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EDITORIAL

The new age of radiomic risk profiling: perivascular fat at the heart of the matter

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This editorial refers to 'A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography', by E.K. Oikonomou *et al.*, doi:10.1093/eurheartj/ehz592.

Atherosclerosis is a complex process driven by immunological, metabolic, and mechanical abnormalities along with aberrant cholesterol metabolism and sterile activation of inflammatory pathways. While it is well established that the humoral milieu in the vessel wall is critical for disease progression,[1,2] the contribution of the perivascular tissue to atherosclerosis development is much less well understood. Perivascular adipose tissue (PVAT) displays a proinflammatory phenotype in coronary artery disease (CAD) and, by measuring PVAT inflammation by the computed tomography (CT)-based fat attenuation index (FAI), has been shown to be associated with cardiovascular disease (CVD) outcomes.[3] Oikonomou *et al.*, in this issue of the *European Heart Journal*, introduce an artificial intelligence (AI) machine learning-informed fat radiomic profile (FPR) assessed by CT for major adverse cardiac events in patients with CAD.[4] This extends far beyond determining calcification scores by CT or the association between PVAT inflammation and CVD outcomes, as previously reported in the CRISP CT study. These findings clearly support the hypothesis and notion that (i) PVAT inflammation drives and worsens CVD outcomes as an underlying mechanism and (ii) monitoring PVAT inflammation by FPR is superior to relying upon established risk factors and classical clinical chemistry parameters, imaging modalities, or biomarkers.

While an array of established clinical markers have enhanced our capacity for patient stratification, they may inaccurately reflect the local disease burden. It is biologically conceivable that PVAT inflammation adjacent to the lesion would directly affect coronary plaque formation and stability. However, the precise causative mechanisms remain elusive. Oikonomou *et al.* now introduce the concept of the FPR, which, in addition to inflammation, also incorporates knowledge about PVAT fibrosis and vascularity, both of which are well-known factors influencing adipose tissue health in obesity.[4,5] This represents further evidence that the localized adipose tissue pathology in CAD is phenotypically similar, and probably mechanistically related, to generalized adipose tissue dysfunction in obesity. The authors obtained PVAT expression profiles from patients and linked these expression patterns to the FAI and clinical outcome, using AI-based FRP to more accurately predict CVD risk on top of traditional risk factor models including age, sex, systolic blood pressure, diabetes mellitus, body mass index, smoking status, presence of obstructive CAD, total cholesterol and HDL levels, and Agatston coronary calcium score (*Figure 1*). However, to therapeutically target adipose tissue dysfunction in both CAD and obesity, more research is needed. First, further detailed studies should aim to dissect in detail whether PVAT inflammation drives local inflammation in the adjacent lesion or rather impacts plaque stability and phenotype via other remote and hitherto unidentified mediators. In either case, detecting high-risk patients by assessing local PVAT via the FRP is a more immediate and direct measure as compared with systemic markers such as cholesterol levels, C-reactive protein, or insulin resistance; which might explain the improved diagnostic precision conferred by FRP. Alternatively, PVAT inflammation may merely reflect the overall immunometabolic state of the patient, such that PVAT is actually a marker of the general inflammation status and thus a local representation of the systemic metabolic state. Whether PVAT, due to its unique positioning close the vasculature, is more susceptible to inflammation compared with other visceral or subcutaneous adipose tissue depots is still unknown.

In the area of PVAT and immunometabolic disorders, there is relatively little basic research available to date. In particular, there is only limited epistasis-type research investigating the role of PVAT in atherogenesis or plaque stability, perhaps due to a lack of specific PVAT-directed models, such as conditional transgenics restricted to PVAT-resident adipocytes. The identity of paracrine mediators or cellular determinants leading to PVAT inflammation, responsible for the effects of PVAT on plaque inflammation and stability, remain to be elucidated. From the metabolic perspective, it is reasonable to

