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EDITORIAL COMMENT

Detecting Coronary Inflammation With Perivascular Fat Attenuation Imaging

Making Sense From Perivascular Attenuation Maps*

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Inflammation has long been implicated in human atherogenesis (1), which has been confirmed by recent clinical trials (2,3). Although simple therapeutic interventions such as statins (2) reduce vascular inflammation, significant residual inflammatory risk remains. Noninvasive imaging using positron emission tomography (PET) (4) can indirectly detect coronary inflammation, but is expensive and requires high-end equipment. The development of more accessible noninvasive imaging methods to identify coronary inflammation would allow targeted deployment of anti-inflammatory treatments, which would facilitate a more personalized approach to individual care.

The perivascular adipose tissue (PVAT) surrounding the coronary arteries exerts paracrine effects on the vascular wall, promoting atherogenesis (outside-to-inside signaling) (5). However, in the presence of vascular disease, the human cardiovascular system secretes distress signals (e.g., oxidized lipids), which diffuse into the perivascular space (inside-to-outside signaling) (6,7). PVAT adipocytes sense these signals and modify their intracellular signaling, shifting their secretome towards a vasoprotective phenotype (8). Nature appears to have given PVAT a role in protecting the coronary arteries, by sensing early vascular disease signals and responding in a bidirectional feedback loop. However, the intracellular pathways driving the PVAT "defense" response are also involved in adipogenesis (lipid formation) and lipolysis (lipid elimination) (8,9). Our recent work has shown that pro-inflammatory cytokines released from the inflamed arterial wall (e.g., tumor necrosis factor-α, interleukin-6, interferon-γ) induce lipolysis and inhibit PVAT adipogenesis, also promoting perivascular edema (9). This local "cachexia" phenomenon in the PVAT microenvironment causes a gradient of perivascular lipid accumulation, with a higher water/lipid ratio closer to the inflamed vascular wall compared with non-PVAT that is distant from the vascular wall (9).

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This landmark discovery led us to develop a method to detect inflammation-induced changes of PVAT by analyzing perivascular attenuation (or density) gradients from routine coronary computed tomography angiography (CTA) data sets (9). This principle, in which high vascular inflammation drives changes in PVAT (9), is supported by the fact that vascular injury increases the uptake of fluorodeoxyglucose in PVAT, as imaged by PET (10). Our original method (9) relied on the principle that a shift of PVAT content from a lipid to an aqueous phase would cause a shift of PVAT attenuation from −190 to −30 Hounsfield units. The method was first used to analyze PVAT attenuation gradients around atherosclerotic plaques, independent of their anatomical location (**Figure 1**) (9), and it was found to be an excellent tool to distinguish unstable plaques from their stable counterparts in acute coronary syndromes. The addition of artificial intelligence and radiotranscriptomic approaches in nearly 2,000

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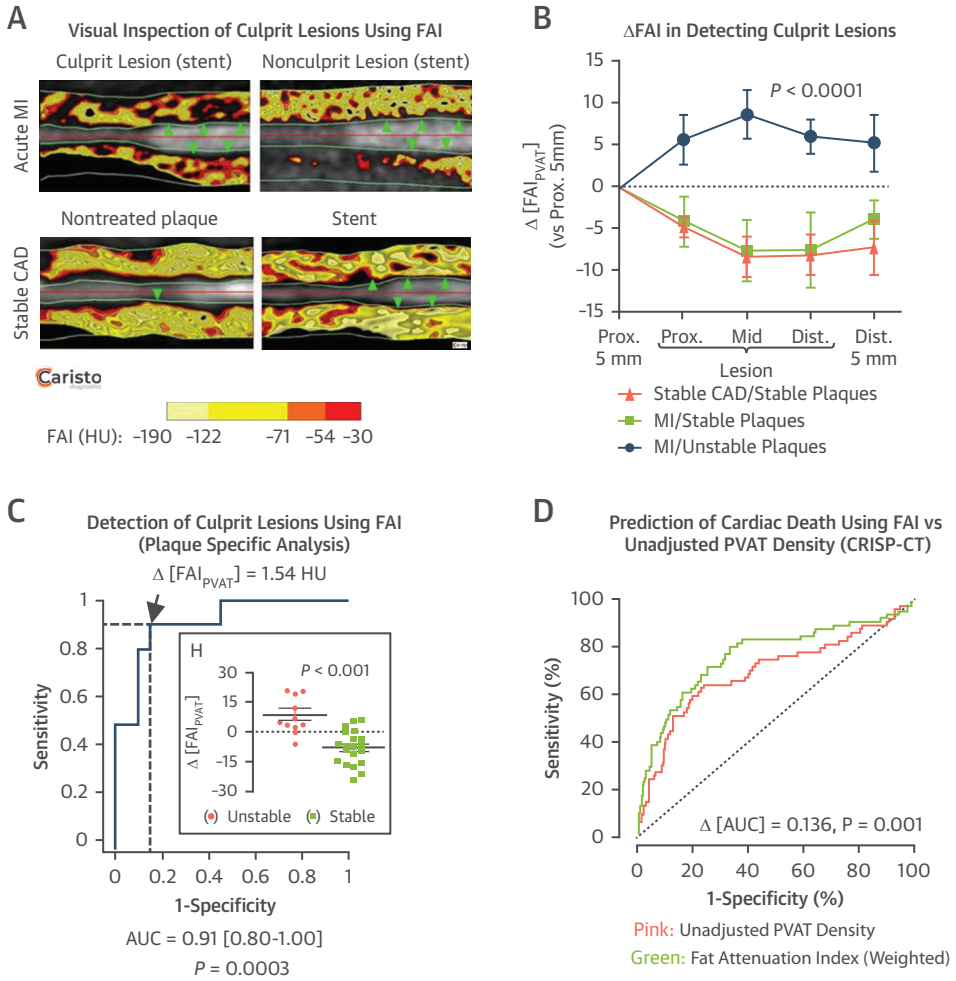
FIGURE 1 Perivascular FAI Mapping and Detection of Culprit Coronary Lesions



