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EDITORIAL COMMENT

Imaging the Intersection of Oxidative Stress, Lipids, and Inflammation

Progress Toward Personalized Care of Atherosclerosis*

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Imaging of atherosclerotic disease has evolved substantially over the last several decades. Measurement of luminal narrowing has traditionally provided important evaluations of cardiovascular disease (CVD) risk, and measurement of vessel wall morphology further refines risk assessment. More recently, molecular imaging techniques have been developed to characterize the biological processes within the atherosclerotic milieu. It is hoped that imaging of vessel wall biology will substantially improve our ability to track disease activity and further sharpen prediction of CVD risk.

Among the biological processes relevant to the atheroma, inflammation looms prominently. Decades of research data provide incontrovertible evidence that atherosclerosis is a chronic inflammatory condition. Bone marrow-derived monocytes localize to areas with vascular damage, transmigrate into the vessel intima, and eventually engulf oxidized lipoproteins and transform into foam cells, where they contribute to inflammation in the growing atheroma. There, inflammatory cells participate in all phases of atherosclerotic disease, from initiation to progression, rupture, and atherothrombosis (1).

Clinical and epidemiological data support an important role for inflammation in driving complications of atherosclerosis. In lipid-lowering studies, on-treatment measures of inflammation, such as high-sensitivity C-reactive protein (CRP) levels, predict cardiovascular disease events similarly to low-density lipoprotein (LDL) cholesterol levels. The PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study, for example, demonstrated that LDL and CRP represent independent treatment targets, as recurrent CVD events are lowest in individuals in whom both biomarkers are substantially reduced, compared with those demonstrating a reduction in only 1 or in neither of these biomarkers (2). Very recently, the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial provided new insights into the role of inflammation in promoting atherosclerotic disease events. In that study, canakinumab, an anti-inflammatory monoclonal antibody targeting interleukin (IL)-1β, significantly reduced the primary CVD endpoint by 15% (3). Importantly, the reductions in CVD occurred in concert with reductions in CRP, despite a lack of change in LDL cholesterol (3). Accordingly, the CANTOS study shows that inflammation plays a causal role in atherosclerotic diseases.

It should therefore not be surprising that imaging inflammation within the atheroma can provide important disease insights, as shown by studies employing 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT). Clinically, 18F-FDG PET/CT imaging is used to report metabolically active tissues, such as tumors and inflamed or infected tissues. Uptake of FDG within the blood vessel wall reliably associates with the accumulation of inflammatory cells, such as macrophages; yields insights into the progression of the underlying atheroma; and provides incremental value for predicting CVD risk above risk scores or extent of coronary artery calcification (1). However, although FDG-PET/CT imaging of inflammation has proven clinically useful for evaluation of myocardial

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sarcoidosis, prosthetic valve endocarditis, and implanted device infections (1), FDG-PET/CT imaging of atherosclerosis remains largely a research tool; its clinical utility is hindered by 2 important limitations. First, FDG uptake demarcates metabolically active cells rather than inflammation per se; thus, interpretation of the FDG signal needs to be contextual. Second, measurement of coronary arterial activity is substantially compromised by obfuscating uptake by the adjacent myocardium, hence diminishing the utility of coronary FDG-PET. Accordingly, although there is substantial enthusiasm for imaging biological processes within the atheroma, especially those that relate to inflammation, novel approaches are needed.

Another potentially attractive target for molecular imaging of atherosclerosis may be oxidation-specific epitopes (OSEs), because they exist at the intersection of oxidative stress, lipid metabolism, and inflammation. Oxidation of lipids subsequently produces highly reactive degradation products that generate structural neo-epitopes, such as OSEs. OSEs are recognized by the innate immune system; OSEs present on ox-LDL drive their uptake by macrophages and promote their conversion to foam cells along with potentiation of inflammation within plaques. Furthermore, elevated circulating OSE concentrations predict CVD risk (4). Accordingly, detection of OSEs may be useful for assessing a stimulus for inflammation that is particularly relevant to atherosclerosis.

