Optimizing FDG-PET/CT imaging of inflammation in atherosclerosis

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INTRODUCTION

Positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG-PET) has been shown to detect metabolic activity as a marker of local inflammation of the arterial wall or atherosclerotic plaque. Inflammation is a key factor in the pathogenesis of atherosclerosis and atherosclerotic plaque rupture underlying many of its complications.¹ Significant correlations between 18F-FDG-PET vascular uptake and macrophage content in the atherosclerotic plaque, the presence of cardiovascular risk factors, systemic markers of inflammation, and high-risk anatomical or histological plaque features support the role of 18F-FDG-PET as a prognostic biomarker.^{2,3} Furthermore, retrospective analyses of PET images from patients who had 18F-FDG-PET for cancer imaging suggest that enhanced arterial 18F-FDG uptake is associated with future risk of cardiovascular disease (CVD) events.^{4,5} To better understand the prognostic value of 18F-FDG-PET, the results of the prospective studies are awaited that will provide cardiovascular outcome data for asymptomatic individuals at high cardiovascular risk who underwent carotid and aortic 18F-FDG-PET.⁶ Already now, 18F-FDG-PET has been used in several clinical trials of novel anti-atherosclerotic therapies as a surrogate marker of treatment efficacy.^{2,3} It has potential to show the positive effect of therapy in a small patient population that can serve as a proof-of-concept for larger clinical trials based on clinical outcomes. For

wide-spread clinical application and correct interpretation of findings, it is essential that the results of 18F-FDG-PET are reproducible and comparable among different trials and institutions. Therefore, standardization of imaging protocols and data analysis is important.

To measure 18F-FDG-PET signal, circular regions of interest (ROI) are drawn around the artery in axial cross sections to determine mean and maximum standardized uptake values (SUV). Most often, tissue-to-background ratio (TBR), which may be considered to best reflect the vessel wall uptake, is reported by correcting the arterial SUV with SUV for blood pool activity in the superior vena cava. Validation studies have demonstrated that 18F-FDG-PET of carotid, aortic, and peripheral arteries is highly reproducible over 2 weeks period in asymptomatic patients with documented CVD or risk factors for CVD.^{7,8} Based on these results and analysis of previous literature, Rudd et al made recommendations for standardization of 18F-FDG-PET vascular imaging in 2008.⁸ It was advised that the use of combined PET/CT scanners is desirable to facilitate accurate co-registration of the PET and CT images of the arteries. For arterial imaging, a longer circulation time than for cancer imaging, preferably at least 90 minutes, was recommended. This allows sufficient 18F-FDG to accumulate in the arterial wall where 18F-FDG becomes permanently trapped and to permit background levels of 18F-FDG in the blood to become reduced by as much as possible. Since then, 18F-FDG-PET has been used in many clinical trials, and new methodological studies have been published.

In this issue of the journal, Gholami et al address the strengths and weaknesses of the various imaging protocols and measurement strategies used in arterial 18F-FDG-PET based on the recent literature.⁹ They note that high 18F-FDG dose is not necessary to obtain sufficient image quality and accurate lesion quantification that is important to optimize the radiation dose to the patient. In contrast, timing of imaging after tracer injection has significant effect on arterial 18F-FDG signal. Optimal circulation time of 18F-FDG for arterial

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imaging may be longer than 90 minutes, but authors note that more comparative studies are needed to define it.^{9–11} Similarly, even moderate hyperglycaemia can lower 18F-FDG uptake by plaque cells.¹⁰ This is probably mainly based on competition between glucose and 18F-FDG as metabolic substrates and more tracer remains in circulation. Therefore, it may be advisable to avoid fasting glucose levels above 7 mmol/L (126 mg-dL).^{9,10} Diet interventions can efficiently reduce physiological glucose uptake by the myocardium that is essential for 18F-FDG imaging of coronary arteries.¹² However, as Gholami et al note more comparative studies on the effects of different diet interventions and pre-scan glucose levels on the atherosclerotic uptake of 18F-FDG would be still needed.

Different approaches have been applied for measurement of arterial 18F-FDG uptake in different studies as described by Gholami et al.⁹ 18F-FDG uptake values from multiple sections can be averaged within an entire artery or arteries. This can offer an accurate estimate of overall plaque activity and may be best suited for monitoring the response to systemic treatments for atherosclerosis. On the other hand, measuring 18F-FDG uptake in a selected arterial segment is probably optimal for detecting and monitoring the effects of local, plaque-based therapy. Furthermore, selection of the most active or diseased segments for analysis may be preferred because they may be most likely to show positive treatment effects due to the presence of active inflammation or atherosclerosis. Selection of the artery or segments for analysis (i.e., index vessel or most diseased segments) can be based on 18F-FDG uptake at baseline or at follow-up as well as the presence of morphological evidence of atherosclerosis in CT or MRI images. A source of variation is that a generally accepted vessel-specific threshold for abnormal 18F-FDG signal in atherosclerosis has not been defined yet.⁹ Relatively small studies with methodological differences have compared in vivo 18F-FDG signal with the histological basis of 18F-FDG uptake in atherosclerotic plaques.¹³ Furthermore, it may be that 18F-FDG uptake is present only transiently during the natural course of atherosclerotic plaque development.^{14,15} Authors conclude that there is a need for studies aiming to find out which of the 18F-FDG analysis methods best reflect the true value of 18F-FDG uptake in the vessel wall and histological correlates of inflammation.

Coronary arteries are challenging targets for 18F-FDG-PET due to small size, cardiac, and respiratory motion in images and high physiological tracer uptake in the adjacent myocardium. However, evaluation of coronary arteries is important because large proportion CVD events are related to coronary artery disease. Imaging small structures, such as atherosclerotic plaques, with PET is challenging owing to partial volume and scatter

effects given the low spatial resolution of the technique. Measured SUV might not, therefore, reflect true tracer uptake within the lesion. However, studies have not so far demonstrated superiority of partial volume-corrected arterial 18F-FDG quantification over non-corrected in the carotid arteries imaged by both PET and magnetic resonance imaging (MRI).¹³ Proof-of-concept studies have shown the potential feasibility of detecting 18F-FDG accumulation in the coronary arteries.³ 18F-FDG signal was shown to be higher in the culprit lesions of acute coronary syndromes (unstable angina or acute myocardial infarction) than in stable coronary atherosclerotic plaques.¹⁶ There are ongoing efforts to improve 18F-FDG-PET of coronary plaques, such as application of diet interventions to suppress myocardial glucose uptake¹² and motion correction using respiratory and ECG signals.¹⁷ This should open possibilities to study how well 18F-FDG uptake in the coronaries and peripheral arteries correlates with each other, and thus whether peripheral artery 18F-FDG-PET is appropriate as a surrogate of coronary artery inflammation.

Novel tracers applied to atherosclerosis imaging might improve the specificity of the PET inflammatory signal and help to overcome obstacles complicating coronary artery imaging.^{1,2} Initial reports have described successful visualization of 18F-NaF reflecting active calcification in the coronary arteries of patients with acute coronary syndromes.¹⁸ Other potential tracers are being tested humans, such as those targeting macrophage receptors^{1,2,19} or neovascularization.²⁰ Arterial 18F-FDG is a promising technique, but as highlighted in the article of Gholami et al, information about basic protocols and signal analysis is needed for wide-spread application of molecular imaging of atherosclerosis, especially in the coronary arteries.

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