Trends in Cardiovascular Medicine 29 (2019) 198–199

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

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

Editorial commentary: Noninvasive imaging for vascular inflammation – A journey to the deep

Dinesh K. Kalra, MD

Rush University Medical Center, Department of Cardiology, 1717 W. Congress Pkwy, Kellogg 320, Chicago, IL 60612, USA

Look deep into nature, and then you will understand everything better.

– Albert Einstein

The role of inflammation in coronary disease has been recognized since the days of Rudolph Virchow, the 19th century pathologist. There are two fundamental processes underlying most acute coronary syndromes (ACS) – the more common one is rupture of a thin cap fibroatheroma (TCFA) and the second one is erosion of the intima. The former is responsible for most large myocardial infarctions (MI) and is universally associated with intense inflammatory activity in the TCFA that results in their rupture, whereas the role of inflammation in plaque erosion is less strong [1]. Vulnerable plaques have a thin collagen cap (<60 μm), an abundance of macrophages and a large lipid (necrotic) core, spotty calcification, and expansive remodeling (Glagov phenomenon). The inflammatory cascade in the arterial wall at the site of atheroma starts with monocyte mobilization which is followed by transformation of these monocytes into phagocytic tissue macrophages. Subsequently, phagocytized lipids, including oxidized LDL and cellular debris, deposit in the atheroma's necrotic core. Matrix metalloproteinases chew away at the collagen cap that covers atheroma especially at the edges leading to a vulnerable TCFA [2,3].

The holy grail in coronary atherosclerosis and inflammation has been identification of such vulnerable plaques before they rupture – this quest has proved difficult because there are far more nonobstructive plaques that do not lend themselves to prospective identification as lurking volcanoes but can nevertheless produce infarction. Only a minority of plaques with known high-risk features lead to MIs and many such ruptures are clinically silent due to countervailing fibrinolytic mechanisms [4,5]. As such, the pursuit to identify these vulnerable plaques has relied heavily on noninvasive imaging of adverse plaque characteristics including inflammation. Nuclear techniques, magnetic resonance imaging (MRI), computed tomography (CT) angiography, and contrast enhanced ultrasound (US) are all currently used and provide complementary insights into arterial wall inflammatory activity. Other invasive imaging tools such as optical coherence tomography and Virtual histology intravascular US and near infrared spectroscopy can also detect vulnerable plaque but are not the focus of discussion here which is limited to noninvasive imaging tools.

In this elegant and concise review by Pelletier-Galarneau and Ruddy [6], the authors describe the clinical application of PET-CT in studying plaque inflammation. ^{18}F-fluorodeoxyglucose (FDG), a positron-labeled glucose analogue is the most commonly used tracer for in vivo imaging of plaque activity, with FDG being used to study glucose uptake by stimulated inflammatory cells.

The first clinical study applying this technique was done in patients with recent strokes and showed increased FDG uptake in carotid plaques [7]. In addition to inflammation, other features that occur commonly in vulnerable plaques i.e. neo-revascularization and local hypoxia are also responsible for the increased FDG uptake. A second, ^{11}Carbon based PET tracer called PK11195 which has an affinity to the translocator protein (TSPO) on activated phagocytes, can also visualize inflamed carotid plaques in patients with recent strokes [8,9]. Both of these tracers have also been useful outside of the carotid vasculature i.e. in studying disease flare ups in large-vessel vasculitis, such as giant-cell arteritis and Takayasu arteritis.

As opposed to extracardiac imaging, coronary FDG PET can be challenging because it requires specific dietary preparation with a very low carbohydrate, high fat diet to suppress myocardial uptake. Despite this preparation, there is often myocardial contamination and it is difficult to tease out inflamed coronary foci from adjacent myocardial uptake. In one study, coronary artery FDG uptake could not be accurately assessed in 49% of cases due to myocardial spillover [10]. Furthermore, the coronaries move during cardiac contraction and relaxation, and there is additional translational/respiratory motion, and they are small in caliber compared to the adjacent myocardium, all of which further complicate the use of this technique for coronary purposes. To overcome these limitations, instead of FDG, Derlin et al. studied the chemokine receptor CXCR4 which is upregulated in unstable plaque and co-localizes with CD68 inflammatory cells. They showed that Pentixafor ^{68}Ga (a ligand for CXCR4) PET-CT visualized in-vivo culprit coronary plaques and distinguished them from non-culprit plaques in 37 patients with ST elevation myocardial infarction.