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In a study published in this issue of the *Journal*, Senders at al. (5) report on the development and testing of a novel PET probe to image tissues that contain high levels of OSEs. To do so, they constructed an antigen-binding fragment (Fab) antibody library from human fetal cord blood. After multiple rounds of screening against the OSE malondialdehyde-acetaldehyde (MAA), they identified a Fab, LA25, as an attractive candidate due to its specificity for MAA epitopes and its expression characteristics. Binding and competition assays showed that LA25 specifically bound to MAA-LDL and substantially inhibited binding of MAA-LDL to macrophages. In analyses performed on human coronary specimens, LA25 minimally accumulated in locations with pathological intimal thickening, but significantly accumulated in advanced fibroatheromas and ruptured plaques. The control antibody, termed LA24, localized minimally to those lesions.

In vivo studies using LA25 were similarly encouraging. The authors radiolabeled both LA24 and LA25 using ^{89}zirconium for testing in animal models. After injection into ApoE-deficient mice, radioactivity within the aortic plaques was more than 3 times greater for ^{89}Zr-LA25 compared with the control Fab, ^{89}Zr-LA24, as assessed by ex vivo autoradiography of resected murine aortae. Moreover, the ^{89}Zr-LA25 activity colocalized to macrophage-rich areas. In the next step, the authors employed the tracer for imaging atherosclerosis in larger animals. Using PET/magnetic resonance, they observed an approximately 32% increase in radiotracer uptake in the aortas of atherosclerotic rabbits relative to control subjects. Furthermore, radiotracer accumulation correlated with vessel wall area, macrophage staining, and lipid content. Of additional note, the tracer did not substantially accumulate within the myocardium. Together, these in vivo observations suggest that it may be feasible to image OSE-rich plaques in humans, and potentially within the coronary arteries given the relatively low myocardial background activity.

However, as the authors suggest, more work is needed to optimize the technique for use in humans. Once ready for human imaging, the utility of the OSE-targeted tracer will be compared to that of existing tracers used for atheroma imaging, such as FDG. Additionally, studies will be needed to evaluate whether detection of OSE-rich plaques provides incremental value for risk stratification over available methods that detect lipid-rich plaques, such as CT, or even over traditional risk scores, coronary calcium, and angiographic scores. Moreover, studies will need to determine whether or not such relatively expensive imaging approaches are ultimately cost-effective, especially when inexpensive circulating biomarkers are available. If they are not cost-effective, then the imaging tools might remain in the research realm.

As we begin to migrate away from the monolithic treatment of atherosclerosis (e.g., aspirin and statins for all) to an era of personalization utilizing highly expensive therapies (such as PCSK9 antagonists or, potentially, anti-inflammatory drugs, such as canakinumab), the additional cost and risks introduced by such therapies should more intensely motivate personalized assessment of CVD risk and pharmacotherapy selection. Physicians may approach therapeutic decisions for chronic atherosclerosis in a manner similar to how clinicians approach many types of cancer. In oncology, disease staging is usually based on molecular pathology characterization and guides the initial choices of therapy, and molecular-structural restaging allows ongoing titration or addition/subtraction of therapies to match the residual risk and disease burden. Such a personalized approach has yielded substantial gains in survival

and quality of life for individuals with cancer. A more personalized approach to antiatherosclerosis therapies, in part guided by advanced imaging, may likewise prompt important reductions in CVD events.

To realize the promise of personalized therapy for atherosclerosis, tools to assess and monitor atherosclerotic disease activity must continue to improve, particularly in the coronary arteries where noninvasive imaging faces its greatest challenges due to motion and small target volumes. Although substantially more work on OSE-targeted tracers is needed, the study by Senders at al. (5) is an important step in the right direction. Ultimately, more sophisticated assessments of CVD risk are needed to match the growing complexity of decision making in the treatment of atherosclerotic disease.

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