Editorial in response to: PET/CT evaluation of ^{18}F-FDG uptake in pericoronary adipose tissue in patients with stable coronary artery disease: Independent predictor of atherosclerotic lesion formation?

Is there prognostic value in evaluation of ^{18}F-FDG uptake in the pericoronary adipose tissue?

Stephanie L. Thorn, PhD,[a] and Albert J. Sinusas, MD[a]

[a] Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven

Received Feb 25, 2016; accepted Feb 25, 2016
doi:10.1007/s12350-016-0458-7

See related article, pp. 1075–1084

Atherosclerosis is a chronic progressive disease that can lead to ischemic heart disease or cerebrovascular stroke, two of the worlds' leading causes of death.[1] Atherosclerosis involves a complex process, and is driven by a cyclic inflammatory response initiated by deposition of low density lipoprotein within arterial walls. Therefore, inflammation is one of the key modulators of plaque development and can lead to plaque rupture or erosion.[2] Recent investigative efforts have focused on technologies and subsequent methodologies that not only detect atherosclerotic plaque and assess the severity of a stenosis, but also attempt to identify the features associated with plaque instability.

The choice of the appropriate diagnostic tools to interrogate this disease process is a relevant and hotly debated topic.[2,3] In current clinical practice, the identification of atherosclerosis plaques tends to be late, with identification in patients presenting with symptoms of angina or evidence of stress-induced myocardial ischemia, who are sent for a coronary angiogram for identification of the culprit lesion and often undergo subsequent revascularization. Although frequently used to identify these coronary lesions, coronary angiograms are limited in assessing anatomic plaque characteristics and late stages in the progression. Technologies such as intravascular ultrasound, optical coherence tomography, and near-infrared spectroscopy have been well documented to provide high-resolution images for better visualization and characterization of plaque.[2,4] However, these technologies are highly invasive, and therefore not widely used in clinical practice for screening of asymptomatic patients or confirming the diagnosis of coronary artery disease (CAD).

Efforts have also been directed at developing non-invasive imaging methods for the identification of the molecular events that precede that gross anatomical changes or physiological consequences of plaque progression. Targets for non-invasive nuclear imaging of atherosclerotic plaques and related molecularly targeted radiolabeled probes include apoptosis (^{99m}Tc-Annexin A5), proteolytic enzymes (^{99m}Tc-RP805, targeted at matrix metalloproteinases), calcification (^{18}F-NaF), angiogenesis (^{99m}Tc- and ^{18}F-labeled RGD peptides targeted at $\alpha v\beta 3$ integrin activation), and many other markers of inflammation.[5] In the forefront of the nuclear imaging radiotracers targeted at imaging of inflammatory cells within the atherosclerotic plaque is the positron emission tomography (PET) imaging of the glucose analogue 2-[^{18}F]fluoro-2-deoxyglucose (FDG).[6–8] Although FDG was developed and approved

Reprint requests: Stephanie Thorn, PhD, Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven; *stephanie.thorn@yale.edu*

J Nucl Cardiol 2017;24:1085–8.
1071-3581/$34.00

Copyright © 2016 American Society of Nuclear Cardiology.

as an oncologic radiotracer for tumor identification, FDG imaging has moved into the cardiovascular realm as an imaging agent for assessment of myocardial viability, hibernating myocardium, and more recently assessment of inflammatory myocardial conditions like cardiac sarcoidosis. In the application of imaging inflammation associated with atherosclerosis, FDG is taken up by the highly glycolytic macrophages through GLUT 1/3 transporters and has also shown strong correlation with other inflammatory markers.[9–11] Therefore, FDG PET imaging can provide an index of focal inflammation in the atherosclerotic plaque and is thought to provide an index of plaque instability. While FDG imaging has shown promise in imaging atherosclerotic plaques in carotid arteries, technical issues arise when imaging coronary arteries. As Gholami et al[12] recently reviewed, methodologies for pre-scan patient preparation (fasting, blood glucose levels) and optimal imaging time post-FDG injection can all preclude the quality and reproducibility of results by affecting the target-to-background ratio.

