Invited commentary

Inflammation goes with the flow: Implications for non-invasive identification of high-risk plaque

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The development and identification of high-risk plaques has garnered much research interest over the last few decades. Multiple basic science and clinical studies have established that high-risk, rupture-prone, plaques develop due to inflammation and exhibit large necrotic cores, thin fibrous caps, paucity of smooth muscle cells, expansive remodeling, neovessels and microcalcifications [1]. Such plaques develop in regions of low endothelial shear stress (ESS), an environment that favors inflammation, lipid deposition, and vascular remodeling (Fig. 1) [2,3]. Coronary heart disease events occur more likely at the site of such high-risk “unstable” plaques if the plaque ruptures [1]. In contrast, non-high-risk plaques consist of predominantly fibrotic lesions often with limited inflammation, thick fibrous caps, smaller necrotic cores, dense calcifications, and constrictive remodeling. These plaques tend to develop in regions of higher ESS [2]. They evolve either directly from early fibroatheromas or from plaques which undergo repetitive (often sub-clinical) disruption and healing, ultimately leading to thick fibrous cap formation. Non-high-risk plaques usually manifest with stable angina and many refer to them as “stable,” as they have less liability to rupture and cause acute cardiovascular events [1]. Proteoglycan-rich plaques, often without evident inflammation, can give rise to superficial erosions, another cause of coronary artery thrombosis [1]. Despite numerous advances in understanding the pathobiology of atherosclerosis, no validated imaging techniques can reliably identify high-risk plaques [4,5].

In this issue of Atherosclerosis, Wenning et al. provide further experimental evidence that low ESS promotes inflammation and plaque progression, and that non-invasive imaging can visualize such processes [6]. This study imaged thirty-five ApoE−/− mice that consumed a high cholesterol diet with serial 18F-FDG PET/CT to test whether carotid artery glucose uptake, a process associated with inflammation, differs between plaques located upstream (area of low ESS) and downstream (area of oscillatory ESS) of a surgically-implanted cuff. The mice were imaged in-vivo at 4, 6 and 8 weeks with 18F-FDG PET/CT and ex-vivo after 8 weeks, using immunohistochemical analysis. The authors report significantly increased 18F-FDG uptake in plaques upstream, where ESS is low and promotes inflammation, versus plaques downstream, which experience oscillatory ESS associated with fibroproliferation. Moreover, they report a strong correlation between background-corrected 18F-FDG uptake in upstream plaques with plaque size, degree of stenosis and macrophage content, as determined morphologically. The authors conclude that 18F-FDG PET/CT identifies low ESS-induced inflamed plaques and distinguishes them from non-inflamed plaques.

The report extends our understanding of how 18F-FDG-PET/CT can disclose inflamed plaques, previously associated with low ESS in validated animal studies [7]. While many groups have demonstrated a correlation between 18F-FDG uptake and markers of plaque inflammation [8], the demonstration of this phenomenon in mice has been limited. The current study supports the close association, and potential synergism, of low ESS and inflammation in high-risk plaque formation and lends plausibility to the hypothesis that vascular events occur more likely under conditions which promote plaque progression and local inflammation within a particular hemodynamic microenvironment.

The novel study by Wenning et al. has several limitations. The inferior spatial resolution of PET/CT compared to histopathology provides a challenge to co-registration of histologic sampling, PET/CT findings and ESS along the cuff. The small size of the mouse carotid arteries presents a particular technical challenge. Also, since perivascular tissue resembles brown adipose tissue – which is 18F-FDG avid – the observed perivascular 18F-FDG uptake might not
result solely from inflammation. Also, in vitro studies show that hypoxia rather than inflammation cause increased glucose uptake in macrophages [9]. Thus, while the increased macrophage content observed in upstream plaques that experience low ESS do reflect inflammation, the associated local hypoxia might drive the increase in 18F-FDG uptake in these regions. Finally, the preparation used by Wenning et al. does not necessarily recapitulate native atherosclerosis, as it involved a mechanical intervention to potentiate lesion formation. Thus, the inflammation identified in their experiments could reflect in part local vascular injury [10]. It is further unknown whether the findings in the mouse carotid artery apply to regions that experience low ESS along the coronary arteries, which are more tortuous. Further prospective studies should probe the ability of 18F-FDG, as well as of other tracers, to identify plaque inflammation at sites of low ESS, and ultimately determine that these lesions provoke future cardiovascular events.

