Technical considerations for quantification of ^{18}F-FDG uptake in carotid atherosclerosis

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In this issue of the *Journal of Nuclear Cardiology*, Johnsrud et al.[1] have explored the correlation between different quantification methods of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake and plaque inflammation in endarterectomy specimens of patients with severe carotid stenosis. It has been over a decade since the initial reports of ^{18}F-FDG accumulation in unstable carotid plaques and its correlation with indices of plaque vulnerability.[2] This has elicited great enthusiasm to investigate the role of ^{18}F-FDG PET in risk stratification of patients with carotid artery disease. However, the clinical utilization of ^{18}F-FDG PET in the management of atherosclerosis has been hampered by multiple factors, including striking technical variabilities in image acquisition and quantification protocols between various studies as well as metabolic and biological complexity of ^{18}F-FDG uptake in the vessel wall.

Despite the recent declines in the incidence and age-adjusted mortality rate,[3] stroke has remained a major global health issue. In the United States, approximately 800,000 people suffer from a new ($\sim$ 75%) or recurrent ($\sim$ 25%) stroke every year; and about 130,000 people die from it, which puts stroke as the 5th leading cause of death.[3]

Carotid atherosclerosis is a common and a potentially preventable cause of ischemic stroke, accounting for $\sim$ 15% of cases.[3,4] Currently, atherosclerosis is suspected as a possible etiology of stroke if the patient has significant disease (> 50% luminal stenosis) in a clinically relevant artery, in accordance with the Trial of Org10172 in Acute Stroke Treatment (TOAST) classification system.[5] However, strokes caused by thromboembolic complications of unstable non-stenotic or mildly stenotic (< 50%) plaques are not accounted for in this classification;[5] and such cases may instead be classified as cryptogenic.[6] This may result in an underestimation of the true contribution of carotid atherosclerosis as the etiology of ischemic stroke. It is now well established that a large number of acute coronary syndromes originate from acute complications (e.g., rupture or ulceration) of vulnerable, but mildly stenotic, plaques, which triggers the activation of thrombotic cascade and luminal occlusion. [7] It is plausible to assume similar pathophysiology may contribute to plaque vulnerability in patients with mild carotid stenosis, which by current management guidelines will not be candidates for invasive interventions.[8]

Traditionally, the decision to proceed with carotid intervention to prevent new or recurrent stroke has been primarily based on the patients' symptoms and the extent of luminal stenosis, as detected by catheter angiography or non-invasive imaging. Large randomized clinical trials dating back to 1980s have shown that carotid interventions (endarterectomy and more recently stenting) reduce the risk of stroke compared to medical therapy in symptomatic or asymptomatic patients with severe stenosis (> 70%) and in symptomatic patients with moderate stenosis (50%-70%).[8–10] However, this approach has several shortcomings, for example:

1. Asymptomatic moderate and severe carotid artery atherosclerosis is highly prevalent, particularly in elderly men.[11] The prevalence of moderate and severe stenosis in men > 80 years reaches to $\sim$7.5% and $\sim$3.1%, respectively. Comparatively, in women older than 80 years, the prevalence of moderate and severe stenosis is $\sim$5% and $\sim$0.9%.[11]

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Fortunately, about 80% of patients with high-grade stenosis remain stroke-free during long follow-up periods (~10-15 years). Therefore, recommending invasive interventions, which carry a considerable risk of complications (e.g., peri-procedural stroke, myocardial infarction, and cranial nerve injury) based on the extent of stenosis may not be ideal.

2. There is a 1.6% annual risk of stroke in patients with asymptomatic mild-to-moderate stenosis. While, some of these cases are likely caused by vulnerable plaques, these patients are not usually considered as candidates for carotid interventions.[12]
3. Advances in risk factor modifications and medical therapy, e.g., intensive statin therapy, since the original trials have significantly reduced the risk of stroke in patients who are treated non-invasively. Thus, more information is required to establish whether the severity of stenosis can still be used as a reliable criterion to identify patients who benefit from endarterectomy versus medical therapy.[10]

Development and validation of non-invasive imaging techniques that can identify high-risk carotid atherosclerotic lesions have been a subject of extensive research over the past decade. Characteristics of vulnerable plaques that may be imaged non-invasively include intra-plaque hemorrhage,[13,14] thin fibrous cap,[15,16] large necrotic core,[14,16] and high inflammatory burden.[17] Such detailed characterization of carotid plaques through non-invasive approaches may ultimately improve the risk stratification of patients and allow for more accurate selection of patients who benefit from invasive interventions.