Computed tomography (CT) has come to the forefront as a technique that can easily characterize atherosclerotic plaque, and has proven value for risk stratification for coronary events in patients with CAD.[13] With the addition of intravascular contrast and multidetector technology, CT can define obstructive coronary lesions, calcifications, positive vascular remodeling, and even the soft hypodense lipid core.[14,15] The identification of at least 2 of these characteristics was shown in a large clinical trial to have a strong correlation with major cardiovascular adverse events.[15]

A newer approach for assessing and risk stratifying atherosclerotic plaque involves the evaluation of the influence of epicardial adipose tissue (EAT) and pericoronary adipose tissue (PCAT). EAT is defined as the fat located between the serous epicardium and the pericardial sac[16] and has been demonstrated to be increased in patients with CAD.[17,18] However, PCAT is defined as the fat present on the external coronary lumen, and has been shown to be increased in volume in patients with plaque compared to those without plaque.[19] Recently, evidence has emerged demonstrating the association of EAT and PCAT in the inflammatory process, and for providing a source for multiple bioactive factors and pro-inflammatory cytokines.[20,21] More importantly, high volumes of EAT and PCAT have been associated with the early development of atherosclerotic plaque, thereby providing a methodology for risk stratification.[22] These data suggest that an estimation of the inflammatory potential of EAT or PCAT may help in identifying patients at higher risk for unstable atherosclerotic plaque, although a definitive risk association between them is still not established.

In this issue of the *Journal of Nuclear Cardiology®*, Mazurek and colleagues describe methodology to investigate whether PCAT-related inflammation is increased in patients with CAD. The importance of this study is in determining if FDG uptake of PCAT may provide a means to measure plaque inflammation and risk for disease progression. The study investigates PCAT FDG uptake in patients within 4 weeks of angiographic confirmed CAD with exclusions of patients that may have increased inflammatory response due to diabetes, recent coronary interventions, or other inflammatory conditions. They apply hybrid PET/CT, using CT for identification and localization of PCAT, and PET measurement of FDG uptake in this pre-determined anatomic location. The authors hypothesized that higher inflammation in PCAT as measured by FDG PET may promote atherosclerotic plaque development and correlate with results from cardiac angiograms.

The identification and localization of PCAT with CT is a fairly new technique that is still under investigation, and the optimal methodology for deriving reproducible and reliable results is not yet established. Hell et al[23] recently investigated PCAT in relation to cardiovascular risk factors and EAT volume using dual source CT. The authors found that CT-measured attenuation of PCAT may be influenced by the amount of EAT and the point along the vascular lumen, as PCAT volume and density appear to change from distal to proximal segments of the coronary arteries.[23] With 'where' the measurements of PCAT are assessed influencing the reproducibility of the results, the 'how' this is assessed is of equal importance. The setting of the lower and upper bounds for CT thresholding varies on non-contrast-enhanced and contrast-enhanced CTs, with the lower limits typically set from −250 to −190 and the upper limits set between −50 and −30. These thresholds are important in order to ensure that there is no overestimation or indeed, underestimation of fat measured, and may vary between contrast and non-contrast CT. The authors in the current study use a low-dose, non-contrast CT for localization of both the coronary arteries and the identification of PCAT by thresholding the images to between −30 and −250 Hounsfield units. In the identification of PCAT, the use of a contrast-enhanced CT may be beneficial in order to adequately define the coronary arteries and the lumen. Additionally, the application of cardiac motion correction, with the inclusion of respiratory motion correction, may increase the diagnostic sensitivity of identification and localization of PCAT and decrease the variance seen in the measurements published in the current study.[24,25]

