PET Assessment of Vascular Inflammation and Atherosclerotic Plaques: SUV or TBR?

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The accurate quantification of radiotracer activity in a vascular wall plaque on PET can be problematic. Because most atherosclerotic plaques are small and exhibit complex morphology, it can be quite difficult to properly recover activity within a plaque by PET without sophisticated partial-volume effect correction. The latter becomes particularly challenging when the lesion is below 3 times of the full width at half maximum of the point spread function. As such, before a meaningful conclusion is drawn as to whether ^{18}F-FDG or ^{18}F-NaF signal on PET can serve as a biomarker for vulnerable plaque (*1,2*), it is important to determine whether the plaque signal on PET can be reliably and accurately quantified. Accurate quantification has significant implications for future molecular imaging studies of atherosclerosis both for monitoring disease progression and for therapeutic response (*3,4*).

Maximum standardized uptake value (SUV_{max}) is the most commonly used parameter for measuring lesion activity among patients

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undergoing PET/CT imaging for the initial staging or treatment response evaluation of malignancies. By definition, SUV_{max} indicates the most intense voxel activity within a region of interest whereas mean SUV (SUV_{mean}) represents the mean activity within a region of interest. As it is almost impossible to accurately define the edge of a vascular plaque on CT, SUV_{mean} is impractical in atherosclerotic plaque quantification. Likewise, if the tracer distribution is not homogeneous within a plaque lesion, SUV_{max} may not accurately represent the lesion's overall activity.

In the current issue of *The Journal of Nuclear Medicine,* Huet et al. (*5*) addressed an important topic regarding the variability and uncertainty of ^{18}F-FDG PET imaging protocols used in the literature for assessing inflammation within arterial wall atherosclerotic plaques. They emphasized that most of the publications in the literature were retrospective in nature, using the database of oncology PET/CT images in which SUV was used to characterize vascular inflammation. They demonstrated variability by a factor

of greater than 3 depending on the number of iterations used in the reconstruction algorithm and the postfiltering applied to the reconstructed images. Not only was there a wide variability in the acquisition protocols, for example, the injected activity, time interval from dose injection and PET acquisition, and acquisition duration per bed position, there was a significant (and not inconsequential) variability in the patient population studied. In oncology subjects, there was various confounding radiation and chemotherapy-related vascular inflammation—not to mention alterations in the metabolic milieu—that was related to the underlying malignancy itself. Accordingly, it is possible that SUV signals assessed in oncology subjects may not accurately represent atherosclerotic carotid, coronary, or large artery plaques. Clearly, standardization and protocol harmonization of PET in atherosclerosis imaging is required to facilitate future direct comparison of results from different institutions.

To address these specific issues in a more standardized environment, Huet et al. (*5*) performed additional experiments using simulated atherosclerotic lesions in a phantom system. They observed that the bias in SUV measurement was indeed large irrespective of the acquisition and reconstruction protocol applied. However, they were able to identify various approaches that minimized the biases. The number of iterations used in reconstruction was the most critical factor. Although the bias was high, the variability of the bias was not so high within a system. Given the systematic factors, the smallest bias observed was with SUV_{max}. For a small-size lesion, despite the bias, the SUV_{max} appeared to be still useful for representing plaque activity. When both the size and the activity were decreased, the measured SUV_{max} decreased as well, similar to what has been observed with atherosclerotic plaque assessment in the literature. Even if the measurement was not perfectly accurate, SUV_{max} conveyed information regarding the features of the lesion, representing both the activity and the lesion size. These phantom studies of simulated atherosclerotic lesions demonstrated that optimized protocols may significantly reduce the SUV_{max} measurement errors in wall activity estimates.

A unique parameter that is used only in studies of PET imaging of vascular inflammation and atherosclerotic plaques is the target–to–blood pool ratio (TBR), which was introduced in the literature in 2006 (*6*) and has been widely used in publications thereafter. TBR is derived by dividing the vascular wall SUV with the venous blood pool SUV, to correct for blood uptake. TBR is often calculated from SUV_{max}, leading to maximum TBR (TBR_{max}), or from SUV_{mean} over a region of interest drawn around a plaque and venous blood pool, leading to mean TBR (TBR_{mean}). In some papers, $TBR_{meanofmax}$ is also used, which is derived by averaging the TBR_{max} over all transaxial slices of a plaque. Independent of

how the ratio is derived, TBR is thought to represent vascular plaque tracer activity. For instance, in the case of ^{18}F-FDG, TBR is thought to represent plaque inflammation. Indeed, vascular wall plaque TBR on ^{18}F-FDG PET/CT has been shown to correlate well with plaque macrophage density (6), and 1 study showed that intra- and inter-interpreter agreement of TBR measurement within 2 wk was high (7). However, reproducibility of a measurement does not equate to accuracy. To determine whether TBR is close to the quantity's actual (true) value, we need to examine next all variables that may affect TBR from subject to subject as well as in the same subject studied before and after medical therapy or an intervention.