HIGH-RESOLUTION CAROTID MRI

MRI and MRA of carotid arteries have been commonly utilized clinically to determine the severity of luminal compromise. Recent improvements in the spatial resolution and development of new sequences have allowed for detailed structural characterization of carotid plaques, and identification of features that are associated with plaque vulnerability.[18] While MRI has a low sensitivity for detection of molecular processes that contribute to plaque vulnerability, it has a great potential for structural characterization of carotid plaques with a number of avenues yet to be explored. For example, dense fibrous tissue, loose fibrous matrix, and lipid/necrotic core can be accurately and reproducibly differentiated using T1, T2, proton density, and time-of-flight images.[19] High-resolution MRI is also capable to differentiate between the intact and ruptured fibrous cap with ~ 90% agreement with histological analysis of endarterectomy specimens.[15] The T1-shorterning effect caused by intra-plaque hemorrhage may be detected by various sequences, e.g., magnetization-prepared rapid gradient echo (MP-RAGE), time-of-flight, and fast spin echo.[20,21] Additionally, dynamic contrast-enhanced MRI provides information on carotid plaque neovascularization.[22]

^{18}F-FDG PET

Complementing the structural information obtained by MRI, PET can track ongoing metabolic, molecular and cellular processes that contribute to the pathogenesis of plaque vulnerability. So far, a large number of PET tracers have been tested in pre-clinical investigations, which target various aspects of atherosclerosis, such as vessel wall inflammation, plaque hypoxia, protease activity, and extra-cellular matrix remodeling.[7] However, the most commonly used PET tracer in the clinical setting is ^{18}F-FDG, reflecting its widespread availability as a Food and Drug Administration (FDA)-approved radiopharmaceutical with excellent safety profile. Multiple studies have shown the association of ^{18}F-FDG uptake and the inflammatory burden of carotid plaques and its capacity to retrospectively identify culprit lesions after strokes or transient ischemic attacks.[23] ^{18}F-FDG PET has also been promising in prospective risk stratification of patients with carotid artery disease and in prediction of the future risk of cardiovascular events.[23]. However, the routine application of ^{18}F-FDG PET in the clinical practice and risk stratification of patients with carotid atherosclerosis has been challenged by several limitations, which will be briefly discussed here.

LIMITED BIOLOGICAL SPECIFICITY

^{18}F-FDG accumulation in sites of inflammation, including atherosclerosis, has been commonly attributed to the high glycolytic activity of inflammatory cells, particularly activated macrophages.[7,23] However, glucose uptake represents a nearly ubiquitous metabolic process; hence, the uptake by other vascular and perivascular cells limits the specificity of ^{18}F-FDG PET for imaging of plaque inflammation.[7,23–26] This is particularly problematic in imaging of coronary arteries, in which the high background uptake of ^{18}F-FDG by the myocardium obscures the visualization of coronary plaques and complicates the quantification of uptake.[27]

Among different constituents of plaques, macrophages, particularly upon activation into pro-inflammatory states, have been considered as the main contributors to ^{18}F-FDG uptake.[28] However, recent data suggest that ^{18}F-FDG uptake may not adequately characterize the metabolic divergence of macrophages upon

activation into different pro-inflammatory (M1) or anti-inflammatory (M2) polarization states.[24–26,29]

Striking technical variability is another limitation of ^{18}F-FDG PET of atherosclerosis.[30,31] This is of particular concern as the small size of plaques and their close proximity to blood pool make them prone to partial-volume effects, which influence the accuracy of ^{18}F-FDG uptake quantification.[31] Therefore, any meta-analysis or comparison between the results of different studies need to be performed with extreme caution to account for these technical variabilities.[32]

PATIENT PREPARATION, IMAGE ACQUISITION, AND RECONSTRUCTION

The fasting period (usually from 4 to 12 hours) and the pre-scan blood glucose level affect ^{18}F-FDG uptake.[32] High levels of glucose reduce ^{18}F-FDG uptake in cultured cells and vessel wall, presumably through competition for glucose transporters, while it increases the blood pool activity.[30,32,33] It is recommended that a blood glucose level < 130 mg/dl is optimal for ^{18}F-FDG PET of vessel wall.[30] But, glucose levels of up to 200 mg/dl have been used in multiple investigations.[32]

The injected dose of ^{18}F-FDG is another potential confounding factor, which varies between studies from 185 to 925 MBq.[30] Low doses of ^{18}F-FDG have been shown not to influence the standardized uptake value (SUV) and target-to-background ratio (TBR).[33] Therefore, doses of 3-4 MBq/kg have been advocated for imaging of atherosclerosis to reduce the patients' radiation exposure, particularly if repetitive scans are being considered.[30]

The wait time post-injection varies from 30 to 210 minutes in different studies. Delayed scans ($\sim$ 2 hours) seem to improve the target-to-background contrast and reduce the influence of partial-volume effect from blood pool, allowing for better visualization and quantification of ^{18}F-FDG uptake in atherosclerotic plaques.[30–32]

Vascular PET is highly susceptible to partial-volume effect due to the small size of the vessel wall, which is usually below or at the resolution of PET. Thus, quantitative ^{18}F-FDG imaging is strongly influenced by the plaque volume and morphology as well as multiple scan-related factors, e.g., voxel size, slice thickness, reconstruction algorithms and attenuation protocols, reviewed elsewhere.[30,31] Plaque uptake seems to be generally underestimated by multiple folds due to the partial-volume effect.[30]

UPTAKE QUANTIFICATION

Standardized uptake values (SUVs) and target-to-background ratios (TBR) are the two most commonly reported parameters for quantification of ^{18}F-FDG uptake in atherosclerosis. SUV is a semi-quantitative measure of uptake and attempts to account for variations in the injected dose of radiotracers and the patient's size through correction for body weight, lean body weight, or body surface area. Mean SUV (SUV_{mean}), maximum SUV (SUV_{max}), or the average SUV_{max} over multiple slices (either throughout or over the most diseased segments of plaques) (mean of SUV_{max}) have often been reported in different studies.[31,32].

