Trends in Cardiovascular Medicine 29 (2019) 449–450

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

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

Editorial commentary: Imaging the aorta for inflammation: Informing practice on emerging molecular techniques ☆,☆☆

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The clinical evaluation of an inflammatory process in the development of aortic diseases can be broadly categorized into 3 distinct groups: atherosclerotic occlusive aortic disease, aortic aneurysm formation and inflammatory aortopathies such as Takayasu's aortitis. Clinicians currently rely on clinical and radiographic assessments including computerized tomography (CT) and magnetic resonance imaging (MRI) to risk stratify patients. Each of those single modality and mainly anatomical imaging tools have inherent limitations and there remains an unmet clinical need for advanced techniques to improve disease characterization. The detection as well as the degree and extent of vascular inflammation and whether this imaging based detection and characterization is of incremental value is of high interest.

On the atherosclerosis front, multiple clinical trials have correlated the presence of aortic inflammation in the aorta and its response to anti-atherosclerotic interventions [1–3]. There is a high level of consistency between the responses to therapy as measure by Fluorodeoxyglucose-positron emission tomography/computed tomographic imaging (FDG-PET/CT) and the development of future atherosclerotic events. This approach may be predictive of the relative efficacy of newer compounds and obviate the need for large outcomes trials.

For the detection and management of aortic aneurysms, echocardiography and ultrasound technology provide significant structural and functional data on the aortic valve, aortic root and ascending and descending aorta [4]. Ultrasound also provides relevant information regarding the morphological aortic wall changes including cross sectional diameter and the presence of dissection, intramural hematoma or ulcer [5] without the risks associated with radiation and the use of contrast. Ultrasound, however, is inconclusive in characterizing inflammatory changes [6]. CT and MRI are complimentary with improved resolution in selected patients.

Advanced CT angiography (CTA) can characterize aortic wall inflammation and identify its different etiologies such as in Takayasu aortitis (double ring appearance) [7] but there is limited sensitivity and specificity to detect early inflammatory changes in the aorta. MRI is superior to CT/CTA in tissue characterization of arterial wall inflammation, in distinguishing etiological diseases (atherosclerotic, infectious and non-infectious aortitis) and in detecting early inflammatory changes. However, MRI partly has a lower spatial resolution than CT and CTA, calcium detection can be suboptimal and it requires significantly longer acquisition time and patient involvement (breath holds, narrow tunnel) in the image acquisition process [4]. Furthermore, although anatomical imaging procedures provide aortic morphology and periaortic changes with unmatched spatial resolution, they are unable to characterize the biological activities within and around the aortic wall.

In this edition of Trends in Cardiovascular Medicine, Syed and colleagues provide a comprehensive overview of the newest developments in metabolic imaging, concentrating mainly on 18F-NaF (18F-Sodium fluoride) imaging [8]. 18F-NaF imaging has been tested in routine clinical experience with extensive longitudinal patient follow up (e.g. growth in aortic size). However, additional new and upcoming tracers should in theory improve patient care.

While 68Ga-DOTATATE ([68Gallium-DOTA0-Tyr3] octreotate) has been used in clinical patients in the context of vascular imaging since it binds preferentially to atherosclerotic plaques with high macrophage infiltration (the main oncological indication currently being in diagnosis of neuroendocrine tumors), treoblastin is showing promise in animal studies. [9–12]. The same holds true for CXCR4 imaging (68Ga-Pentixafor) which has been used in clinical patients in a wide variety of oncological and cardiovascular indications [13–17]. CXCR4 imaging is actually one of the most promising existing tracers because the CXCR4/CXCL12 pathway can be blocked by a commercially available blocker (AMD 3100, oral application) that enables interventional imaging studies. The CXCR4/CXCL12 pathway partially regulates macrophages through upregulation of CXCR4 by stimulation with oxidized low-density lipoproteins. It partly overlaps with 68Ga-DOTATATE that can image activated macrophages via a different pathway, and 18F-NaF, which identifies dense macrophage infiltration. The CXCR4/CXCL12 pathway also partly regulates B- and T-cells (B-cell development and CXCR4 mediated chemotaxis), neutrophils (CXCR4-maintained homeostasis and neutrophil activation), platelets (amplification of platelet activation and survival), endothelial cells (upregulation by vascular endothelial growth factor/hypoxia/shear stress) and vascular smooth muscle cells (proliferation and migration

☆ **Disclosures:** There are no relevant conflicts to this paper.
☆☆ **Funding:** No funding sources.
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https://doi.org/10.1016/j.tcm.2019.01.008

and upregulation in injured arterial wall contributing to intimal hyperplasia). It therefore may have a complementary role in atherosclerotic aortic disease evaluation and stratification.

With emerging artificial intelligence algorithms, there is an opportunity to greatly enhance image quality even from sparse data. “Normal dose images” can be simulated and calculated at a fraction of today’s clinically accepted doses [18]. This in return offers not only the possibility to greatly reduce the radiation burden for the patient, but also offers the possibility to acquire multi-tracer examination (e.g. all three above mentioned tracers with complementary macrophage imaging pathways) within one image session.

Finally, even if 18F-FDG is an unspecific tracer, it still holds great potential. With the upcoming clinically available parametric imaging, the summarized FDG-image can be divided into the “metabolic rate image” which displays the actual metabolically trapped FDG in the cell and the “distribution image” of the non-trapped FDG [19]. This differentiation should lead to better characterization of aortic inflammatory conditions.

