The dream of imaging coronary artery inflammation with FDG PET/CT imaging

R. Glenn Wells, PhD, FCCPM,[a] and Terrence D. Ruddy, MD, FRCPC[a]

[a] Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Canada

Received May 16, 2016; accepted May 17, 2016
doi:10.1007/s12350-016-0549-5

See related article, pp. 1161–1170

''Always dream and shoot higher than you know you can do.''
—William Faulkner

THE HOPE

Inflammation plays a major role in the development of atherosclerotic plaque[1] and has been proposed as a marker of plaque vulnerability to identify patients at risk of vascular events.[2] Plaque inflammation is characterized by increased macrophage infiltration and FDG uptake has been shown to correlate strongly with the number of macrophages present in plaques.[3] Rudd et al showed that FDG accumulated and could be measured in vivo in carotid artery plaques associated with recent transient ischemic attacks but that asymptomatic arteries had less FDG accumulation.[4] Thus, FDG uptake can be used to measure the degree of inflammation in tissues as confirmed with carotid endarterectomy specimens using CD-68 immunohistochemistry.[5] FDG uptake in carotid arteries has also been shown to correlate with anatomical and histological features of plaques that are at high risk for rupturing.[6] Carotid inflammation measured with FDG PET/CT has been shown to predict subsequent ipsilateral cerebrovascular events in a prospective study of 60 patients with recent stroke.[7]

Much of the work investigating the use of PET/CT to image vulnerable plaques with FDG has focused on major vessels such as the aorta and carotids. Similar studies with FDG PET/CT imaging of coronary plaques are limited in number due to the difficulty of imaging the smaller coronary vessels. Consequently, studies that have explored plaque inflammation imaging in the coronary arteries have tended to target plaques in the left main artery and proximal major arteries.[8-10] Results are less conclusive with coronary imaging, with one study showing FDG uptake in the appropriate culprit lesion in patients with acute coronary syndromes as compared to patients with stable coronary artery disease,[8] and another study[9] demonstrated that FDG uptake was lowered in the left main artery following treatment with pioglitazone which is suspected of having a plaque-stabilizing effect. However, one conflicting study in 40 myocardial infarction patients[11] showed no differences in FDG uptake between culprit and non-culprit plaques and identifiable focal coronary FDG uptake in only 4 of 40 patients with stable angina. Robust identification of plaque inflammation with FDG in the coronary arteries, while an attractive possibility, remains elusive, particularly in the more distal coronary arteries.

THE LIMITATIONS

There are several challenges to measuring vulnerable plaque in the coronary arteries using FDG.[12] Some of the technical issues that need to be overcome are[13] (1) Interference from the background signal of FDG uptake in the myocardium. (2) The signal dilution from partial volume effects. The voxel size typically used for PET imaging is 4-6 mm and the best resolution achievable in most PET scanners is similarly about 4-5 mm. The size of the plaques being targeted is smaller than this as the coronary arteries start at approximately 4 mm in diameter. When the target being imaged is small, the signal from that target is diluted into the volume of the voxel and the signal intensity is correspondingly diminished. (3) Finally, movement of the heart due to cardiac contraction and respiratory motion which blurs out the signal over a larger volume and thus also decreases signal intensity.

The presence of myocardial signal drowns out the signal from the arterial plaque located immediately

Reprint requests: R. Glenn Wells, Cardiac Imaging Program, University of Ottawa Heart Institute, Ottawa, Canada; *gwells@ottawaheart.ca*
J Nucl Cardiol 2017;24:1171–4.
1071-3581/$34.00

adjacent to the epicardial surface. Uptake of FDG in the heart can be diminished, however, by appropriate patient preparation, namely a very low-carbohydrate and high-fat diet.[10] This diet directs metabolism of the heart to consume primarily free fatty acids for fuel, and thus minimizes the uptake of FDG in the cardio-myocytes. Protocol has been used very successfully in other imaging studies such as the detection of cardiac sacroidosis[14]—where again the signal of interest is that from inflammatory processes rather than glycolosis of the heart muscle—and is a critical component of the cardiac inflammation studies of atherosclerotic plaque done to date.[8-11]

