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EDITORIAL COMMENT

Lipoprotein Apheresis and Acute Reduction of Arterial Inflammation

FDG-PET as an Imaging Biomarker of Nonpharmacological Effects on the Vessel Wall*

Sotirios Tsimikas, MD

Molecular imaging is broadly defined as a technique that incorporates targeted contrast agents into available imaging modalities to detect and quantitate molecular, cellular, biological, and physiological pathways relevant to atherogenesis and cardiovascular disease (CVD) (1,2). The main forces driving development of molecular imaging techniques have been the disconnect between quantification of anatomic atherosclerotic disease and their pathological and histological characteristics of plaque vulnerability, a need to better predict acute clinical syndromes, and the difficulty in predicting acute events based on size of individual lesions. Therefore, anatomic and functional techniques may provide a complementary approach to imaging high-risk lesions to better understand their biological properties and clinical consequences.

Of the many molecular imaging techniques that are being evaluated or in clinical use, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has the largest clinical experience. FDG is a glucose isomer that is taken up by metabolically active cells, such as cancer cells and macrophages. In animal models of CVD, FDG uptake correlates with the presence of activated macrophages and is proportional to the extent of chronic inflammation (3). Recent cell culture evidence also points to the possibility that FDG cellular uptake may reflect hypoxia-stimulated processes rather than inflammation (4). Irrespective of the mechanism, the FDG-PET imaging studies to date generally reflect clinical expression of CVD. For example, FDG uptake has been shown to be associated with the presence of carotid and aortic atherosclerosis and is reduced with statin therapy (5). By contrast, recent FDG-PET studies with cholesteryl ester transfer protein and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) inhibitors have largely reflected the failure of the subsequent clinical trials (6,7).

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In this issue of the *Journal*, van Wijk et al. (8) evaluated the effect of lipoprotein apheresis and its association with aortic and carotid artery inflammation. The target-to-background ratio (TBR) of FDG-PET uptake was measured in 38 subjects, 24 with familial hypercholesterolemia (FH) and 14 normolipidemic controls. Twelve of the FH patients had TBR assessed at baseline and again after undergoing lipoprotein apheresis 3 days later. The FH patients had a higher mean TBR compared with healthy controls and a modest, but significant, correlation was present between baseline arterial TBR and low-density lipoprotein cholesterol (LDL-C) levels. The main finding of the study is that FH patients experienced a significant reduction in TBR to the level of normolipidemic controls following only a single apheresis session.

This study provides 3 important insights: 1) it demonstrates for the first time the rapid attenuation of vascular wall inflammation of a nonpharmacological approach by an imaging technique; 2) it reflects the role of apolipoprotein B (apoB)-containing lipoproteins

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From the Division of Cardiovascular Diseases, University of California San Diego, La Jolla, California. Dr. Tsimikas is named as co-inventor and receives royalties on patents held by the University of California San Diego; was a consultant to Sanofi/Genzyme; and holds dual appointments at the University of California San Diego and as an employee of Isis Pharmaceuticals during his sabbatical leave.

[LDL, Lp(a), intermediate-density lipoprotein, very-low-density lipoprotein] in inflammatory pathways that can be rapidly reversed when they are removed from the circulation; and 3) it suggests that vessel wall inflammation is likely a downstream effect of the accumulation and modification of apoB-containing lipoproteins. The chemical modification of lipoproteins in the vessel wall generates neoepitopes that act as danger-associated molecular patterns, such as oxidation-specific epitopes present on oxidized lipoproteins, cell membranes, and apoptotic cells, triggering activation of the innate and adaptive system, whose response is to generate inflammation (9).

Several caveats should be noted in interpreting this study. First, this is a pilot study that needs to be confirmed in larger datasets that will afford better matching of clinical characteristics. Second, patients had FH with elevated LDL-C, and many were statin intolerant; therefore, extrapolation to more modest LDL-C levels cannot be made. Finally, complete data on high-sensitivity C-reactive protein, Lp(a), and other inflammatory biomarkers were not available; thus any mechanisms of TBR reduction beyond lowering of apoB-containing lipoproteins cannot be inferred.

WHAT IS THE CLINICAL EFFICACY AND OUTCOMES OF LDL APHERESIS? The various methods of lipoprotein apheresis share the commonality of removing apoB-containing lipoproteins, which include very-low-density lipoprotein and triglyceride-rich remnants, and LDL and Lp(a) (10). In the United States, lipoprotein apheresis is approved for patients with the severe hypercholesterolemia phenotype (11) on maximally tolerated therapy with LDL-C >300 mg/dl or LDL-C >200 mg/dl and the presence of coronary artery disease. Lipoprotein apheresis results in significant reduction of LDL-C and Lp(a) ranging from 50% to 80% in 1 session, often reducing LDL-C from >200 to <50 mg/dl. However, as a result of both enhanced synthesis and reduced hepatic clearance of LDL particles (11), the LDL-C returns to baseline within 1 to 2 weeks, so the time-averaged LDL-C reduction is ~40%, in line with a modestly potent statin. Although we have no randomized trials in patients on apheresis, retrospective data in FH patients document significant reduction in cardiovascular events with statin therapy and with apheresis, even with modest reductions in LDL-C (10).

IS THE PUTATIVE REDUCTION IN INFLAMMATION DUE TO LDL-C AND Lp(a) LOWERING, OR IS THERE AN INTERMEDIARY EFFECT NOT REFLECTED BY THESE LIPOPROTEINS? There have been several studies documenting salutary effects of lipoprotein apheresis on vascular function, often involving a single LDL apheresis session, including acute improvement in brachial artery reactivity (12), endothelium-dependent coronary reactivity (13), coronary blood flow as measured by ^{13}N-ammonia (14), and intravascular ultrasound-detected coronary atheroma regression (15). Additionally, a recent study has provided mechanistic data demonstrating that apheresis reduced Lp(a) and its associated oxidized phospholipids, and Lp-PLA_2 mass, but with an increase in Lp-PLA_2-specific activity (16). Because Lp(a) levels in FH patients are generally 2-fold higher than in non-FH patients, these effects may contribute to the benefit of apheresis. Two recent observational studies provided evidence that patients with elevated Lp(a) undergoing apheresis had substantially reduced events after apheresis compared with before apheresis (17,18).

In conclusion, van Wijk et al. (8) should be congratulated on performing this unique translational study that takes advantage of a therapeutic technique coupled to an imaging technique to provide insights into acute plaque biology. Because apheresis has been shown to reduce cardiovascular events in patients who have both high LDL-C and high Lp(a), one could hypothesize that the FDG signal reduction noted here should reflect the clinical benefit in patients with appropriate responses. Future studies, such as the PREMIER (Plaque Regression and Progenitor Cell Mobilization with Intensive Lipid Elimination Regimen) trial (19), using virtual histology intravascular ultrasound with apheresis may provide additional insights into the effect of apheresis in patients with the most vulnerable plaques, those with acute coronary syndromes.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Sotirios Tsimikas, Vascular Medicine Program, University of California San Diego, 9500 Gilman Drive, BSB 1080, La Jolla, California 92093-0682. E-mail: stsimikas@ucsd.edu.

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