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STATE-OF-THE-ART PAPER

Imaging Atherosclerotic Plaque Inflammation by Fluorodeoxyglucose With Positron Emission Tomography

Ready for Prime Time?

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Inflammation is a determinant of atherosclerotic plaque rupture, the event leading to most myocardial infarctions and strokes. Although conventional imaging techniques identify the site and severity of luminal stenosis, the inflammatory status of the plaque is not addressed. Positron emission tomography imaging of atherosclerosis using the metabolic marker fluorodeoxyglucose allows quantification of arterial inflammation across multiple vessels. This review sets out the background and current and potential future applications of this emerging biomarker of cardiovascular risk, along with its limitations. (J Am Coll Cardiol 2010;55:2527–35) © 2010 by the American College of Cardiology Foundation

Atherosclerosis remains the leading killer in the U.S. Inflammation (1) and plaque erosion (2) are the main drivers of clinical events such as myocardial infarction, which usually result from the sudden rupture of macrophage-rich atherosclerotic plaques. Although anatomic imaging with X-ray angiography can identify arterial stenoses, no information is obtained about the degree of plaque inflammation.

Fluorodeoxyglucose (FDG) with positron emission tomography (PET) is a molecular imaging technique that is highly sensitive to metabolically active processes using glucose as a fuel. FDG is an analog of glucose that is administered intravenously, with a half-life of 110 min. It is generally allowed to circulate for an hour before PET imaging begins. PET imaging has a relatively low spatial resolution (3 to 4 mm), mandating the use of concurrent structural imaging (either computed tomography [CT] or magnetic resonance imaging [MRI]) to guide localization of the FDG signal.

In oncology, FDG uptake by tumor makes PET the gold standard for detection of metastatic disease (3). In cardiology, FDG PET is routinely used to estimate myocardial glucose consumption; in jeopardized myocardium, uptake of FDG implies viability and likely positive response to myocardial revascularization (4).

Recently, arterial FDG PET imaging has been suggested as a biomarker to report on the metabolic activity of atherosclerosis (5). As well as identifying symptomatic lesions (6), it may have a role in monitoring the response of atherosclerosis to therapy (7). Future applications might include the prediction of plaque rupture and clinical events.

This review covers background, current applications, and highlights challenges for FDG PET atherosclerosis imaging.

Rationale for FDG PET Atherosclerosis Imaging: Plaque Inflammation

Plaque rupture, the most common cause of myocardial infarction, accounts for approximately 70% of all sudden deaths. The thin cap fibroatheroma (Fig. 1) is now recognized as the plaque type that is most likely to rupture. It is identified histologically by a large necrotic core, a thin

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CT = computed tomography
FDG = fluorodeoxyglucose
GLUT = glucose transporter protein
MRI = magnetic resonance imaging
PET = positron emission tomography

overlying fibrous cap, and macrophage and T-lymphocyte infiltration (8). There may also be revascularization and spotty calcification within the plaque. The degree of macrophage infiltration correlates well with lesion progression (9). Thin cap fibroatheromas have a volume of approximately 0.1 mm^3 and are more common in the proximal coronary arteries. Fibrous cap thinning is thought to arise from depletion of collagens caused by an imbalance between synthesis and breakdown of extracellular matrix attributed to a host of degrading metalloproteinases produced by macrophages (10,11).

Uptake of FDG Into Plaque Cells

Because FDG is a glucose analog, cells participating in the inflammatory process must use exogenous glucose as a fuel if they are to be detected by PET imaging. It is also advantageous that inflammatory cells have a substantially higher rate of glucose uptake than neighboring cell types (12–14), which they use to power cellular motility and phagocytosis (15,16). Macrophages can also metabolize free fatty acids; this needs oxygen to generate adenosine triphosphate, whereas glucose metabolism does not. The interior of a plaque is an anaerobic area even in the presence of an increased vaso vasorum (17). Thus, glucose is the major substrate for macrophages resident in plaque (18).

Like glucose itself, facilitative transport via the glucose transporter protein (GLUT) system is the most important way for FDG to enter human cells (19). After entry, FDG becomes phosphorylated to FDG-6-phosphate by hexokinase. Activated macrophages have 10 times higher levels of hexokinase activity than resting cells (20). In contrast to glucose-6-phosphate, FDG-6-phosphate cannot be metabolized further along the glycolytic pathway and therefore accumulates within cells in direct proportion to their metabolic activity. This phenomenon is referred to as metabolic trapping. FDG can theoretically escape from the cell by dephosphorylation. However, this is generally a negligible process because of the low intracellular levels of the dephosphorylation enzyme. The FDG uptake of any cell is thus determined by several factors: the expression of GLUTs through the cell membrane, the activity of the hexokinase

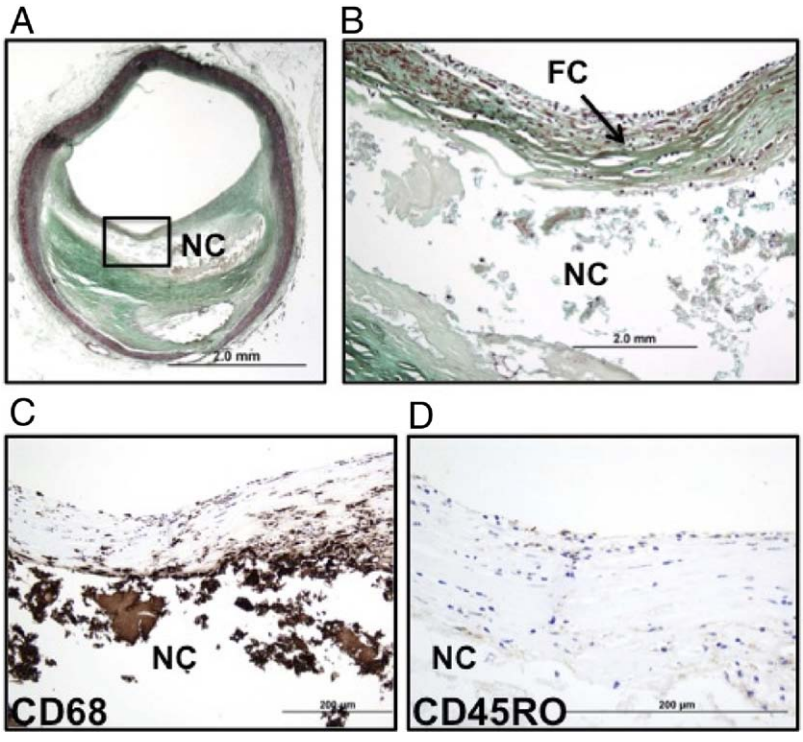

Figure 1 Pathology of High-Risk Plaque

Thin-cap fibroatheroma, the precursor lesion to plaque rupture. **(A)** An eccentric plaque with a large superficial necrotic core (NC) and overlying thin-fibrous cap (FC) (Movat pentachrome stain). **(B)** Higher magnification image of the thin fibrous cap heavily infiltrated by inflammatory cells. The necrotic core is formed by loose cellular debris. **(C)** Higher magnification represented by the area within the **black box in A** showing a thin fibrous cap infiltrated by $CD68^+$ macrophages. **(D)** Similar area with scattered $CD45RO^+$ T lymphocytes.

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