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EDITORIAL COMMENT

Imaging Inflammatory Changes in Atherosclerosis

Multimodal Imaging Hitting Stride*

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Atherosclerosis is largely an inflammatory disorder marked by infiltration of monocytes into the arterial wall (1,2). Activated macrophages produce proinflammatory cytokines and contribute to lesion progression, adding to the lipid-rich necrotic core and (via the production of degradative enzymes) thinning of the fibrous cap. Indeed, the predominant theory of atherosclerosis holds that inflammation plays a critical role in all phases of atherosclerosis, from initiation, to progression, to subsequent atherothrombosis. As a result, intense interest has focused on methods that could be used to report changes in inflammation within the arterial wall as a way to risk-stratify patients or to evaluate the effects of pharmacologic therapies.

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Positron emission tomography (PET) has emerged as an important tool in this respect because it can be used noninvasively, uses a U.S. Food and Drug Administration–approved imaging agent (^{18}F-2-deoxy-D-glucose [FDG]), and is currently used for cancer detection imaging. FDG uptake reflects the rate of glycolysis, which is higher in areas containing metabolically active tumor cells and in inflamed tissues. Several clinical studies have shown high FDG accumulation in human atherosclerotic arteries, with uptake of deoxyglucose in macrophage-rich regions and positive correlations between FDG uptake and the amount of immunohistochemical staining and gene expression for macrophage-specific markers (3–7). Indeed, the link between macrophage activation and enhanced glycolysis is well established by a body of research that spans nearly a century (8). A large body of evidence from research in basic cellular physiology demonstrates that activated macrophages have an unusually high metabolic rate (9,10) and avidly accumulate FDG (11). Glycolysis is further stimulated by classic or innate activation pathways (but not by alternative pathways) (12). However, in a recent report (13), the investigators proposed that hypoxia, more so than cytokine stimulation, plays an important role in the induction of glycolysis within macrophages in culture. Hence, the exact mechanism linking macrophage activation to enhanced glycolysis and increased arterial FDG uptake remains an area of ongoing investigation. These considerations notwithstanding, FDG imaging represents an important tool for assessment of inflammatory responses to antiatherogenic compounds.

The arterial PET signal might also be clinically meaningful. Several studies have shown a connection between the FDG signal and clinical risk factors or risk scores (14–17). Additionally, arterial FDG uptake is higher soon after stroke (3) and myocardial infarction (18). Furthermore, a link between arterial FDG uptake and risk for subsequent clinical events is being actively investigated. A small number of studies have so far reported that higher arterial FDG uptake is associated with substantially increased risk for subsequent stroke and myocardial infarction (19,20). However, large prospective studies will be needed to further define the potential clinical utility of arterial FDG PET.

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In the meantime, the use of FDG PET for imaging trials is becoming well established. The initial human experience with FDG PET for assessing treatment efficacy was initially limited to evaluation of statins. In 2 prior single-center trials, statin therapy resulted in a significant reduction in arterial FDG uptake after 3 months (21,22). Those studies provided glimpses into the possibility of using FDG PET for the evaluation of therapeutic efficacy. However, the fact that they were single-center experiences and limited to only 1 class of drugs raised the question of whether FDG PET could be useful in a multicenter trial setting and for the evaluation of drugs other than statins. For those questions, the recently published dal-PLAQUE study (23) provided important answers. That study reported on the use of PET and magnetic resonance imaging (MRI) to evaluate the safety and efficacy of dalcetrapib, a novel high-density lipoprotein (HDL)–raising cholesterol ester transfer protein antagonist. In that multicenter trial, dalcetrapib was associated with a significant attenuation in vascular remodeling at 2 years, as assessed by MRI. Interestingly, although the increase in HDL concentration did not correlate with changes in arterial wall remodeling, increases in HDL concentrations did correlate with reductions in carotid inflammation (by PET). Moreover, the reduction in arterial inflammation seen as early as 6 months was correlated with the subsequent reduction in vascular remodeling seen at 2 years. Hence the combined use of PET and MRI produced complementary information and provided useful insights into the potential utility of HDL-raising strategies. Several completed and ongoing trials have used or are using FDG PET to evaluate the effect of novel drugs directed against arterial inflammation. The results of a number of those studies are expected over the next several months.

