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EDITORIAL COMMENT

PET/MR Imaging of Atherosclerosis

Insights Into Atheroma Structure and Biology*

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Atherosclerosis is characterized by biologically complex plaques whose erosion or rupture precipitates atherothrombotic events. Traditionally, the detection of atherosclerotic disease has relied solely on the identification of luminal narrowing, either directly with arteriography or, indirectly, through stress testing. More recently, the assessment of the gross morphological features of plaques has become routine through the use of techniques including coronary intravascular ultrasound, optical coherence tomography, coronary computed tomography (CT) arteriography, carotid ultrasound, and magnetic resonance imaging (MRI) of the vessel wall. However, these techniques do not fully resolve the structural complexity of plaque or the biological basis of the disease. Approaches to simultaneously derive physiological, structural, and biological data would be attractive, especially as the options for treating atherosclerosis become broader and the decision making becomes more complicated.

Basic and clinical evidence suggests that an atheroma's path (towards repair or progression) may be critically swayed by the activity of the inflammatory environment within the plaque. Recently, CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) has provided additional proof of the inflammatory hypothesis, by demonstrating that anti-inflammatory approaches substantially reduce the incidence of cardiovascular disease events. Accordingly, assessment of the inflammatory activity within the atheroma may provide important insights regarding the underlying atherosclerotic process.

Positron emission tomography (PET) imaging, using ^{18}F-fluorodeoxyglucose (^{18}F-FDG), has been extensively employed to image viability and to identify tumor activity. Further, it is increasingly in use to identify areas of infection and inflammation, including inflammation associated with sarcoidosis, infected valves, and devices (1,2). The same tendency of ^{18}F-FDG to accumulate in areas of inflammation has been leveraged to quantify the accumulation of inflammatory cells within the atheroma (3). Such measures of arterial inflammation have been shown to associate with the subsequent rate of progression of the underlying plaque, and also to predict CVD risk above risk scores or extent of coronary artery calcification (4). They have also been widely used to assess the efficacy of novel therapies (4).

Although much work has been done to study the separate utility of assessment of atheroma morphology and inflammatory activity, limited data exist on the value of assessing both types of features together. This is due to the fact that the method to measure biological activity (PET/CT) provides limited data on plaque characteristics, and requires a separate acquisition using dedicated MRI or coronary computed tomography (CT) arteriography scanning. However, with the development of PET/MR, a new opportunity has emerged, for simultaneous assessment of structure and biology.

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In this issue of *iJACC*, Calcagno et al. (5) report a study designed to develop PET/MR imaging to quantify plaque inflammation, permeability, and burden. Additionally, using this multimodality imaging tool, they evaluated the efficacy of a leukotriene A4 hydrolase (LTA4H) inhibitor in a rabbit model of atherosclerosis. The authors first induced atherosclerotic plaques in 49 New Zealand white male rabbits fed a high-fat diet. Four months after initiation of the high-fat diet, the rabbits were allocated to 1 of 3

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groups (on top of continued high-fat feedings): 1) placebo; 2) low-dose of the LTA4H inhibitor; or 3) high dose of the inhibitor. To assess the impact of BI691751 on atherosclerosis, the animals were imaged at baseline (just before initiation of therapy), 1 month, and 3 months. Multiparametric imaging included ^{18}F-FDG PET for assessment of arterial inflammation in the ascending aorta of the animals. Additionally, structural MR data were simultaneously derived to assess plaque burden (as vessel area). Dynamic contrast enhanced MRI was also performed to assess plaque neovascularization and permeability. Blood biomarkers were measured at each of those intervals. Furthermore, the animals were sacrificed at the 3-month mark and histopathological assessment was performed.

As expected, LTB4 values were reduced in the animals that received the inhibitor. No significant differences were observed in total cholesterol and triglycerides. However, arterial inflammation, as assessed using the ^{18}F-FDG PET, was modestly lowered only in the group of rabbits that received the low dose of the LTA4H inhibitor. On the other hand, neither neovascularization or permeability (by dynamic contrast-enhanced MRI) nor plaque burden (vessel wall area, by structural MRI) differed across the 3 groups. On ex vivo analysis, there were no differences in macrophage density or total neovessel count; however, significant differences were found in the number of new vessels in the tunica media.