Coronary CTA alone can identify features of unstable plaque and is a powerful tool beyond providing just the anatomical stenosis severity. Features such as low attenuation plaque denoting lipid core, spotty calcification signifying areas of intraplaque hemorrhage and napkin ring appearance are able to pinpoint vulnerable plaques [12]. PET-CT allows one to superimpose physiological data regarding metabolic processes on top of these CT data to get

E-mail address: dinesh_kalra@rush.edu

https://doi.org/10.1016/j.tcm.2018.09.012

a more complete picture of what is happening in the arterial wall from an inflammatory perspective. Novel tracers such as ^{18}NaF allow us to study microcalcification in coronary plaque as a surrogate of intraplaque hemorrhage/injury and the subsequent healing process [10]. This technique has proven useful in coronary and aortic valve calcification and identifies vulnerable plaque prospectively [7,10].

PET-MR similarly allows a true hybrid imaging solution to assessing vascular inflammation [11]. Moreover, PET MR carries less radiation than PET-CT because the MR component is free of ionizing radiation and allows simultaneous functional imaging of cardiac structures and function, for which CMR has already established itself as a reference standard. Specific molecular probes in PET-MR can detect inflammation, thrombosis, apoptosis, necrosis, angiogenesis, fibrosis or other alterations of the extracellular matrix. PET-MR also provides superior motion correction and myocardial blood flow assessment.

Apo E double knockout mice are prone to early aortic atherosclerosis and thus serve as a good animal model to study inflammation in vivo. Using MRI with gadolinium based liposomal particles that latch onto integrin$\alpha 4\beta 1$ (a cytokine that recruits monocytes), Woodside et al were able to demonstrate inflammatory activity in aortic vulnerable plaques in such mice. Another MRI technique to study plaque behavior uses the native T1 uptake of coronary atheroma. T1 is a measure of magnetic relaxation properties of a tissue after a radiofrequency pulse is applied and is often used to characterize tissue structure. Thus, inflamed plaque has a higher non-contrast T1 uptake and Noguchi et al. have shown that a ratio of 1.4 in signal intensity between inflamed plaque and neighboring myocardium was able to identify vulnerable plaque that led to downstream ACS in their study of 568 patients over 55 months of follow up [13].

High in-plane resolution imaging with multicontrast T1, T2, and proton density weighting can identify positive remodeling and lipid-rich necrotic core. Prospective studies have confirmed that T1-weighted MR imaging of acute plaque hemorrhage or intraluminal thrombus formation accurately identifies culprit and high-risk plaque in the carotids and coronary arteries, as well as patients with an increased risk of future cardiovascular events [14–16].

Despite the promise of these various technologies in imaging inflammation, many of these are in the preclinical arena, and are not yet quite ready for widespread use. It goes without saying that any such technique would have to demonstrate a good positive and negative predictive value and prospectively show an improvement in patient management and reduction in adverse events along with cost effectiveness and safety before generalized applicability. The race is ongoing to find a test that fits the bill for all these features.

Recent reports of quelling vascular inflammation with anti-inflammatory agents have rekindled interest in this field. The CANTOS trial was the first large trial to report a benefit with the IL-1ß monoclonal antibody Canakinumab [17]. IL-1ß has multiple roles in atherothrombosis via the so called “inflammasome” including being a procoagulant, promoting monocyte adhesion to endothelial cells and causing smooth muscle cell hypertrophy. This trial randomized more than 10,000 patients to either canakinumab or placebo, on top of standard post-MI therapy including beta blockers and statins and demonstrated a 15% reduction in major adverse cardiac events with this drug that lowered IL-6 and CRP without any change in LDL. Many other trials (COLCOT, CIRT, LoDoCo2) exploring suppression of inflammatory pathways are underway and it will be exciting to explore a new paradigm of risk reduction after 40 years of focusing on the lipid pathway [18].

The availability of multiple imaging modalities has deepened our understanding of plaque biology and inflammation in the pathogenesis of ACS, yet much work remains to be done to identify the vulnerable patient rather than just the vulnerable plaque. Much like monitoring seismic activity to predict large earthquakes, we will have to develop more precision-medicine imaging strategies to prevent our patients from succumbing to the onslaught of cardiovascular catastrophes.