The partial volume effect (PVE) is the reduction in signal intensity measured with PET due to a source whose size is small relative to the resolution of the PET scanner. The resolution of an image is dictated by both the inherent PET spatial resolution and also the discretization of the image itself. The maximum resolution of PET is on the order of 4-5 mm full-width at half-maximum (FWHM). To accurately represent a given spatial resolution requires 2-3 pixels per FWHM distance. In other words, using an image pixel size greater than about 2 mm will lead to loss of some of the high-frequency information available in the measured data due to discretization of the image. The use of voxels that are 4 mm on a side will negatively impact on resolution, leading to a maximum measurable resolution of 8-12 mm. Normally, this is not an issue in cardiac PET imaging as additional low-pass filtering is applied to the image to reduce the appearance of high-frequency noise in the image. For example, in myocardial perfusion imaging (MPI) with Rb-82, one might use a 12-mm filter to obtain images acceptable for clinical review which will produce effective resolutions much worse than the maximum inherent resolution of the system. However, when the reconstruction has been optimized for high resolution, a smaller voxel size may be needed.

In addition, when the size of the structure of interest is small, then even with perfect resolution, the PVE will dilute the signal. The apparent volume of a signal is limited by the voxel volume. A 2-mm-diameter sphere occupies only 6.5 % of a voxel which is (4 mm),[3] and so the apparent concentration of the activity in the sphere will be reduced by more than a factor of 20. However, the volume of a 2 mm sphere is 50 % of a (2 mm)[3] voxel leading to a reduction of only a factor of 2. The finite resolution of the scanner blurs the signal location and, particularly for small sources, can substantially increase the apparent volume which further dilutes the apparent signal strength. Therefore, smaller voxels will be helpful in increasing the measured concentration of FDG in small structures such as the coronary arteries.

The detectability of a signal is influenced by the strength of that signal over background, but also by the magnitude of noise in the image. Many studies have demonstrated the ability of time-of-flight (TOF)-PET to improve the signal-to-noise ratio (SNR) of images.[15] TOF is the localization of a positron-electron annihilation event along a line-of-response (LOR) in the PET scanner based on the difference in the arrival times of the two 511 keV photons. For an annihilation event that occurs closer to one side of the scanner, the annihilation photon traveling toward the near side will have a shorter distance to travel, and thus arrive sooner than the photon traveling toward the opposite side of the scanner. The spatial resolution of the localization is dependent on the timing resolution of the PET scanner. Modern scanners using lutetium oxyorthosilicate (LSO) or lutetium-yttrium oxyorthosilicate (LYSO) scintillation crystals have timing resolution on the order of 500 ps which translates into a spatial resolution of 7.5 cm FWHM. This spatial resolution is not good enough to allow direct identification of the site of annihilation, but does restrict the distance over which a signal is backprojected along the LOR during image reconstruction. Instead of back-projecting with equal weighting over the full length of the LOR, the signal is backprojected over a Gaussian weighted segment of the LOR with FWHM of 7.5 cm. This in turn restricts the distance over which noise can influence the image (the noise-correlation length) and leads to an improvement in the SNR. Therefore, TOF-PET has the potential to improve the detection of FDG uptake in plaques over standard non-TOF-PET.

THE SOLUTIONS

The paper by M. Suda et al in this issue[16] of the Journal employs both TOF-PET and reduced voxel sizes to improve the detectability of small FDG signals in a phantom study of coronary plaque imaging. They acquire data from 4-mm and 2-mm diameter sources on the epicardial surface of an anthropomorphic cardiac phantom and compare detectability for images reconstructed with non-TOF-PET and a 4x4x4 mm voxel size to those with TOF-PET and a $2 \times 2 \times 2$ mm voxel size. They show that TOF-PET with a $2 \times 2 \times 2$ mm voxel size greatly reduced the activity concentration ratio of the source over the background myocardium that was needed for visualization.