Normalization of vessel wall SUV to that of a reference tissue (most commonly SUV_{mean} of blood pool) has been widely used to remove the influence of compounding factors, such as the clearance rate and blood glucose level, on the estimated ^{18}F-FDG uptake. The normalization may be performed through either subtraction of the blood pool SUV from vessel wall SUV (i.e., corrected SUV), or more commonly by calculating the ratio of plaque-to-blood pool SUV (i.e., TBR). Both corrected SUV and TBR remove the effect of blood pool spill-in the vessel wall; thus, may more accurately represent the ^{18}F-FDG uptake and plaque inflammation,[32,34] though they will be influenced by factors which alter the blood pool activity, e.g., renal failure and increased ^{18}F-FDG uptake by circulating cells.[30] Importantly, TBR is more reproducible under different scan settings[32] and has been shown to have a higher association with plaque inflammation and macrophage burden compared to SUV.[32] However, the potential of the various quantification techniques in prediction of long-term risk of carotid atherosclerosis progression and stroke is not yet available.

Johnsrud et al.[1] recruited 44 patients with carotid artery atherosclerosis associated with $> 70\%$ stenosis for ^{18}F-FDG PET/CT. Of these patients, 30 underwent endarterectomy and histological assessment of inflammation to evaluate the correlation between different ^{18}F-FDG uptake quantification methods and histological indices of inflammation. ^{18}F-FDG uptake has been quantified using various parameters, including mean SUV_{max}, maximal SUV_{max} throughout the plaques or through the most diseased segment, blood background-corrected SUV (cSUV), and TBR. The authors have found strong correlations between the various ^{18}F-FDG uptake quantification parameters (correlation coefficients of 0.57-0.99, $P < 0.001$). Inter-observer variability analysis, performed through assessment of the correlation between two independent nuclear medicine physicians, showed a higher agreement for uncorrected SUV_{max} (correlation coefficients of 0.96-0.98) compared to both cSUV and TBR (correlation coefficients of 0.63-0.68 for TBR and 0.90-0.93 for cSUV).

The study reports moderate correlations between the different ^{18}F-FDG uptake parameters and the extent

of inflammation in endarterectomy specimens (correlation coefficients of 0.44-0.59, $P < 0.02$). Correlations between ^{18}F-FDG uptake and histology were overall very similar using the different parameters, although they were slightly stronger when mean SUV_{max} was used compared to the other parameters.

A strength of this study is the concurrent comparison between the different quantification methods and histology in patients who have undergone endarterectomy in a relatively short interval from ^{18}F-FDG PET. A more detailed histological approach, including immunological profiling of inflammatory cells, and determining the correlation between different quantitative measures of ^{18}F-FDG uptake and other indices of plaque vulnerability (e.g., thin fibrous cap, large necrotic core, intraplaque hemorrhage) would have brought a more in-depth insight into this topic.

Together, this study demonstrates a higher inter-observer agreement for SUV_{max} and a slightly higher association between SUV_{max} and plaque inflammation. However, it should be noted that SUV is highly prone to variations in tracer dose as well as patients' (e.g., body weight) and scans parameters, which adversely influence the reproducibility of quantification compared to TBR.[30] Therefore, the use of TBR has been recommended for quantification of ^{18}F-FDG uptake in atherosclerosis by the Cardiovascular Committee of the European Association of Nuclear Medicine.[30]

CONCLUSION

^{18}F-FDG uptake has been shown to be associated with carotid plaque inflammatory burden and risk of cardiovascular events in a number of investigations.[23] However, the application of ^{18}F-FDG in clinical practice has been hampered by several limitations, including the limited biological specificity of ^{18}F-FDG towards inflammatory cell,[24–26] myocardial and skeletal muscle uptake interfering with visualization and quantification of vascular uptake, and lack of standardized protocols leading to large variabilities in patients' preparation, image acquisition/reconstruction and quantification. Over the recent years, there has been a growing interest in optimization of image acquisition and quantification methods and standardization of vascular ^{18}F-FDG PET.[30–32] This approach may ultimately lead to development of more reliable and reproducible protocols, which allow for widespread clinical utility and validation in large cohorts of patients to determine the value of ^{18}F-FDG PET in predicting the risk of stroke and disease outcome. Additionally, other novel PET tracers have been developed, which may overcome the limited biological specificity of ^{18}F-FDG. While most such approaches are still in the pre-clinical stage, a few have already provided promising results in early clinical studies, e.g., ^{18}F-NaF, ^{68}Ga- and ^{64}Cu-DOTATATE, ^{11}C-choline, and ^{11}C-acetate;[30] and their clinical utility is beginning to be explored.

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