Editorial

Non-invasive evaluation of culprit lesions by PET imaging: shifting the clinical paradigm away from resultant anatomy toward causative physiology

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Abstract: Although coronary angiography is the gold standard for assessing coronary artery disease (CAD), there is at best a weak correlation between degree of stenosis and the risk of developing cardiac events. Plaque rupture is the most common type of plaque complication, accounting for about 70% of fatal acute myocardial infarctions or sudden coronary deaths. Recently, the feasibility of ^{18}F-fluoride PET/CT in the evaluation of atherosclerotic lesions was assessed. Radionuclide techniques allow non-invasive biologic assessment of atherosclerotic plaques. This may help to further shift the clinical paradigm in coronary disease away from anatomy toward causative physiology and biology.

Keywords: Atherosclerotic plaques; coronary artery disease (CAD); leukocyte scintigraphy; ^{18}F-fluoride PET/CT; ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT culprit lesions

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Coronary artery disease (CAD) is a major cause of mortality and morbidity in Europe and its management consumes a large proportion of national healthcare budgets (1).

Although coronary angiography is the gold standard for assessing CAD and vessel stenosis, accumulating evidence has underscored that there is at best a weak correlation between degree of stenosis and the risk of developing cardiac events. This is particularly due to the difficult visualization of coronary lesions at high risk of rupture (2), whose primary role in acute coronary syndromes is widely recognized (3). Plaque rupture is the most common type of plaque complication, accounting for about 70% of fatal acute myocardial infarctions or sudden coronary deaths, and many retrospective autopsy series have suggested that thrombotic coronary death is caused by plaque features and associated factors (2).

In recent years, interest in the early detection of inflamed coronary atherosclerotic plaques has grown, boosted by the increasing availability of techniques allowing for non-invasive evaluation of such lesions.

Molecular imaging holds great promise to detect and follow-up culprit coronary lesions. In particular, positron emission tomography (PET), due to its favorable physical characteristics such as high spatial and temporal resolution, has gained increasing attention. PET, by targeting various biologic pathways of culprit lesions, can aid not only in providing disease detection, but also in monitoring response to therapy and assessing risk stratification.

A variety of approaches to detect coronary vessel inflammation have been pursued, using existing or novel radiotracers. ^{18}F-fluorodeoxyglucose (FDG) has been implemented as the first radiotracer. Its capability of being actively incorporated into inflammatory cells due to their increased glucose metabolism along with its relatively widespread availability constitutes major advantages in the clinical environment. While this technique holds promise (4), the presence of myocardial glucose metabolism represents a limiting factor for visualization of coronary arteries in its close proximity.

Although strict dietary preparations and improvements

in the acquisition protocol have been proposed in order to reach higher accuracy for FDG imaging (5), the implementation of alternative tracers appears desirable for the evaluation of coronary lesions.

Recently, Joshi *et al*. (6) assessed the feasibility of ^{18}F-fluoride PET/CT in the evaluation of atherosclerotic lesions. The authors evaluated 80 patients (40 with myocardial infarction and 40 with stable angina) using a quantitative approach. All patients underwent ^{18}F-fluoride and ^{18}F-FDG PET/CT, CT coronary angiography and CT calcium scoring. The results of their work show that ^{18}F-fluoride uptake was significantly higher for the lesions at high risk of rupture, when compared to stable ones. Conversely, ^{18}F-FDG showed a suboptimal diagnostic performance, which was at least in part due to interference from normal myocardial metabolism.

This paper offers a new perspective on non-invasive evaluation of high risk lesions: Concordance between the intensity of uptake of the molecular imaging marker and the presence of plaque instability, demonstrated by histopathology, suggests that ^{18}F-fluoride PET/CT could be employed as a gatekeeper for invasive CAD workup and as a guide for risk-based therapeutic decision making. This newly generated hypothesis would need to be tested in subsequent prospective trials.

Such prospective trials would then also allow controlling for other issues that limit the work by Joshi *et al*. (6), such as the presence of stent placement prior to imaging, the varying time between the acute event and PET/CT, and the lack of a rigid, standardized and ready-for-clinics approach for fusion of PET plaque images and CT angiography.