Heart movement represents another technical challenge to imaging FDG uptake in plaques within the coronary arteries. Motion of the heart, through cardiac contraction or respiratory motion, will introduce motion blurring into the image. The effect of motion is to distribute the signal over a greater volume and so further dilute the signal strength, similar to the effect of spatial

resolution. As with the PVE, motion blurring thus leads to reduced SNR and reduced detectability of small signals. The study by M. Suda et al also considers cardiac motion. They found that motion had little impact on the non-TOF 4x4x4 mm reconstruction but substantially degraded detectability for the TOF reconstruction. This suggests that the level of motion blurring introduced in their study did not significantly increase the blurring already present due to the conventional reconstruction. However, when the partial volume effects are reduced with the high-resolution TOF reconstruction, the effects of motion became apparent, causing a substantial reduction in the measured source-to-background ratios. This in turn highlights the need for some form of motion correction in order to maximize the detection of FDG uptake in coronary artery plaques.

Simple ECG- or respiratory gating of the data reduces heart motion, but greatly increases the noise in the images. Consequently, gating alone has not been shown to improve detectability.[8] Other more sophisticated approaches to motion compensation have been developed in the context of MPI.[17,18] Methods of 4D or even 5D (compensating for both cardiac and respiratory motion) reconstruction have been proposed. In these approaches, the counts from each gated frame are registered back to a reference frame. Thus, instead of building the image from the counts in a single frame, the counts from all of the frames over the entire acquisition are used. These kinds of approaches show considerable promise as they can potentially avoid the noise-amplification problem simple gating techniques while reducing the partial volume losses in signal caused by motion blurring.

For a robust implementation of signal detection in the coronary arteries, careful consideration must also be given to the correction of effects such as attenuation and scatter. Detection of weak signals on the edge of the heart wall will be very sensitive to errors in AC, such as those caused by mis-registration of the transmission map. Particularly at the lateral wall of the left ventricle, small errors could shift the epicardial surface into the lung, falsely depressing signals from the arteries on the surface, or shift the edge of the lung inside the myocardium and falsely elevate residual lung uptake. TOF-PET is potentially helpful here in that it is more robust to errors[15] and also it can allow independent correction for attenuation without the need for CT[19] which removes the potential for errors due to mis-registration.

The ability to identify and characterize plaque in vivo in the coronary arteries is an exciting possibility. The paper by M. Suda and colleagues represents a useful step along the road to achieve this goal. Their work demonstrates the benefits that can be obtained through optimization of the image reconstruction, in this case through choice of voxel size and restricting noise-correlation lengths with TOF technology. Further clinical studies are needed to determine the extent to which this optimization can improve coronary plaque imaging in vivo with FDG. FDG plaque imaging in the heart is hindered by the background signal caused by tracer uptake in the myocardium. An important aspect of the work by Suda et al is that their approach is not restricted to FDG. It is equally applicable to other PET tracers which may have improved physiological characteristics for plaque imaging like F-18-NaF[11] or F-18-labeled RGD peptides.[20] Imaging inflammation in the coronary arteries has, to date, been restricted to the left main and proximal coronary arteries. Improving the detectability of small plaques will expand the extent of the coronary tree that can be evaluated and so significantly enhance the value of this test for assessment of coronary artery disease.

