Atherosclerosis 234 (2014) 476–478

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Invited commentary

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

Yiannis S. Chatzizisis, Ron Blankstein, Peter Libby*

Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA, USA

ARTICLE INFO

Article history:
Received 16 February 2014
Accepted 19 February 2014
Available online 28 February 2014

Keywords:
Atherosclerosis
Inflammation
Shear stress

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 micro-calcifications [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 ^{18}F-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 ^{18}F-FDG PET/CT and ex-vivo after 8 weeks, using immunohistochemical analysis. The authors report significantly increased ^{18}F-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 ^{18}F-FDG uptake in upstream plaques with plaque size, degree of stenosis and macrophage content, as determined morphologically. The authors conclude that ^{18}F-FDG PET/CT identifies low ESS-induced inflamed plaques and distinguishes them from non-inflamed plaques.

The report extends our understanding of how ^{18}F-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 ^{18}F-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 ^{18}F-FDG avid - the observed perivascular ^{18}F-FDG uptake might not

DOI of original article: http://dx.doi.org/10.1016/j.atherosclerosis.2014.03.008.
* Corresponding author. Tel.: +1 617 732 8086; fax: +1 617 264 5111.
E-mail address: plibby@partners.org (P. Libby).

http://dx.doi.org/10.1016/j.atherosclerosis.2014.02.019

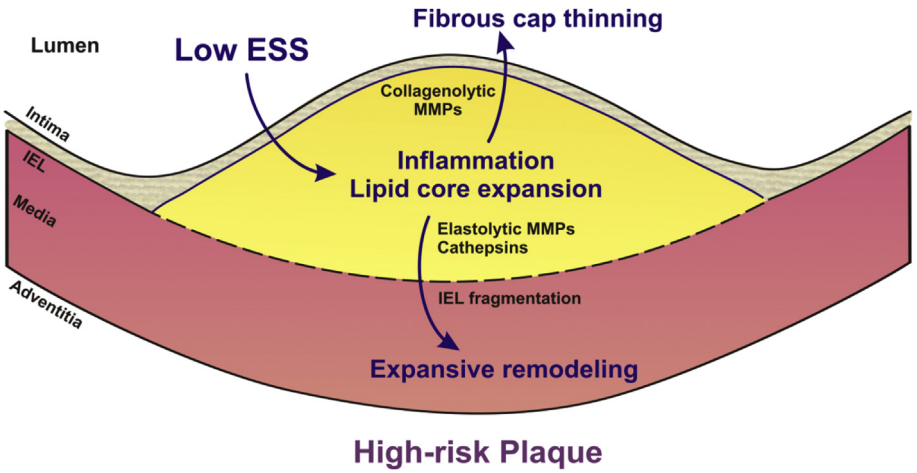

Fig. 1. Pathobiologic mechanisms linking low ESS, inflammation and high-risk plaque formation: Low ESS promotes lipid core expansion and plaque inflammation, which increase the expression and activity of collagenolyting matrix metalloproteinases (MMPs), as well as of elastolytic MMPs and cathepsins. Collagenolytic MMPs promote fibrous cap thinning, whereas elastolytic MMPs and cathepsins mediate internal elastic lamina (IEL) fragmentation, extension of inflammation to the media and expansive remodeling, ultimately leading to thin capped fibroatheroma formation.

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 ^{18}F-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 ^{18}F-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.