TBR varies as a function of how plaque activity (numerator) and blood pool activity (denominator) are measured. The venous blood pool SUV is obtained from the superior venal cava, inferior venal cava, jugular vein, or right atrium, a method that is variable in the published studies. Blood activity of the radiotracer from pre- to posttherapeutic studies can be variable both for biologic reasons (e.g., differential clearance from the kidneys or hepatobiliary pathway) and from errors and variability as a function of the region involved in the TBR calculation. Accordingly, one can expect greater variability in TBR estimates than in SUV estimates.

^{18}F-FDG clearance from the blood pool is fast, with only a small amount of the radiotracer persisting in the blood, approximately 1 h after injection, when ^{18}F-FDG PET images are acquired. Thus, the venous blood pool SUV is usually low, and even slight changes in the venous blood pool SUV may lead to a significant variability in the TBR measurement. Blood pool ^{18}F-FDG can be affected by many factors including time of PET imaging after ^{18}F-FDG injection, which may range from 45 to 90 min or longer; variability in blood cell uptake, blood cell density, and the rate of blood flow in veins along with a time-dependent decrease in SUV in the superior vena cava and jugular vein (8); and a significant negative correlation between estimated glomerular filtration rate and the blood pool SUV for ^{18}F-FDG and positive correlation between the estimated glomerular filtration rate and TBR in the same subjects (9). Despite these variables, no corrections have been attempted or implemented in the published studies to adjust for these factors on TBR for plaque quantification.

Despite the broad application of TBR in the literature, particularly in the field of atherosclerosis PET imaging, its biologic significance and physiologic or mathematic explanation have not been provided. It has been suggested that TBR represents a blood-corrected uptake measurement. Huet et al. (5) discussed the rationale of TBR from the physics perspective. They pointed out that blood activity adds to vascular wall activity because of the spatial blurring of PET images (imperfect spatial resolution) and the tissue fraction effect. They applied a mathematic model that incorporated observed wall activity (reflecting the summation of real wall activity plus blood activity) adjusted by weighting factors that took into consideration the spill-out of wall activity in neighboring regions. They argued that the variance of TBR is the sum of the variance in observed wall activity and of the variance of the estimated blood activity, making TBR less reproducible than SUV.

To correct for blood uptake, it is our opinion that subtraction of venous SUV from arterial SUV would be a more rational solution than dividing the 2 measured values, as is done in TBR. The fact that the clearance of ^{18}F-FDG from the venous blood pool can be quite variable from subject to subject, depending on their renal clearance, metabolic milieu, diabetes mellitus, and glucose utilization in various organs, dividing the vascular wall SUV with the venous blood pool SUV may introduce more variability and confusion to the TBR measurement than confidence.

In conclusion, successful imaging of vascular inflammation and atherosclerotic plaque requires not only an ideal radiotracer that reflects the biology of the disease process but also the technology and a measurement system that is both accurate and precise. Improved spatial resolution and implementation of partial-volume correction on future PET/CT systems may bring the field closer to that realization. In the meantime, incorrect use of quantification parameters may lead to misinterpretation of study results.

REFERENCES

1. Chen W, Dilsizian V. ^{18}F-fluorodeoxyglucose PET imaging of coronary atherosclerosis and plaque inflammation. *Curr Cardiol Rep.* 2010;12:179–184.
2. Chen W, Dilsizian V. Targeted PET/CT imaging of vulnerable atherosclerotic plaques: microcalcification with sodium fluoride and inflammation with fluorodeoxyglucose. *Curr Cardiol Rep.* 2013;15:364–369.
3. Narula J, Dilsizian V. From better understood pathogenesis to superior molecular imaging, and back. *JACC Cardiovac Imaging.* 2008;1:406–409.
4. Dilsizian V, Narula J. Epilogue: setting tiny targets for greater goals.... *Nat Clin Pract Cardiovac Med.* 2008;5:S112–S113.
5. Huet P, Burg S, Le Guludec D, Hyafil F, Buvat I. Variability and uncertainty of ^{18}F-FDG PET imaging protocols for assessing inflammation in atherosclerosis: suggestions for improvement. *J Nucl Med.* 2015;56:552–559.
6. Tawakol A, Migrino RQ, Bashian GG, et al. In vivo ^{18}F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *J Am Coll Cardiol.* 2006;48:1818–1824.
7. Rudd JH, Myers KS, Bansilal S, 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;50:892–896.
8. Oh M, Kim JY, Shin KH, et al. Imaging atherosclerosis in the carotid arteries with F-18-fluoro-2-deoxy-D-glucose positron emission tomography: effect of imaging time after injection on quantitative measurement. *Nucl Med Mol Imaging.* 2010;44:261–266.
9. Derlin T, Habermann CR, Hahne JD, et al. Quantification of [^{18}F]-FDG uptake in atherosclerotic plaque: impact of renal function. *Ann Nucl Med.* 2011;25:586–591.