FDG-PET in ischemic strokes of unknown origin: Have we found the needle in the haystack?

Meron Teklu, BA,[a] and Nehal N. Mehta, MD, MSCE[b]

[a] National Institutes of Health, National Heart, Lung and Blood Institute, Bethesda, MD
[b] Lab of Inflammation and Cardiometabolic Diseases, National Heart, Lung and Blood Institute, Bethesda, MD

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Atherosclerotic cardiovascular disease is a major cause of global morbidity and mortality.[1] Advances in preventive measures, diagnostic methods and treatments over the past few decades have begun to reduce this burden. [2] Non-invasive imaging modalities such as 18F-fluoro-deoxyglucose positron emission tomography (FDG-PET) and computed tomography angiography (CTA) allow for identification of high-risk plaque features and vessel-wall characterization beyond luminal stenosis. Used in concert, these imaging techniques can assess the presence of vascular inflammation and atherosclerotic plaque content (and thus vulnerability), factors that provide important clues about risk of future plaque rupture.[3,4]

FDG-PET is a valuable tool in assessing inflammatory vascular and plaque features associated with high-risk characteristics in cardiac and neurologic atherosclerotic conditions. Aortic vascular inflammation associates with non-calcified coronary burden and low attenuation plaque assessed by coronary CTA.[5] Patients with acute coronary syndromes have been shown to have higher coronary artery and culprit lesion FDG uptake compared to those with stable angina and lesions of stable coronary syndromes, respectively.[6] In patients with severe carotid stenosis who underwent subsequent carotid endarterectomies, FDG uptake associated with histological plaque macrophage burden.[7,8] PET imaging may even have a role in assessing risk of stroke recurrence. In 60 patients with carotid stenosis and a recent stroke, transient ischemic attack (TIA), or retinal embolism, FDG uptake in the carotid plaque ipsilateral to the event independently predicted recurrence within 90 days.[9] A recent study found similar results in 3 pooled cohorts of 196 patients with carotid stenosis and a recent stroke or TIA, in which an increase in the maximum standard uptake value led to a two-fold increase in risk of stroke recurrence.[10] These investigations demonstrate a possible future role of FDG-PET as a prevention and risk stratification tool.

In this retrospective observational study in the current issue of the JNC, Mikail et al. investigate the value of combined FDG-PET and CTA for identifying high-risk characteristics in 44 patients with recent ischemic stroke of unknown origin and confirmed large (> 3mm), non-stenotic (< 50%) carotid plaques. These images were obtained approximately one week (± one week) after the neurological event. The authors identified a total of 51 plaques with 44 ipsilateral (stroke was on the same side as the plaque), and 7 contralateral to the stroke. The authors present three important findings: (1) FDG vascular uptake was higher in the carotid artery ipsilateral to the stroke (TBR of 2.24 vs. 1.84 in the most diseased segment), (2) FDG uptake was higher in hypodense (< 30 Hu) plaques by CTA, and (3) when evaluating segments of the carotid artery with the highest FDG uptake, CTA acquired factors such as degree of luminal stenosis, plaque thickness, prevalence of hypodense plaques, and surface of hypodense area were all significantly higher in the artery *ipsilateral* to the stroke. In post-stroke imaging of carotid atherosclerosis, FDG-PET and CTA offer more information about features of plaque stability than ultrasonography. This small but important study

Reprint requests: Nehal N. Mehta, MD, MSCE, Lab of Inflammation and Cardiometabolic Diseases, National Heart, Lung and Blood Institute, Bethesda, MD 20892; *nehal.mehta@nih.gov*
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demonstrates that FDG-PET permits identification of characteristics highly associated with plaque rupture, and therefore may play a role in identifying causes of some strokes traditionally classified as cryptogenic.

Cryptogenic strokes account for 25-40% of all ischemic strokes.[11–13] Though antiplatelet therapy and aggressive risk factor reduction are recommended for the long term management of cryptogenic strokes, these strategies are made more difficult without identification of a specific cause.[14] The current work by Mikail et al. indicates a possible role of FDG-PET in identifying a potential target in strokes of unknown origin. Inflammation was higher in the carotid artery ipsilateral to the region of cerebral ischemia, and the difference was approximately a 22% higher TBR in the most diseased segment. Additionally, when focusing on the most diseased segment of the carotid artery, the prevalence of hypodense plaques by CTA was 41% in the ipsilateral and 11% in the contralateral artery, which is nearly four-fold higher. Whether these differences would uphold to adjustment for known risk factors for strokes was not examined here and should be evaluated in larger, future studies. Finally, despite the small sample size, another important observation is that 44% of patients initially classified as having strokes of unknown origin *had plaque* in their carotid arteries, underscoring the importance of cardiovascular prevention in these patients.

Disclosures

The authors have indicated that they have no financial conflict of interest.

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