Noninvasive Imaging of Atherosclerosis: The Biology Behind the Pictures

It is now realized that atherosclerotic plaques do not always impinge on lumen diameter and that clinical events due to plaque rupture, such as myocardial infarction and stroke, occur more as a consequence of plaque composition than of size. The inflammatory cell content of plaque is the most important determinant of plaque rupture, since inflammatory cells, particularly macrophages, destroy the protective fibrous cap of the plaque, thereby exposing its thrombogenic contents to the circulation (*1*). In the coronary circulation, myocardial infarction is more likely to arise from rupture of a clinically silent and angiographically unimpressive plaque than from one that is symptomatic (causing angina) and angiographically significant (*2*). These observations have stimulated a move away from angiography, which is generally performed only on symptomatic patients and defines only lumen diameter, to alternative imaging techniques that can define the distribution and composition of stenotic and nonstenotic lesions. On pages 1816–1821 of the current issue of *The Journal of Nuclear Medicine*, Ben-Haim et al. (*3*) report a study combining 2 such methods, namely CT and ^{18}F-FDG PET, to look for atherosclerotic lesions in 122 patients aged 66 ± 9 y undergoing tumor imaging, only 15% of whom had experienced a clinical vascular event. CT-identified calcification or ^{18}F-FDG PET hot spots were present at 349 sites in 100 patients. Calcification was present at 320 (92%) of the sites, whereas PET hot spots were present at only 52 (15%). Calcification and increased ^{18}F-FDG uptake coincided at only 23 sites (7%). So why, if both methods are identifying atherosclerotic lesions, is there such discrepancy between them?

CT measures calcium, and calcification is an almost universal component of atherosclerotic plaques. It occurs at a microscopic level in very early lesions and, in advanced lesions, can progress to frank bone formation (*4*). Detection of calcification by CT is an all-or-nothing phenomenon, with positivity being defined as a signal above an arbitrary threshold number of Hounsfield units. A high threshold will underestimate calcification, and vice versa. Generally speaking, the presence or absence of calcium in the vessel wall is taken to include or exclude the presence of atherosclerosis (*5*). However, vascular calcification is not always confined to atherosclerotic lesions. In elderly patients, particularly those with diabetes or renal disease, medial calcification that is unrelated to atherosclerosis can develop. Thus calcification, particularly in large arteries, may not always be in atherosclerotic lesions. Therefore, there are technical reasons why measurement of vascular calcification by CT may overestimate the prevalence of atherosclerotic lesions. In view of that, the apparent prevalence of atherosclerotic plaques reported by Ben-Haim et al. (*3*) on the basis of their CT measurements is not unexpected in a population of the age studied.

^{18}F-FDG uptake is a measure of metabolic activity, and ^{18}F-FDG PET of atherosclerosis is in its infancy, with few published data to consider. Active vasculitic processes are known to be associated with enhanced ^{18}F-FDG uptake, as, for example, in Takayasu's or giant cell arteritis (*6,7*). However, studies from our laboratory have shown that there is no measurable ^{18}F-FDG uptake into the normal vessel wall but that ^{18}F-FDG is taken up by inflammatory cells, predominantly macrophages, in atherosclerotic plaques (*8*). Preliminary results from experimental models of atherosclerosis indicate that ^{18}F-FDG uptake is directly proportional to plaque macrophage content and mirrors experimentally induced changes in macrophage content. Thus, ^{18}F-FDG PET identifies only plaques that are actively inflamed. However, there are currently no data on the sensitivity of ^{18}F-FDG PET to quantify plaque macrophage content. Virtually all plaques contain some macrophages, yet not all plaques appear to take up ^{18}F-FDG. It is probable that measurable amounts of ^{18}F-FDG are taken up only by plaques that are heavily infiltrated by macrophages or when the metabolic activity of the macrophages is particularly high. This is entirely consistent with our observation that the highest ^{18}F-FDG uptake was in plaques that had recently caused a clinical event (*8*). It is plausible that, in the relatively asymptomatic population studied by Ben-Haim et al. (*3*), the prevalence of atherosclerotic lesions was high (as indicated by CT) but the prevalence of actively inflamed plaques was low (as indicated by PET). This would be particularly likely if any of the patients were taking 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to reduce cholesterol levels (28% were known to be hyperlipidemic). Animal and clinical data indicate that statins promote plaque stability by reducing plaque inflammation (*9,10*).

Although the above may explain why CT predicted a higher prevalence of atherosclerosis than did PET, it doesn't explain the relative lack of coincidence of CT-positive and PET-pos-

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itive lesions. An explanation for this observation probably lies in the cell biologic events underlying the pathogenesis and progression of atherosclerosis. The currently accepted paradigm proposes that accumulation of oxidized, atherogenic lipids in the vessel wall triggers an inflammatory reaction in the subendothelial (intimal) space, the course of which is determined by the balance between inflammatory cells, macrophages, and lymphocytes, tending toward plaque instability, and vascular smooth muscle cells that form the all-important protective fibrous cap over the thrombogenic lipid core, tending toward plaque stability (*11*). Histologic evidence suggests that plaques undergo waves of inflammatory cell activity that cause clinical or subclinical plaque rupture. In the case of subclinical rupture, vascular smooth muscle cells "heal" the lesion by forming a new fibrous cap at the expense of lesion growth. It is probable that measurable uptake of ^{18}F-FDG occurs only during periods of plaque inflammatory cell activity and may therefore be somewhat transient.

One of the consequences of inflammation is cell death, particularly by apoptosis. Indeed, inflammatory cell apoptosis ensures that the inflammatory process is self-limiting once the triggering event has passed. Macrophage apoptosis is common in atherosclerosis (*12*). Furthermore, plaque inflammatory cells induce vascular smooth muscle cell apoptosis both by direct cell–cell contact (*13*) and by elaborating cytotoxic cytokines (*14*). By so doing, inflammatory cells weaken the fibrous cap, since vascular smooth muscle cells are the only cells capable of synthesizing and maintaining it. Research from our laboratory has shown that apoptotic bodies are capable of concentrating calcium and phosphate ions to nucleate hydroxyapatite by a mechanism that mimics the function of matrix vesicles in developing bone (*15*). Thereafter, the surrounding smooth muscle cells adopt an osteogenic phenotype that facilitates matrix mineralization (*16*). Thus, calcification is an actively regulated and cumulative process that probably results from bursts of inflammatory cell activity. This may well explain why nearly all plaques contain some calcium and why the detection of calcium by CT is such a sensitive marker for the presence of atherosclerosis but does not necessarily predict future events.

CT and ^{18}F-FDG PET therefore measure different features of atherosclerotic plaques. Inflammation, as measured by enhanced ^{18}F-FDG uptake, may be transient but dangerous; calcification, as measured by CT, is cumulative, probably permanent, and of debatable pathophysiologic significance. Based on this paradigm, one would anticipate a high prevalence of CT-positive lesions in a predominantly asymptomatic Western population older than 50 y with a substantially lower prevalence of PET-positive lesions and a few, presumably larger, PET-positive/CT-positive lesions having areas of both past and current inflammation. This paradigm would predict that PET-positive/CT-negative lesions will become PET-negative/CT-positive with time. Only longitudinal studies will tell if this is the case.

It has taken the best part of 50 y for us to learn that angiography tells us very little about atherosclerotic plaques. It is crucial that we learn more quickly what newer imaging techniques are telling us. This can be achieved only if interpretation of the image is informed by an understanding of the underlying cell biology.

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