Overall, this excellent review by Syed et al. highlight both the available and upcoming molecular imaging techniques that bring great promise to enable physicians to detect and characterize inflammatory aortic diseases earlier in more detail. This should lead to improved patient outcomes.

References

[1] Tawakol A, Singh P, Rudd JH, Soffer J, Cai G, Vucic E, et al. Effect of treatment for 12 weeks with rilapladib, a lipoprotein-associated phospholipase A2 inhibitor, on arterial inflammation as assessed with 18F-fluorodeoxyglucose–positron emission tomography imaging. J Am Coll Cardiol 2014;63(1):86–8.

[2] Fayad ZA, Mani V, Woodward M, Kallend D, Abt M, Burgess T, et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet (London, England). 2011;378(9802):1547–59.

[3] Rudd JH, Myers KS, Bansilal S, Machac J, Rafique A, Farkouh M, et al. (18)Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials. J Am Coll Cardiol 2007;50(9):892–6.

[4] Hartlage GR, Palios J, Barron BJ, Stillman AE, Bossone E, Clements SD, et al. Multimodality imaging of aortitis. JACC Cardiovasc Imaging 2014;7(6):605–19.

[5] Evangelista A, Mukherjee D, Mehta RH, O’Gara PT, Fattori R, Cooper JV, et al. Acute intramural hematoma of the aorta: a mystery in evolution. Circulation 2005;111(8):1063–70.

[6] Halapas A, Kalogeropoulos AP, Georgiopoulou VV, Chen EP, Gravanis MB, Martin RP, et al. Takayasu’s arteritis mimicking aortic intramural hematoma in a female patient with chest pain. Hell J Cardiol 2008;49(4):280–3.

[7] Restrepo CS, Ocazionez D, Suri R, Vargas D. Aortitis: imaging spectrum of the infectious and inflammatory conditions of the aorta. Radiographics 2011;31(2):435–51.

[8] Syed MBJ, Fletcher AJ, Dweck MR, Forsythe R, Newby D. Imaging aortic wall inflammation. Trends Cardiovasc Med 2019. In press.

[9] Tarkin JM, Joshi FR, Evans NR, Chowdhury MM, Figg NL, Shah AV, et al. Detection of atherosclerotic inflammation by (68)Ga-DOTATATE PET compared to [(18)F]FDG PET imaging. J Am Coll Cardiol 2017;69(14):1774–91.

[10] Wan MYS, Endozo R, Michopoulou S, Shortman R, Rodriguez-Justo M, Menezes L, et al. PET/CT imaging of unstable carotid plaque with (68)Ga-labeled somatostatin receptor ligand. J Nucl Med 2017;58(5):774–80.

[11] Pedersen SF, Sandholt BV, Keller SH, Hansen AE, Clemmensen AE, Sillesen H, et al. 64Cu-DOTATATE PET/MRI for detection of activated macrophages in carotid atherosclerotic plaques: studies in patients undergoing endarterectomy. Arterioscler Thromb Vasc Biol 2015;35(7):1696–703.

[12] Mojtahedi A, Alavi A, Thamake S, Amerinia R, Ranganathan D, Tworowska I, et al. Assessment of vulnerable atherosclerotic and fibrotic plaques in coronary arteries using (68)Ga-DOTATATE PET/CT. Am J Nucl Med Mol Imaging 2015;5(1):65–71.

[13] Lapa C, Luckerath K, Rudelius M, Schmid JS, Schoene A, Schirbel A, et al. [68Ga]Pentixafor-PET/CT for imaging of chemokine receptor 4 expression in small cell lung cancer–initial experience. Oncotarget 2016;7(8):9288–95.

[14] Vag T, Steiger K, Rossmann A, Keller U, Noske A, Herhaus P, et al. PET imaging of chemokine receptor CXCR4 in patients with primary and recurrent breast carcinoma. EJNMMI Res 2018;8(1):90.

[15] Lapa C, Schreder M, Schirbel A, Samnick S, Kortum KM, Herrmann K, et al. [(68)Ga]Pentixafor-PET/CT for imaging of chemokine receptor CXCR4 expression in multiple myeloma—comparison to [(18)F]FDG and laboratory values. Theranostics 2017;7(1):205–12.

[16] Derlin T, Sedding DG, Dutzmann J, Haghikia A, Konig T, Napp LC, et al. Imaging of chemokine receptor CXCR4 expression in culprit and nonculprit coronary atherosclerotic plaque using motion-corrected [(68)Ga]pentixafor PET/CT. Eur J Nucl Med Mol Imaging 2018;45(11):1934–44.

[17] Weiberg D, Thackeray JT, Daum G, Sohns JM, Kropf S, Wester HJ, et al. Clinical molecular imaging of chemokine receptor CXCR4 expression in atherosclerotic plaque using (68)Ga-pentixafor PET: correlation with cardiovascular risk factors and calcified plaque burden. J Nucl Med 2018;59(2):266–72.

[18] Wang Y, Yu B, Wang L, Zu C, Lalush DS, Lin W, et al. 3D conditional generative adversarial networks for high-quality PET image estimation at low dose. NeuroImage 2018;174:550–62.

[19] Rahmim A, Lodge MA, Karakatsanis NA, Panin VY, Zhou Y, McMillan A, et al. Dynamic whole-body PET imaging: principles, potentials and applications. Eur J Nucl Med Mol Imaging 2019;46(2):501–18.