Beyond stenosis: Further progress in multi-modal evaluation of carotid disease

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According to estimates from the American Heart Association, someone has a stroke every 40 seconds.¹ Stroke is a leading cause of disability in United States leading to \$73.7 billion direct and indirect cost to the economy.¹ Current approach to estimate an individual's risk for a stroke involves identification of various risk factors such as diet, smoking, hypertension, dyslipidemia, physical inactivity, and diabetes mellitus. The risk of stroke is particularly increased in patients with two or more of these risk factors.^{2,3}

Further risk stratification involves assessment of degree of carotid stenosis. It is well established that patients with substantial carotid stenosis have an increased risk of future strokes which can be reduced with carotid endarterectomy.^{4,5} More recently, it has become evident that structural information beyond luminal encroachment may aid in determination of stroke risk.^{6,7} Efforts are currently underway to develop imaging techniques which can provide information about plaque biologic activity and composition with the expectation that the additional information may improve the identification of high-risk plaques and allow for better targeting of therapies to reduce stroke.

Among plaque characteristics associated with stroke, several stand-out as potentially important, including plaque echolucency^{7,8} and plaque inflammation.⁹ Echolucency is assessed using B-mode ultrasound. Plaques that appear echolucent on US tend to be lipid-rich when examined histologically, while plaques that are echogenic have a higher content of fibrous tissue and calcification.^{10,11}

Moreover, plaque echolucency has been shown to predict subsequent risk of CVA.^{7,8} Plaque inflammation can also be measured using non-invasive imaging techniques. FDG-PET imaging is validated as a method for measuring carotid plaque inflammation. Several studies have demonstrated a good correlation between carotid PET measures of FDG uptake and histopathologic measures of macrophage infiltration and inflammatory gene expression seen in specimens subsequently removed at endarterectomy.^{12–14} The arterial FDG signal is reproducible,¹⁵ correlates well with atherosclerotic risk factors,^{16–19} and is modifiable by anti-atherosclerotic therapies.^{20,21} Furthermore, prior studies have observed a link between FDG uptake and atherothrombotic symptoms^{22,23} as well as subsequent atherothrombotic events. Paulmier et al²⁴ compared cardiovascular events in patients with ($n = 45$) and without ($n = 56$) arterial FDG uptake, who had PET scans as a part of malignancy work-up. In this study, higher FDG uptake was observed in patients who had previous vascular events or a new event within 6 months after their PET scan. Rominger et al demonstrated in a series of 932 patients, that a high PET signal was an independent predictor for the occurrence of cardio- or cerebrovascular events. In that study, the odds of experiencing a subsequent atherothrombotic event were increased 14-fold in patients with a high FDG-PET signal, even after correcting for atherosclerotic risk factors.²⁵ However, the relationship between PET and structural imaging assessments of carotid plaques is not well established.

In this issue of Journal of Nuclear Cardiology, Choi et al compared FDG uptake (using PET-CT) with high risk ultrasound characteristics (echolucency) of the carotid plaque.

The authors found significantly higher FDG uptake in echolucent plaques as compared to calcified plaques or carotids vessels without plaques ($P < 0.05$). These findings are consistent with prior observations by Graebe et al²⁶ wherein a negative correlation between the extent of echolucency (measured as gray scale median) and FDG uptake was observed ($r = -0.56$, $P < 0.01$). An important difference between the two studies is that the findings by Graebe et al were observed in symptomatic patients, while the present study involved patients who were asymptomatic.

The observed association between FDG uptake and echolucency is encouraging, and advances the case that

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the FDG-PET signal may be relevant. The results hint at the prospect of using multi-modality assessment of plaques, using FDG-PET and US for risk stratification for primary prevention of stroke. However, neither the current study by Choi et al nor the recent study by Graebe et al provide prognostic data to establish whether FDG-PET uptake can predict future cerebrovascular events or if FDG-PET provides incremental value over US assessment of echogenicity. Certainly, prospective studies will be needed to evaluate this.

Future studies should also evaluate a number of different multi-modality approaches to characterize carotid plaques. While US and PET were used in the current study, combined structural and functional imaging can potentially be performed on a single scanner. For example, PET and contrast-enhanced CT imaging can be performed on the same PET-CT scanner. Such an approach could yield information on FDG uptake (by PET) as well as on several high-risk morphological features (by CT angiography) that are linked to an increased risk of ischemic cerebrovascular events, including: the presence of expansive remodeling, lipid-rich necrotic core, and ulceration or plaque surface irregularity.²⁷⁻³⁰

Additionally, technological advances, such as the development of PET-MR, may further enhance the ability to measure both PET activity and plaque morphology. New tracers with high sensitivity and specificity for inflammation may improve the accuracy of PET measures of plaque inflammation. For that matter, novel tracers targeting other relevant pathobiological processes within plaques may expand the tools to more accurately predict risk. For each combination of imaging approaches, studies are needed to evaluate the incremental risk-predictive value of functional imaging (with PET) and structural imaging (for determination of high-risk structural abnormalities). Thereafter, an evaluation of the cost efficacy of such an approach will likewise need to follow. Perhaps, one particularly attractive patient population to initially evaluate multi-modality imaging approaches for risk stratification is patients with asymptomatic moderate carotid stenosis, where there is often difficulty in determining whether surgical or medical therapy is better.

Accordingly, the study by Choi et al adds to the body of knowledge supporting a role for multi-modality atherosclerotic plaque imaging with PET and US. However, large, prospective studies are needed to establish the value of multi-modality plaque imaging for managing patients with carotid atherosclerosis.

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