References

1. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 2012;32:2045-51.
2. Tarkin JM, Joshi FR, Rudd JH. PET imaging of inflammation in atherosclerosis. Nat Rev Cardiol 2014;11:443-57.
3. Ogawa M, Ishino S, Mukai T, Asano D, Teramoto N, Watabe H, et al. (18)F-FDG accumulation in atherosclerotic plaques: immunohistochemical and PET imaging study. J Nucl Med 2004;45:1245-50.
4. 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.
5. 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.
6. Figueroa AL, Subramanian SS, Cury RC, Truong QA, Gardecki JA, Tearney GJ, et al. Distribution of inflammation within carotid atherosclerotic plaques with high-risk morphological features: a comparison between positron emission tomography activity, plaque morphology, and histopathology. Circ Cardiovasc Imaging 2012;5:69-77.
7. Marnane M, Merwick A, Sheehan OC, Hannon N, Foran P, Grant T, et al. Carotid plaque inflammation on 18F-fluorodeoxyglucose positron emission tomography predicts early stroke recurrence. Ann Neurol 2012;71:709-18.
8. Rogers IS, Nasir K, Figueroa AL, Cury RC, Hoffmann U, Vermylen DA, et al. Feasibility of FDG Imaging of the Coronary Arteries Comparison Between Acute Coronary Syndrome and Stable Angina. J Am Coll Cardiol Cardiovasc Imaging 2010;3:388-97.
9. Nitta Y, Tahara N, Tahara A, Honda A, Kodama N, Mizoguchi M, et al. Pioglitazone Decreases Coronary Artery Inflammation in Impaired Glucose Tolerance and Diabetes Mellitus Evaluation by FDG-PET/CT Imaging. J Am Coll Cardiol Cardiovasc Imaging 2013;6:1172-82.
10. Wykrzykowska J, Lehman S, Williams G, Parker JA, Palmer MR, Varkey S, et al. Imaging of Inflamed and Vulnerable Plaque in

Coronary Arteries with 18F-FDG PET/CT in Patients with Suppression of Myocardial Uptake Using a Low-Carbohydrate. High-Fat Preparation. J Nucl Med 2009;50:563-8.
11. Joshi NV, Vesey AT, Williams MC, Shah AS, Calvert PA, Craighead FH, et al. ^{18}F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet 2014;383:705-13.
12. Sadeghi MM. 18F-FDG PET and vascular inflammation: Time to refine the paradigm? J Nucl Cardiol 2015;22:319-24.
13. Emami H, Tawakol A. Noninvasive imaging of arterial inflammation using FDG-PET/CT. Curr Opin Lipidol 2014;25:431-7.
14. Aggarwal NR, Snipelisky D, Young PM, Gersh BJ, Cooper LT, Chareonthaitawee P. Advances in imaging for diagnosis and management of cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging 2015;16:949-58.
15. Surti S. Update on Time-of-Flight PET Imaging. J Nucl Med 2015;56:98-105.
16. Suda M, Kiriyama T, Ishihara K, Onoguchi M, Kobayashi Y, Sakurai M, et al. The high matrix acquisition technique for imaging of atherosclerotic plaque inflammation in fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography with time-of-flight: Phantom study. J Nucl Cardiol 2016. doi:10.1007/s12350-016-0510-7.
17. Lamare F, Le Maitre A, Dawood M, Schäfers KP, Fernandez P, Rimoldi OE, et al. Evaluation of respiratory and cardiac motion correction schemes in dual gated PET/CT cardiac imaging. Med Phys 2014;41:072504.
18. Slomka PJ, Rubeaux M, Le Meunier L, Dey D, Lazewatsky JL, Pan T, Dweck MR, et al. Dual-Gated Motion-Frozen Cardiac PET with Flurpiridaz F 18. J Nucl Med 2015;56:1876-81.
19. Presotto L, Busnardo E, Perani D, Gianolli L, Gilardi MC, Bettinardi V. Simultaneous reconstruction of attenuation and activity in cardiac PET can remove CT misalignment artifacts. J Nucl Cardiol 2015. doi:10.1007/s12350-015-0239-8.
20. Beer AJ, Pelisek J, Heider P, Saraste A, Reeps C, Metz S, et al. PET/CT imaging of integrin αvβ3 expression in human carotid atherosclerosis. J Am Coll Cardiol Cardiovasc Imaging 2014;7:178-87.