While Fluoride holds promise as a marker of plaque vulnerability, the field continues to explore other options for molecular imaging of plaque vulnerability. A retrospective study of oncological patients (7) identified the potential of ^{68}Ga-DOTATATE, a somatostatin-receptor binding tracer to identify active macrophage content in atherosclerotic plaques. In this paper, a strong correlation with coronary risk factors could be demonstrated. These and other PET markers show how promising and flexible molecular imaging of plaque biology may be. But widespread rollout of PET may be hindered by high costs, relatively low availability of PET scanners and the short half-life of PET tracers, requiring a regional cyclotron. By contrast, the more widely available single photon emission computed tomography (SPECT) technology may also be feasible for this purpose, given its recent innovative developments. While conventional SPECT hardware has limited temporal and spatial resolution, which impairs regional delineation of vascular territories, new SPECT hardware equipped with cadmium-zinc-telluride (CZT) solid state scintillators provide improved temporal, spatial and energy resolution (8). Such favourable characteristics may also facilitate application for coronary plaques imaging, while the superior sensitivity and resolution over conventional nuclear imaging holds potential for absolute quantification of biologic mechanisms, similar to what can be currently obtained with PET (9).

Most recently, Glaudemans *et al*. (10) and van der Valk *et al*. (11) supported application of SPECT imaging for the evaluation of high risk coronary lesions. The authors used ^{99m}Tc-labelled leukocytes and ^{99m}Tc-hydrazinonicotinamide (HYNIC)-IL-2 to visualize granulocytes and lymphocytic infiltration into atherosclerotic lesions. A very good diagnostic accuracy was demonstrated, and the degree of radiotracer uptake correlated well with disease severity. Although observations coming from studies investigating SPECT performances are often limited to large peripheral vessels, they can conceptually be applied for coronary artery imaging, capitalizing on higher spatial resolution and improved sensitivity of CZT cameras (12).

A recognized limitation of radionuclide imaging lays in the patients' radioexposure. The dose equivalent of a standard ^{18}F-fluoride PET/CT examination is about 4 to 6 mSv (13). Using SPECT, these values can be reduced to approximately 2.5-3 mSv using ^{99m}Tc-labeled tracers (14). The development of new systems characterized by increased sensitivity allows dramatic reductions of administered doses, while maintaining a comparable or even superior diagnostic accuracy and image quality compared to standard protocols (15). These improvements could also address the requirement for population dose containment.

Another interesting technique helping in the detection and characterization of coronary lesion at increased risk of rupture is frequency-domain optical coherence tomography (FD-OCT). This methodology has been reported to provide detailed microstructural information about the plaque, thus revealing features related to an increased risk of rupture (16). In this issue of the journal, an interesting article by Kataoka *et al*. (17) specifically provides new evidence of the possible role of FD-OCT in the evaluation of coronary lesions.

The authors evaluated 300 patients with stable CAD, who underwent FD-OCT. In their paper, the presence of spotty calcification within the atherosclerotic plaque was associated with other features of plaque vulnerability such as a greater lipid index (averaged lipid arc × lipid

length), thinner fibrous caps and a higher prevalence of microchannels (17). The authors conclude that spotty calcification within the atheroma could contribute to the enhanced plaque vulnerability.

The association of such an alteration with other markers of increased vulnerability suggests a possible target both for the detection and the treatment of culprit lesion and explains also a possible mechanism by which ^{18}F-fluoride is incorporated into atheroma (6). The authors fail, however, to demonstrate incremental value of spotty calcification in predicting an adverse outcome over the other variables considered. Prospective studies are highly warranted in this regard, able to demonstrate whether a similar finding may predict an increased risk of developing cardiac events.

Similarly to coronary angiography, FD-OCT is an invasive technique: radioexposure is significantly lower (1-1.5 mSv), but adverse events including the possible anaphylactic reaction to the contrast agents should be taken into account. From this point of view, PET and SPECT images have been demonstrated to be absolutely safe.

Non-invasive techniques, including SPECT and PET, offer the possibility of a non-invasive biologic assessment of atherosclerotic plaques. A widespread deployment of such techniques needs to be supported by prospective clinical trials, but if successful may have impact on clinical practice by allowing for prediction of individual risk (1,18,19). This may help to further shift the clinical paradigm in coronary disease away from anatomy toward causative physiology and biology.

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