is an error-prone quantity, not only because coronary plaques are difficult to detect and delineate due to movements of the heart and lungs, but also because of the limited spatial resolution of PET, which requires partial volume correction to adjust for count loss in very small lesions [44,45]. Moreover, calculated TBR is strongly dependent on registered blood background activity, which is a major confounder with NaF because it varies from one vessel section to another due to cross-talk from the high uptake in adjacent bone [46]. It is particularly unfortunate that TBR increases with time from tracer administration to image acquisition [39,46,47]. Finally, all sources of error come into play twice with repeat measurements [48], rendering TBR suboptimal for monitoring changes in coronary NaF uptake.

Most of the sources of error are of minor importance when measuring the ACCS. With the AI-based approach, it is quick and easy to delineate the entire heart in 3D to obtain the ACCS expressing ongoing global cardiac atherosclerosis, even before it gives rise to CT-detectable coronary calcification. The large volume of the heart renders partial volume correction superfluous, and inclusion of cardiac blood pool activity is no problem. Given the good reproducibility of the AI method, this approach is particularly suited for characterizing individual patients and following changes over time.

5. Conclusions

Traditional imaging of coronary atherosclerosis and its hemodynamic consequences depicts late stage atherosclerotic changes in epicardial coronary arteries and their consequences for myocardial perfusion. Instead, AI-based assessment of global cardiac NaF uptake in the form of the ACCS offers fast and reliable assessment of global cardiac atherosclerotic burden suited for management triage and monitoring of disease progression with and without intervention.

Conflicts of Interest: The authors declare no conflict of interest.

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