In this issue of *iJACC*, 2 reports (24,25) provide insight into the ability of combined PET and computed tomography (CT) to measure changes in arterial inflammation in response to the diabetes drug pioglitazone, a peroxisome proliferator-activated receptor gamma agonist. Pioglitazone has multiple favorable metabolic effects, including decreasing plasma glucose and improving lipid profiles in patients with insulin resistance. Several large clinical studies have suggested a clinical benefit for pioglitazone in reducing vascular events in patients with type 2 diabetes. However, it remains unknown whether its potentially beneficial effects are in part related to decreasing inflammatory burden of plaques or other effects.

The study by Vucic et al. (24) was designed to address that question. In their study, PET-CT and MRI were used to evaluate the arterial walls of animals made atherosclerotic after prolonged high fat exposure. The investigators report that although arterial wall FDG uptake was increased in control animals (on a hyperlipidemic diet alone), FDG uptake values remained stable in animals treated with pioglitazone. Immunohistochemistry of aortas demonstrated a relative decrease in tissue macrophages and oxidized phospholipid immunoreactivity in the pioglitazone group, while there was no change in metabolic parameters between groups. The investigators report a strong positive correlation between FDG uptake and macrophage density (thus providing further confirmation for several prior human and animal studies) and provide novel data showing that the dynamic contrast-enhanced MRI "area under the curve" parameter correlated with neovessel (but not macrophage) density. Thus, the study sheds light on the possible complementary role of the 2 methodologies, with FDG PET providing insights about changes in inflammation and MRI providing data about structural changes and changes in neovessels.

In the second PET study reported in this issue, Mizoguchi et al. (25) present the results of a single-center, double-blinded, placebo-controlled study evaluating the effect of pioglitazone on the blood vessel wall in humans. In that study, patients with glucose intolerance or type 2 diabetes and carotid atherosclerosis were randomized to either pioglitazone or glimepiride. Patients randomized to either agent had evidence of reductions in both fasting glucose and glycosylated hemoglobin levels. However, pioglitazone alone was associated with significantly increased HDL cholesterol, decreased C-reactive protein, and a reduction in arterial FDG uptake. Multiple stepwise regression analysis demonstrated that the increase in HDL cholesterol levels was independently correlated with attenuation of plaque inflammation.

In summary, both reports suggest that pioglitazone either indirectly or directly reduces plaque macrophage inflammatory activity. Considerable data support multiple mechanisms for the effect of peroxisome proliferator-activated receptor gamma in reducing macrophage recruitment, including direct effects of these agents in inhibiting macrophage inflammatory gene expression (26). Conditional knockout of macrophage-specific peroxisome proliferator-activated receptor gamma in atherosclerosis-prone mice results in increased macrophage atherosclerotic lesion content. Thus, the findings of both studies are

consistent with expectations given the known mechanisms of pioglitazone.

These studies underscore the value of FDG imaging for monitoring inflammatory changes within plaques. However, it is important to note that it remains unclear whether lowering plaque inflammation is the mechanism by which statins and pioglitazone therapy decrease cardiovascular events or even whether, in general, reductions in inflammation would translate into clinical benefit. Thus, demonstrating a reduction in arterial inflammation may not always predict eventual efficacy. Instead, the potential for eventual clinical success of a novel drug should be assessed by tapping into a much broader database of information. This could be achieved by combining FDG PET assessment with imaging of arterial wall structure (e.g., with MRI to evaluate remodeling or plaque progression), a carefully chosen panel of blood marker data, along with thorough monitoring for off-target effects. Then, if the sum of the data suggests benefit, graduation to a phase III clinical endpoint trial could be pursued with greater confidence. It should also be noted that typical trials of PET-CT are conducted with 50 to 150 patients and with 3 to 6 months of observation. This evaluation of changes in wall inflammation could be available in a relatively short period. Thus, although the technology cannot replace large-scale clinical endpoint trials, FDG PET (in combination with MRI or CT) may prove useful for identifying the most promising therapeutics, which in turn could be promoted more efficiently through the drug development process.

The PET studies in this issue provide additional insights into the value of noninvasive imaging of the artery wall. With continued standardization and after further study against clinical endpoints, noninvasive imaging with PET, possibly in combination with MRI and/or CT, might prove useful for the refinement of clinical risk (although demonstration of cost efficacy may prove a particularly daunting challenge). Furthermore, a multimodal imaging strategy that includes PET-CT, by reporting on the biochemical and structural changes in the arterial wall during phase II clinical trials, might provide for a more efficient and cost-effective drug discovery process, all in the hope of eventually yielding new therapies and better outcomes for patients with atherosclerosis.

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Key Words: atherosclerosis ■ diabetes ■ inflammation ■ MRI ■ pioglitazone ■ positron emission tomography.