(A) Maps of fat attenuation index (FAI) around ruptured plaques after an acute myocardial infarction or stable plaques (images from lesions of mid-left anterior descending artery) (from Antonopoulos A et al. [9] with permission). **(B)** Changes in perivascular FAI are strikingly different in unstable lesions versus stable lesions, **(C)** with a high sensitivity and specificity in discriminating the culprit (lesions included were from the right coronary artery [25%], the left anterior descending artery [59%], and the left circumflex artery [16%]). **(D)** In CRISP-CT (14), unadjusted perivascular adipose tissue (PVAT) density had borderline predictive value for cardiac mortality, whereas fully weighted FAI led to improved risk prediction by 13.6% (from the CRISP-CT study [14], and reproduced under Creative Commons Attribution License [CC BY]). AUC = area under the curve; CAD = coronary artery disease; HU = Hounsfield unit; MI = myocardial infarction.

human fat biopsies led to the development of a complex algorithm to decipher perivascular CT attenuation shifts, turning them into a meaningful quantitative biomarker, called the perivascular fat attenuation index (FAI). Perivascular FAI includes a number of corrections related to technical, biological, and anatomical factors that drive the absolute attenuation of PVAT.

The principle that PVAT CT attenuation changes around highly inflamed regions such as ruptured plaques (11,12) or spontaneous coronary dissections (12) was validated by others. In this issue of *iJACC*, Kwiecinski et al. (13) showed that crude measurement of PVAT attenuation (or density) around high-risk plaques was also correlated with ^{18}F-sodium fluoride uptake on PET/CT. This important proof-of-principle study confirmed that severe vascular inflammation drives changes in PVAT attenuation. The investigators focused their analysis on high-risk plaques, as identified by conventional coronary CTA image analysis. Although this crude PVAT attenuation (density) worked well as a qualitative measure, its conversion into a quantitative tool usable in clinical practice has many challenges. PVAT attenuation,

presented as an absolute value, is driven by various factors: 1) technical (e.g., tube voltage, reconstruction algorithms); 2) biological (e.g., background adipocyte size, as determined by the insulin resistance status of the patient, shifts fat attenuation to more negative values, thereby underestimating inflammation in the adjacent artery of PVAT in these patients); and 3) anatomical (e.g., each coronary segment has different PVAT biology and different "normal reference" values). For this reason, in the original description of FAI (9), in addition to the qualitative perivascular measurement around any lesion (replicated in the current work by Kwiecinski et al. [13]), we then focused on the proximal segment of the right coronary artery, using a radioranscriptomic approach to increase the level of confidence value interpretation (linking attenuation values with the local biology from PVAT biopsies) (9). This led to the development of an artificial intelligence–enhanced algorithm (namely CaRi-HEART algorithm) that enabled calculation of weighted PVAT attenuation shifts captured by perivascular FAI, which was measurable in all coronary segments and that required corrections for a large number of factors, including segment-specific thresholds.

In addition to measuring FAI around specific plaques to test for their inflammatory burden (a principle elegantly confirmed in this paper by Kwiecinski et al. [13]), focused analysis on a reference segment (e.g., proximal right coronary artery) provides information on the background inflammatory status of the entire coronary tree, even in the absence of visible local atheroma. The CRISP-CT (Cardiovascular RISk Prediction using Computed Tomography) study (14) demonstrated that the perivascular FAI around the proximal segments of the major coronary arteries had a striking prognostic value for cardiac death and nonfatal myocardial infarction in 4,000 individuals. CRISP-CT showed that FAI in "healthy" standardized coronary segments predicted outcomes independently of high-risk plaque features located elsewhere in the coronary tree or the degree of systemic inflammation captured by high-sensitivity C-reactive protein. "Abnormal" fully weighted perivascular FAI was associated with a 6- to 9-fold increased risk of fatal heart attacks in the following 5 years, even after correction for contemporary gold-standard coronary CTA image interpretation. Importantly, the predictive value of the fully weighted FAI in CRISP-CT improved by approximately 14% compared with unadjusted PVAT density (**Figure 1**). From a clinical perspective, perivascular FAI appears to be modifiable both by treatments (abnormal perivascular FAI measured in individuals before statin initiation lost its predictive value for future fatal or nonfatal heart attacks [14]) and by time (it changed dynamically after an acute coronary event [9]).

How do we interpret PVAT attenuation measurements such as FAI in clinical practice? Using an artificial intelligence–enhanced algorithm (such as CaRi-HEART), that learns and improves as the data set enlarges (as applied on FAI) is the only way to personalize this technology for use in clinical practice. The potential of PVAT attenuation measurements, such as FAI, to transform patient risk stratification is considerable. It could identify healthy individuals with abnormal FAI who would benefit from aggressive primary prevention (e.g., statins) or patients with advanced disease. Further clinical trials are needed to show whether perivascular FAI is modifiable by therapeutic interventions and to understand how the residual inflammatory risk identified by this technology can be targeted to reduce cardiovascular risk, the aim being to ultimately improve patient outcomes.

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