Accordingly, this multimodality and multiparametric analysis showed minimal effect of the leukotriene A4 hydrolase inhibitor BI691751 on plaque inflammation, and no effect on plaque size and neovascularization. Perhaps more significantly, it provided an excellent example of a feasible approach and the potential value of joint PET and MR assessment of atherosclerosis.

Although the reported PET/MR vascular imaging approach is encouraging, several hurdles remain before it could be clinically translated into humans. First, quantitation of tracer activity has not been as solidly established using PET/MR as it has using PET/CT. Importantly, for PET/MR, the approach to correct for attenuation of photons (as they travel through tissues such as muscle, fat, and bone) remains an area of debate. Likely as a result of this, several groups have observed that quantitative values derived from PET/CT tend to be different from those derived using PET/MR (6). Perhaps related to this issue, in the Calcagno et al. (5) study, the PET assessments of ^{18}F-FDG uptake correlated with histological measures of inflammation more weakly than is typically seen with PET/CT approaches. Further work is needed to refine quantitation of vascular activity using this approach.

The assessment of coronary plaques remains a substantial challenge for both MRI and ^{18}F-FDG PET. In the coronary circulation, ^{18}F-FDG plaque imaging is hampered by competing uptake by myocardial cells, while MRI assessment of atheroma is hampered by coronary motion. However, multiple approaches are being used to counter these limitations. Several groups are innovating improved methods for MR assessments of coronary plaques (7,8). Further, beyond ^{18}F-FDG, several additional tracers are available for coronary PET imaging, including ^{68}Ga-dotatate (9) and ^{18}F-NaF (10). PET/MR imaging of the carotids, where MRI imaging already provides substantial value for clinical decision making, is closer to translation than it is in the coronary arteries. It is conceivable that the combined structural and biological information from simultaneously derived PET/MR imaging could more selectively identify a subgroup of individuals with carotid stenosis for revascularization versus medical therapy.

The options for treatment of atherosclerosis are growing (with the addition of PCSK9 inhibitors, and potentially, anti-inflammatory drugs such as canakinumab). With the expanded set of therapies, a more personalized approach to treatment of atherosclerosis is needed. To meet this need, more sophisticated tools are required, to better evaluate atherothrombotic risk, and potentially, to follow the response to therapy. The study by Calcagno et al. (5) thus offers a timely example of the opportunities afforded by advanced PET/MR imaging, which provides complementary structural and biological measurements and a clearer assessment of the underlying atherosclerotic process.

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REFERENCES

1. Blankstein R, Osborne M, Naya M, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol 2014;63:329–36.

2. Sarrazin JF, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol 2012;59:1616–25.

3. Tawakol A, Migrino RQ, Bashian GG, et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol 2006;48:1818–24.

4. Joseph P, Tawakol A. Imaging atherosclerosis with positron emission tomography. Eur Heart J 2016;37:2974–80.

5. Calcagno C, Lairez O, Hawkins J, et al. Combined PET/DCE-MRI in a rabbit model of atherosclerosis: integrated quantification of plaque inflammation, permeability, and burden during treatment with a leukotriene A4 hydrolase inhibitor. J Am Coll Cardiol Img 2018;11:291–301.

6. Robson PM, Dey D, Newby DE, et al. MR/PET imaging of the cardiovascular system. J Am Coll Cardiol Img 2017;10:1165–79.

7. Robson PM, Dweck MR, Trivieri MG, et al. Coronary artery PET/MR imaging: feasibility, limitations, and solutions. J Am Coll Cardiol Img 2017;10:1103–12.

8. Karolyi M, Seifarth H, Liew G, et al. Classification of coronary atherosclerotic plaques ex vivo with T1, T2, and ultrashort echo time CMR. J Am Coll Cardiol Img 2013;6:466–74.

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

10. 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;383:705–13.

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