References

[1] Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852–66. doi:10.1161/CIRCRESAHA.114.302721.

[2] Skålén K, Gustafsson M, Rydberg EK, Hultén LM, Wiklund O, Innerarity TL, et al. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. Nature 2002;417:750–4. doi:10.1038/nature00804.

[3] Ross R. Atherosclerosis–an inflammatory disease. N Engl J Med 1999;340:115–26. doi:10.1056/NEJM199901143400207.

[4] Madder RD, Goldstein JA, Madden SP, Puri R, Wolski K, Hendricks M, et al. Detection by near-infrared spectroscopy of large lipid core plaques at culprit sites in patients with acute ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2013;6:838–46. doi:10.1016/j.jcin.2013.04.012.

[5] Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. Circulation 2000;101:598–603.

[6] Pelletier-Galarneau M, Ruddy TD. Molecular imaging of coronary inflammation. Trends Cardiovasc Med 2018. doi:10.1016/j.tcm.2018.08.004.

[7] Dweck MR, Joshi NV, Rudd JHF, Newby DE. Imaging of inflammation and calcification in aortic stenosis. Curr Cardiol Rep 2013;15:320. doi:10.1007/s11886-012-0320-8.

[8] Gaemperli O, Shalhoub J, Owen DRJ, Lamare F, Johansson S, Fouladi N, et al. Imaging intraplaque inflammation in carotid atherosclerosis with 11C-PK11195 positron emission tomography/computed tomography. Eur Heart J 2012;33:1902–10. doi:10.1093/eurheartj/ehr367.

[9] Pugliese F, Gaemperli O, Kinderlerer AR, Lamare F, Shalhoub J, Davies AH, et al. Imaging of vascular inflammation with [^{11}C]-PK11195 and positron emission tomography/computed tomography angiography. J Am Coll Cardiol 2010;56:653–61. doi:10.1016/j.jacc.2010.02.063.

[10] Dweck MR, Chow MWL, Joshi NV, Williams MC, Jones C, Fletcher AM, et al. Coronary arterial ^{18}F-sodium fluoride uptake: a novel marker of plaque biology. J Am Coll Cardiol 2012;59:1539–48. doi:10.1016/j.jacc.2011.12.037.

[11] Robson PM, Dweck MR, Trivieri MG, Abgral R, Karakatsanis NA, Contreras J, et al. Coronary artery PET/MR imaging: feasibility, limitations, and solutions. JACC Cardiovasc Imaging 2017;10:1103–12. doi:10.1016/j.jcmg.2016.09.029.

[12] Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49–57. doi:10.1016/j.jacc.2009.02.068.

[13] Noguchi T, Kawasaki T, Tanaka A, Yasuda S, Goto Y, Ishihara M, et al. High-intensity signals in coronary plaques on noncontrast T1-weighted magnetic resonance imaging as a novel determinant of coronary events. J Am Coll Cardiol 2014;63:989–99. doi:10.1016/j.jacc.2013.11.034.

[14] Brinjikji W, Huston J, Rabinstein AA, Kim G-M, Lerman A, Lanzino G. Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. J Neurosurg 2016;124:27–42. doi:10.3171/2015.1.JNS142452.

[15] Matsumoto K, Ehara S, Hasegawa T, Sakaguchi M, Otsuka K, Yoshikawa J, et al. Localization of coronary high-intensity signals on T1-weighted MR imaging: relation to plaque morphology and clinical severity of angina pectoris. JACC Cardiovasc Imaging 2015;8:1143–52. doi:10.1016/j.jcmg.2015.06.013.

[16] Xie Y, Kim Y-J, Pang J, Kim J-S, Yang Q, Wei J, et al. Coronary atherosclerosis T1-weighed characterization with integrated anatomical reference: comparison with high-risk plaque features detected by invasive coronary imaging. JACC Cardiovasc Imaging 2017;10:637–48. doi:10.1016/j.jcmg.2016.06.014.

[17] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31. doi:10.1056/NEJMoa1707914.

[18] Libby P. Interleukin-1 beta as a target for atherosclerosis therapy: biological basis of CANTOS and beyond. J Am Coll Cardiol 2017;70:2278–89. doi:10.1016/j.jacc.2017.09.028.