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EDITORIAL

Epicardial Fat and Coronary Vulnerability

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Coronary artery disease (CAD) represents the major cause of mortality and long-term disability worldwide. Despite new improvements in primary and secondary prevention methods, CAD-related mortality and morbidity demonstrate an increasing trend in the last decades.[1–3]

CAD represents the most common and severe consequence of atherosclerosis.[4] Atherosclerotic plaque rupture, leading to acute coronary syndromes as the most severe outcome, consists in a complex biomechanical process resulting from the interaction between traditional risk factors, structural features, hemodynamical stresses, and biological processes.[5,6] In the last years, an increased attention has been given to the role of epicardial adipose tissue (EAT) as a marker of cardiovascular risk, as well as to the assessment of atheromatous plaque instability.[7,8] Recent reports suggest that an increased volume of EAT is directly associated with the presence of high-risk features in the coronary plaques, as subjects with unstable coronary lesions have significantly larger EAT volumes than those without high-risk plaques.[8]

EAT represents an adipose depot rich in proinflammatory and proatherogenic molecules. Based on the anatomic proximity of EAT to the arterial adventitia of coronary arteries, the "outside in" hypothesis of atherosclerosis has been recently launched, according to which EAT components may trigger vascular inflammation and plaque destabilization through paracrine and vasocrine mechanisms.[9–13] It has been demonstrated that the amount of EAT is directly correlated with both the length and the severity of coronary lesions, at the same time being associated with the transformation of atherosclerotic plaques into a vulnerable phenotype, considered to be "high risk" for major cardiovascular events.[11]

In a large study conducted by Nerlekar *et al.*, a strong correlation was found between several CT features of vulnerable atherosclerotic plaques, such as low-attenuation lesions and positive remodeling at the lesion site.[9] In the largest study to date, Motoyama *et al.* identified plaque features strongly correlated with future acute coronary syndrome (ACS) development in 3,158 subjects.[14] Moreover, in a trial of non-obese subjects who underwent repeated coronary CT follow-up in a 4-year period, increased EAT volume proved to be associated with high-risk plaques as well as with future ACS despite optimal treatment of CV risk factors.[15] However, the major weakness of these trials remains

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the assessment of EAT as a homogeneous depot, a fact that completetly ignores the biologically significant phenotypic variability of perivascular adipose tissue (PVAT) versus non-PVAT depots in the human heart.[15–19] Linear thickness by 2-dimensional assessment was reported to present a modest correlation with EAT volume,[20] under the conditions in which EAT volume assessment displayed a significant association with high-risk plaque features with more precise confidence limits.[9]

It has been recently demonstrated that the adipose tissue surrounding the coronary arteries changes in response to inflammation inside the arteries.[21] Interestingly, the SMART trial identified the low PVAT attenuation on CT as associated with an adverse metabolic profile, the correlation being independent of PVAT volume. This fact suggests that fat quality measures might add complementary information to the one provided by PVAT quantity.[22] In the same cohort, lower PVAT attenuation was also correlated with the level of calcifications in the coronary arteries. Similarly, Abazid *et al*. observed a negative association between PVAT and coronary calcification score, independent of PVAT volume.[23]

Given the absence of dedicated analysis algorithms, in most studies, PVAT imaging has been limited to the crude analysis of total EAT. In this context, a detailed analysis technique of coronary PVAT was recently developed as a sensor for coronary inflammation and vascular disease, based on the observation that in the presence of inflammation, a blockage appears in the differentiation of perivascular preadipocites.[24] This variation can be identified by a new, patented technique for computed tomography image analysis, creating a new measurement named the Fat Attenuation Index (FAI), which accurately measures the amount of inflammation in the coronary arteries. The FAI can be calculated using a novel, artificial intelligence-powered set of algorithms, and could provide a numerical index of adipose depot composition.[25] Perivascular FAI proved to track timeline changes in coronary inflammation, as significantly decreased FAI values were identified surrounding culprit lesions in subjects with AMI at 5 weeks after the acute assessment.[25] Therefore, early detection of subclinical CAD could be performed in low-risk to intermediate-risk patients via perivascular noninvasive detection of coronary inflammation by FAI.[26] Perivascular FAI could enable the assessment of inflammatory burden and hence the level of coronary plaque vulnerability, identifying subjects at high risk for developing acute coronary events. These observations further highlight the importance of qualitative over quantitative features in the assessment of human PVAT in order to identify vulnerable patients.

In this issue of JIM, three articles address the topic of increased vulnerability for acute coronary events.[27–29] The vulnerability is addressed either in terms of systemic vulnerability, based on multiomics approach of the vulnerable patient, or local vulnerability, highlighted by particular CT image features indicating a higher risk for rupture. However, none of these articles address the topic of EAT or PVAT, as recently described features of coronary vulnerability. This is aligned with the current literature, which indicates that the role of EAT, as a reservoir of inflammatory biomarkers or rather as a marker of inflammation, has not been completely clarified yet.

CONFLICT OF INTEREST

Nothing to declare.

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