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EDITORIAL

# Identifying the vulnerable patient: pericoronary Adipose tissue attenuation on computed tomography

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The identification of patients with "stable" coronary artery disease who will develop ischemic events during their lifetime is a holy grail in the practice of cardiovascular medicine. Identification of the vulnerable patient is pivotal for optimal decision-making regarding revascularization and pharmacological intervention. The progression of atherosclerosis to the generation of "vulnerable" vessel wall (plaque rupture and endothelial erosion) with subsequent occurrence of thrombotic events is a dynamic process. There is continuous interplay between the diseased vessel wall and the vulnerability of the blood to clot, a term referred to as "thrombogenicity". The atherothrombosis process is critically influenced by inflammation and is therefore comprehensively described as "thrombo-inflammatory syndrome" [1]. In addition to "vulnerable" vessel wall characteristics being associated with subsequent thrombotic events, many plaques with low-risk features are also present in the coronary tree. There is abundant evidence that plaque growth progresses by repetitive healing of acute destabilizing events. These plaques undergo silent healing leading to the generation of layered plaques characterized by distinct layers of organized thrombus and/or collagen. These layered plaques appear as a band of high backscattering signals in optical coherence tomography (OCT) [2, 3]. Using near-infrared light, OCT has been reported to assess lipid accumulation, thin-cap fibroatheroma (TCFA), macrophage accumulation and layered plaque with one or more layers of different optical densities. OCT studies suggested that layered plaques, also described as "biologically active plaques", in patients with acute coronary syndrome (ACS) were associated with local and systemic inflammation and subsequent rapid plaque progression. In these studies, macrophage accumulation was defined as the presence of highly backscattering focal granular regions in the fibrous cap [2–4].

Histopathological studies have validated the recognition of healed plaque with one or more layers of different optical densities assessed by OCT [5]. Autopsy studies revealed that the prevalence of healed plaque is up to 80% in patients with coronary artery disease (CAD) [6]. An OCT study revealed that healed plaques are present in 29% of lesions associated with ACS and are more frequent in patients with hyperlipidemia, diabetes mellitus, and a history of myocardial infarction (MI) [2]. Most of the earlier OCT imaging studies were conducted in patients with ACS.

It has been demonstrated that paracrine inflammatory signals (tumor necrosis factor-α and interleukin-6) from the diseased vessel wall diffuse into the perivascular adipose tissue (PVAT) and influence adipocyte differentiation, proliferation and lipolysis. This causes a respective gradient from a more aqueous/less lipophilic phase close to the vascular wall to a less aqueous/more lipophilic phase in the non-PVAT. The latter changes in the gradient can be assessed by noninvasive computed tomography angiography (CTA) as shifting attenuation from the lipid (more negative Hounsfield unit [HU] values [eg, closer to −190 HU]) to the aqueous phase (less negative HU values [eg, closer to −30 HU]) and is termed as perivascular fat attenuation index (FAI) [7]. Thus, FAI indicates the degree of coronary artery inflammation. CTA can predict vascular atherosclerosis progression/inflammation independent of currently available cardiovascular risk factors and imaging biomarkers. Significantly increased perivascular FAI around culprit/unstable lesions in patients with acute MI and dynamic changes in perivascular FAI around culprit coronary lesions with FAI decreasing significantly 5 weeks after the index event have been demonstrated [7]. In an initial important study, Oikonomou et al. demonstrated that cardiac risk prediction can be greatly enhanced by assessing CTA based perivascular FAI

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and inflammatory burden. The authors demonstrated that high perivascular FAI values (cutoff $\geq -70{\cdot}1$ HU) are an indicator of increased cardiac mortality and can be used for early targeted primary prevention and intensive secondary prevention [8]. An assessment of perivascular FAI can accurately predict plaque progression and discriminate between unstable atherosclerotic plaques and plaque progression [9].

Earlier studies had demonstrated the frequent presence of layered plaques and their relation to plaque vulnerability in patients with SAP based on OCT [2, 10, 11]. Similarly, higher vascular inflammation as indicated by FAI has been demonstrated in culprit lesions than that of non-culprit lesions in patients with ACS compared with patients with stable angina pectoris (SAP) [11–13]. In this issue, Niida et al. analyzed the relationship between layered plaque and markers of plaque vulnerability by OCT and vascular inflammation identified by computed topography angiography (CTA) simultaneously in a single center study of 475 plaques from 195 Japanese patients with stable angina pectoris (SAP) [14]. Higher levels of inflammation as indicated by elevated attenuation in the CTA analysis and higher prevalence of the OCT features of plaque vulnerability, including lipid rich plaque, thin-cap fibroatheroma, microvessels and cholesterol crystals were demonstrated in layered plaques compared with non-layered plaques. As mentioned above, earlier studies demonstrated higher vascular inflammation and plaque characteristics independently in patients with ACS and SAP. The current study is the first to utilize both CTA and OCT in patients with SAP. Interestingly, these "stable" patients had normal BMI (22.4–26.5 kg/m$^2$), normal lipid profile, lower levels of high sensitivity C-reactive protein (hsCRP) and average hemoglobin (Hb)A1c level of 6.1%. Based on these results the authors suggest that the high levels of vascular inflammation and plaque vulnerability associated with layered plaques are responsible for the rapid plaque progression and potentially trigger clinical events. Furthermore, the study results suggest that patients who are considered "stable" often possess the same high-risk characteristics of vulnerable plaque morphology and high-grade inflammation as patients with ACS. The current study was exclusively conducted in an East Asian population, where a recent study in patients undergoing percutaneous coronary intervention demonstrated a 25% residual inflammatory risk indicated by high levels of persistent systemic hsCRP and its association with recurrent ischemic events and major bleeding [15]. The presence of similar levels of high residual vascular wall and systemic inflammatory risk should be explored in a western population, where thrombotic risk is comparatively high [16].

What are the implications of these findings for the practicing clinician? The results of the current study suggest that analysis of PVAT by CTA may identify the "stable' patient who is far from "stable". Niida et al. provide further evidence of a mechanistic link between inflammation identified by CTA and vessel wall vulnerability identified by OCT. Refined CTA techniques that reliably report quantitative metrics on extent of inflammation may provide critical additional information to add precision to the assessment of patient risk. Combining the latter with an assessment of systemic thrombogenicity may further sharpen our identification of the high-risk patient [17].

## Declarations

**Disclosures Dr. Gurbel r**eceived consulting fees and/or honoraria from Bayer, Vectura/Otitopic, Janssen, Cleveland Clinic foundation, Wolters Kluwer Pharma, Web MD Medscape, Baron and Budd, Premier Health Care Resource, Baim Institute, and Medforce; institutional research grants from Accriva Diagnostics, AstraZeneca, Bayer, Cronos, Janssen Pharmaceuticals Inc., Haemonetics, Hikari Dx, Idorisa, Labcorp Drug Development, Novartis, Prolocor, Recor Medical, Vectura Limited, Zoll Medical Corporation; in addition, Dr. Gurbel has two patents, Detection of restenosis risk in patients issued and Assessment of cardiac health and thrombotic risk in a patient. Dr. Gurbel was an expert witness in a lawsuit associated with Plavix.
Other authors report no conflict of interests.

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