What are the implications of this study and how can the findings be translated to humans? Currently, there is tremendous interest in identifying plaques, which result in future cardiovascular events, based on the premise that identification and treatment of such plaques (or patients who have them) could prevent such events. To date, two natural history studies (PROSPECT, PREDICTION) in patients who have had previous acute coronary syndromes have attempted to determine whether invasive assessment can identify high-risk plaques [5,11]. These studies have shown that it is extremely difficult to accurately identify the sites of future ruptured lesions. For instance, in the PROSPECT study - the first and largest natural history study of coronary atherosclerosis – fewer than 5% of plaques which had intravascular ultrasound characteristics of possible thin capped fibroatheroma associated with events during a 3.4 year median follow up period [5]. The PREDICTION trial showed that low ESS and increased plaque burden independently predict plaque progression by intravascular ultrasound, however, due to the limited number of events the study did not show any association of low ESS with outcomes [11]. Likely, better identification of high-risk plaques will require simultaneous assessment of multiple plaque characteristics (e.g. severity of inflammation, size of lipid core, degree of remodeling) and local hemodynamic features (e.g. ESS) (Fig. 2). Even if successful at identifying high-risk lesions (or high-risk patients), such imaging methods should ultimately use non-invasive approaches to ease clinical utility. In addition, non-invasive techniques may enable us to study larger cohorts of patients, and thus focus on hard cardiovascular endpoints (e.g. myocardial infarction and cardiac death). Such a large-scale natural history study would be costly and challenging, but also provide enormous benefit, particularly since better methods to identify at-risk patients could guide deployment of newer systemic or local anti-inflammatory treatments. While awaiting such studies, case-control natural history studies may shed some light regarding high-risk plaque characteristics.

Is non-invasive identification of high-risk plaque feasible? Some studies indicate that 18F-FDG may identify inflamed plaques [8,12]. However, co-localization of the 18F-FDG signal with the coronary vessels is limited as 18F-FDG uptake by the myocardium can interfere with plaque imaging. Therefore, 18F-FDG is currently better suited for visualizing medium-sized and large vessels with limited motion and background signal, such as the carotid arteries and aorta. For coronary artery plaques at risk 18F–NaF may be a promising tracer as shown recently in a pioneer clinical study [13]. Coronary CT angiography may also identify anatomical high-risk plaque features, such as large lipid core, expansive remodeling,
and microcalcifications [4]. While coronary CT angiography does not provide information about inflammation, such data could be obtained by combining CTA data with molecular imaging techniques [14]. Methods under development should enable coronary CT angiography to provide ESS measurements through computational fluid dynamic analyses, an approach that could add important information for predicting high-risk plaque formation and progression [15]. Finally, magnetic resonance techniques can provide anatomic and functional plaque imaging, as well as local flow data, applications currently best suited to the carotid arteries and aorta due to limited spatial resolution [14].

If achieved, non-invasive imaging which integrates morphological, molecular and local flow information could enable the localization of future culprit plaques, or at least identify better high-risk patients, which along with advances in therapies could create an opportunity for further reduction in cardiovascular events. Of course, assessment of the added value of any imaging technique to traditional risk calculators and various blood biomarkers will require rigorous evaluation. The ability to image high-risk atherosclerotic plaques non-invasively could provide a tool for evaluating novel therapies, as well as guiding individual patient management. The combination of functional imaging of ESS and inflammation with anatomical information should speed realization of this chimeric goal.

Conflicts of interest

None.

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References