Despite these limitations in their application of the cardiac PET/CT methodology, the investigators demonstrated an increase in FDG uptake and therefore inflammatory activity in the co-registered PCAT segments of the coronary arteries. This increase in SUV values was significantly different from subcutaneous, visceral, and epicardial adipose tissue stores, and there was a significant increase noted in PCAT in patients with CAD vs non-CAD controls. While the authors suggest that PCAT may, therefore, be linked to the development of atherosclerotic plaque, the positive linear correlation was only noted in patients with a BMI > 25 kg/m^2. This agrees with previous studies that found an increase in FDG uptake in coronary artery atherosclerotic plaque and a positive correlation with conventional cardiovascular risk factors including BMI.[26–28] One wonders whether the FDG uptake in the PCAT alone is not influenced by the FDG uptake in the coronary plaque itself. There were several important methodological limitations of the current study: they did not apply motion correction, account for partial volume effects or the reduced clearance of FDG due to the early imaging following injection (30-60 minutes). They performed a normalization of PCAT FDG uptake to background activity within the left atrium, which in itself is also subject to partial volume effects due to spillover and motion.[12] Therefore, there is inherent variability in the estimation of PCAT FDG uptake that could influence the results. However, the overall conclusion that obesity or patients with metabolic syndrome show an increase in inflammation, whether directly from the vascular plaque or from the inflammatory activity of PCAT, is potentially relevant, and may direct the targeting of medical therapies for both vascular plaque and reduction of inflammatory PCAT.

With new clinical trials underway to decrease atherosclerosis through broad-based anti-inflammatory agents and blockade of inflammatory cytokines,[29,30] the development of methodology and new non-invasive imaging procedures that can assess and monitor these therapies in relation to coronary atherosclerotic plaque is of increased importance. We look forward to further evaluations of PCAT, perhaps with preclinical models where the molecular inflammatory markers of the adipose tissue could be correlated to the *in vivo* imaging, and the influence on coronary plaque development.

References

1. Mortality GBD. Causes of Death C. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the global burden of disease study 2013. Lancet 2015;385:117–71.
2. Zimarino M, Prati F, Marano R, Angeramo F, Pescetelli I, Gatto L, et al. The value of imaging in subclinical coronary artery disease. Vascul Pharmacol 2016;. doi:10.1016/j.vph.2016.02.001.
3. Niccoli G, Liuzzo G, Montone RA, Crea F. Advances in mechanisms, imaging and management of the unstable plaque. Atherosclerosis 2014;233:467–77.
4. Koskinas KC, Ughi GJ, Windecker S, Tearney GJ, Raber L. Intracoronary imaging of coronary atherosclerosis: Validation for diagnosis, prognosis and treatment. Eur Heart J 2016;37:524–35.
5. Tavakoli S, Vashist A, Sadeghi MM. Molecular imaging of plaque vulnerability. J Nucl Cardiol 2014;21:1112–28 **(quiz 1129)**.
6. Lederman RJ, Raylman RR, Fisher SJ, Kison PV, San H, Nabel EG, et al. Detection of atherosclerosis using a novel positron-sensitive probe and 18-fluorodeoxyglucose (FDG). Nucl Med Commun 2001;22:747–53.
7. 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;50:892–6.
8. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, et al. Imaging atherosclerotic plaque inflammation with [18f]-fluorodeoxyglucose positron emission tomography. Circulation 2002;105:2708–11.
9. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, 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.
10. Pedersen SF, Graebe M, Fisker Hag AM, Hojgaard L, Sillesen H, Kjaer A. Gene expression and 18FDG uptake in atherosclerotic carotid plaques. Nucl Med Commun 2010;31:423–9.
11. Graebe M, Pedersen SF, Borgwardt L, Hojgaard L, Sillesen H, Kjaer A. Molecular pathology in vulnerable carotid plaques: Correlation with [18]-fluorodeoxyglucose positron emission tomography (fdg-pet). Eur J Vasc Endovasc Surg 2009;37:714–21.
12. Gholami S, Salavati A, Houshmand S, Werner TJ, Alavi A. Assessment of atherosclerosis in large vessel walls: A comprehensive review of fdg-pet/ct image acquisition protocols and methods for uptake quantification. J Nucl Cardiol 2015;22:468–79.
13. Qazi AH, Zallaghi F, Torres-Acosta N, Thompson RC, O'Keefe JH. Computed tomography for coronary artery calcification scoring: Mammogram for the heart. Prog Cardiovasc Dis 2016;. doi:10.1016/j.pcad.2016.01.007.
14. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50:319–26.
15. 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.
16. Marwan M, Achenbach S. Quantification of epicardial fat by computed tomography: Why, when and how? J Cardiovasc Comput Tomogr 2013;7:3–10.
17. Nakazato R, Dey D, Cheng VY, Gransar H, Slomka PJ, Hayes SW, et al. Epicardial fat volume and concurrent presence of both myocardial ischemia and obstructive coronary artery disease. Atherosclerosis 2012;221:422–6.
18. Mahabadi AA, Lehmann N, Kalsch H, Robens T, Bauer M, Dykun I, et al. Association of epicardial adipose tissue with progression of coronary artery calcification is more pronounced in the early phase of atherosclerosis: Results from the Heinz Nixdorf recall study. JACC Cardiovasc Imaging 2014;7:909–16.