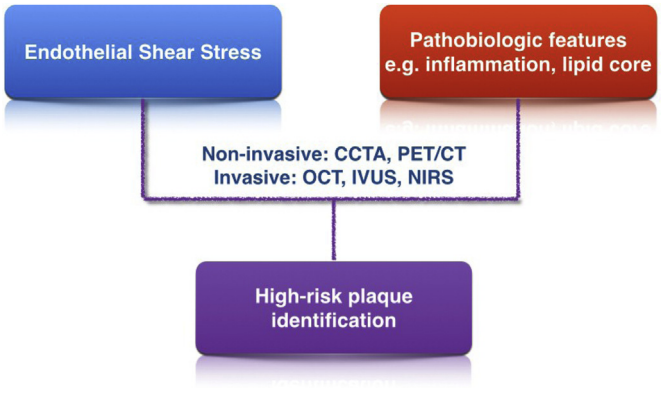

Fig. 2. Non-invasive and/or invasive combined assessment of coronary local endothelial shear stress and pathobiologic plaque features e.g. inflammation, lipid core may allow the identification of high-risk plaque (CCTA: coronary computed tomography angiography, PET/CT: positron emission tomography/computed tomography, OCT: optical coherence tomography, IVUS: intravascular ultrasound, NIRS: near infrared spectroscopy).

Is non-invasive identification of high-risk plaque feasible? Some studies indicate that ^{18}F-FDG may identify inflamed plaques [8,12]. However, co-localization of the ^{18}F-FDG signal with the coronary vessels is limited as ^{18}F-FDG uptake by the myocardium can interfere with plaque imaging. Therefore, ^{18}F-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 ^{18}F–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.

Funding

Dr. Chatzizisis is funded by the Behrakis Foundation, Boston, MA and Dr. Libby by grants from the US National Heart Lung and Blood Institute RO1 HL080472 and PO1 HL048743.

References

[1] Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368:2004–13.
[2] Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007;49:2379–93.
[3] Chatzizisis YS, Baker AB, Sukhova GK, et al. Augmented expression and activity of extracellular matrix-degrading enzymes in regions of low endothelial shear stress colocalize with coronary atheromata with thin fibrous caps in pigs. Circulation 2011;123:621–30.
[4] Blankstein R, Ferencik M. The vulnerable plaque: can it be detected with cardiac CT? Atherosclerosis 2010;211:386–9.
[5] Stone GW, Maehara A, Lansky AJ, et al. PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.
[6] Wenning C, Kloth C, Kuhlmann MT, et al. Serial F-18-FDG PET/CT distinguishes inflamed from stable plaque phenotypes in shear stress induced murine atherosclerosis. Atherosclerosis 2014;234:276–82.
[7] Cheng C, Tempel D, van Haperen R, et al. Atherosclerotic lesion size and vulnerability are determined by patterns of fluid shear stress. Circulation 2006;113:2744–53.
[8] Rudd JH, Narula J, Strauss HW, et al. Imaging atherosclerotic plaque inflammation by fluorodeoxyglucose with positron emission tomography: ready for prime time? J Am Coll Cardiol 2010;55:2527–35.
[9] Mateo J, Izquierdo-Garcia D, Badimon JJ, Fayad ZA, Fuster V. Noninvasive assessment of hypoxia in rabbit Advanced atherosclerosis using 18F-fluoromisonidazole PET imaging. Circ Cardiovasc Imaging; 2014 [In press].
[10] Tanaka H, Sukhova GK, Swanson SJ, et al. Sustained activation of vascular cells and leukocytes in the rabbit aorta after balloon injury. Circulation 1993;88:1788–803.
[11] Stone PH, Saito S, Takahashi S, et al. PREDICTION Investigators. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. Circulation 2012;126:172–81.
[12] Rogers IS, Nasir K, Figueroa AL, et al. Feasibility of FDG imaging of the coronary arteries: comparison between acute coronary syndrome and stable angina. JACC Cardiovasc Imaging 2010;3:388–97.
[13] Joshi NV, Vesey AT, Williams MC, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet 2014;383(9918):705–13.
[14] Camici PG, Rimoldi OE, Gaemperli O, Libby P. Non-invasive anatomic and functional imaging of vascular inflammation and unstable plaque. Eur Heart J 2012;33:1309–17.
[15] Ramkumar PG, Mitsouras D, Feldman CL, Stone PH, Rybicki FJ. New advances in cardiac computed tomography. Curr Opin Cardiol 2009;24:596–603.