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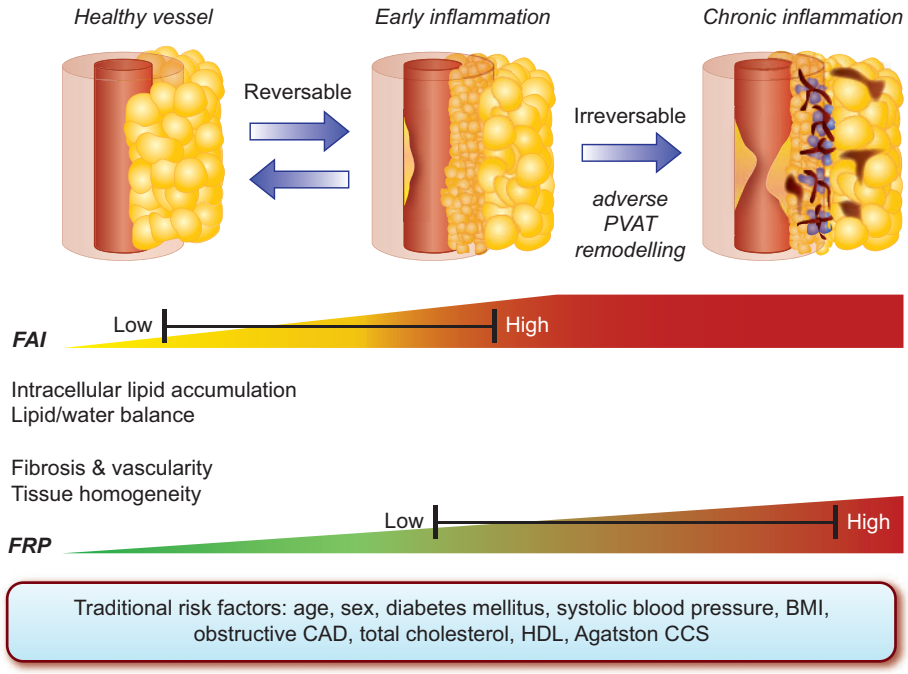

Figure 1 Enhanced cardiovascular risk prediction using an artificial intelligence-informed fat radiomic profile. Imaging of perivascular adipose tissue (PVAT) inflammation and lipid content (Fat attenuation index, FAI) through detecting changes in the Lipid/water balance by computer tomography (CT)-based methods is an informative tool to estimate cardiovascular disease (CVD) risk with good resolution. Additional information on fibrosis & vascularity as well as tissue homogeneity provided to an artificial intelligence to creates a fat radiomic profile (FRP) that better predicts CVD risk than measures of common established risk factors over a broad range. BMI, Body-mass index; CAD, Coronary artery disease; HDL, High-density lipoprotein; CCS, Calcium calcification score.

hypothesize that classical mechanisms of adipocyte overload and inflammatory activation might also hold true for PVAT. Clearly, PVAT is phenotypically very diverse, depending on its location in the body. From an inflammatory perspective, certain PVAT depots are known to display dynamic interaction with immune cells. For instance, in pericardial adipose tissue, larger B-cell clusters have been identified in patients with CAD compared with controls.[6] Likewise, infarcted mice revealed larger B-cell clusters with an increase in granulocyte–macrophage colony-stimulating factor (GM-CSF)-producing B cells in pericardial adipose tissue. This was associated with CCR7-dependent dendritic cell and T-cell expansion, driving neutrophil infiltration and resulting in functional worsening after myocardial infarction. Similar mechanisms may also apply to a coordination of immune cell activation, granulopoiesis, and worsened outcomes in unstable CAD. This has been shown, for example, for arterial tertiary lymphoid organs (TLOs), which can orchestrate territorialized and multilayered B-cell responses in the diseased aorta with germinal centre reactions indicating generation of autoimmune B cells during ageing.[7] Conversely, we recently identified PD-L1+ non-classical monocytes in TLOs under inflammatory conditions in both mice and humans, where they can exert a PD-L1-dependent immunoregulatory function, promoting T cell apoptosis and thus limiting disease.[8] A role for this process remains to be studied in the context of coronary PVAT. Despite our current limitations in understanding the biology underlying the role of PVAT in CVD, this work by Oikonomou *et al.* provides a novel tool to potentially enhance risk assessment and stratification of patients with CAD.[4] It is possible that the FRP is at the forefront of novel AI-based medical procedures. Owing to its non-invasive nature and easy accessibility, this technology provides a further advance over *ex vivo* metabolomics profiling, as recently accomplished to distinguish high-risk plaques in carotid endarterectomy specimens using mass spectrometry or nuclear magnetic resonance.[9,10] As the impact of PVAT on CAD appears to be powerful, it provides the incentive for new basic research on PVAT phenotypes, activity, and elucidation of the underlying mechanisms contributing to adverse CVD outcomes, enabling the development of novel and specific therapeutics, which may also be assessed using the FRP AI-based platform.

Conflict of interest: J.L. is a consultant to and holds stock options in Circle CVI and HeartFlow. The other authors have no conflicts to declare.

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