19. Maurovich-Horvat P, Kallianos K, Engel LC, Szymonifka J, Fox CS, Hoffmann U, et al. Influence of pericoronary adipose tissue on local coronary atherosclerosis as assessed by a novel MDCT volumetric method. Atherosclerosis 2011;219:151–7.
20. Gauss S, Klinghammer L, Steinhoff A, Raaz-Schrauder D, Marwan M, Achenbach S, et al. Association of systemic inflammation with epicardial fat and coronary artery calcification. Inflamm Res 2015;64:313–9.
21. Maurovich-Horvat P, Kallianos K, Engel LC, Szymonifka J, Schlett CL, Koenig W, et al. Relationship of thoracic fat depots with coronary atherosclerosis and circulating inflammatory biomarkers. Obesity 2015;23:1178–84.
22. Gorter PM, de Vos AM, van der Graaf Y, Stella PR, Doevendans PA, Meijs MF, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. Am J Cardiol 2008;102:380–5.
23. Hell MM, Achenbach S, Schuhbaeck A, Klinghammer L, May MS, Marwan M. Ct-based analysis of pericoronary adipose tissue density: Relation to cardiovascular risk factors and epicardial adipose tissue volume. J Cardiovasc Comput Tomogr 2016;10:52–60.
24. Carrascosa P, Deviggiano A, Leipsic JA, Capunay C, De Zan MC, Goldsmit A, et al. Dual energy imaging and intracycle motion correction for ct coronary angiography in patients with intermediate to high likelihood of coronary artery disease. Clin Imaging 2015;39:1000–5.
25. Carrascosa P, Deviggiano A, Capunay C, De Zan MC, Goldsmit A, Rodriguez-Granillo GA. Effect of intracycle motion correction algorithm on image quality and diagnostic performance of computed tomography coronary angiography in patients with suspected coronary artery disease. Acad Radiol 2015;22:81–6.
26. Saam T, Rominger A, Wolpers S, Nikolaou K, Rist C, Greif M, et al. Association of inflammation of the left anterior descending coronary artery with cardiovascular risk factors, plaque burden and pericardial fat volume: A pet/ct study. Eur J Nucl Med Mol Imaging 2010;37:1203–12.
27. Ben-Haim S, Kupzov E, Tamir A, Israel O. Evaluation of 18f-fdg uptake and arterial wall calcifications using 18f-fdg pet/ct. J Nucl Med 2004;45:1816–21.
28. Bural GG, Torigian DA, Chamroonrat W, Houseni M, Chen W, Basu S, et al. Fdg-pet is an effective imaging modality to detect and quantify age-related atherosclerosis in large arteries. Eur J Nucl Med Mol Imaging 2008;35:562–9.
29. Awan Z, Genest J. Inflammation modulation and cardiovascular disease prevention. Eur J Prev Cardiol 2015;22:719–33.
30. Tousoulis D, Oikonomou E, Economou EK, Crea F, Kaski JC. Inflammatory cytokines in atherosclerosis: Current therapeutic approaches. Eur Heart J 2016. doi:10.1093/eurheartj/ehv759.