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

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Keywords: FDG, PET/CT, atherosclerosis, inflammation, plaque, arterial wall, SUV, TBR
Accurate quantification of radiotracer activity in a vascular wall plaque on PET can be problematic. Since 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 18F-FDG or 18F-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. The latter has significant implications for future molecular imaging studies of atherosclerosis both for monitoring disease progression and therapeutic response (3,4).

**SUV: max or mean?**

SUVmax is the most commonly used parameter for measuring lesion activity among patients undergoing PET/CT imaging for the initial diagnosis, staging, or evaluating treatment response of malignancies. By definition, SUVmax indicates the most intense voxel activity within a region of interest while SUVmean 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, SUVmean is impractical in atherosclerotic plaque quantification. Likewise, if the tracer distribution is not homogeneous within a plaque lesion, SUVmax may not accurately represent the lesion’s overall activity.

In the current issue of the *Journal*, Huet et al. (5) address a very important topic regarding the variability and uncertainty of 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, where 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 post-filtering applied to the reconstructed images. Not only was there a wide variability in the acquisition protocols, e.g. injected activity, time interval from dose injection and PET acquisition, the acquisition duration per bed position, etc., there was a significant (and not inconsequential) variability in the patient population studied. In oncology subjects, there are all sorts of confounding radiation and chemotherapy related vascular inflammation, not to mention alterations in the metabolic milieu, that are related to the underlying malignancy itself. Accordingly, it is possible that SUV signals assessed in oncology subjects may have no relation to atherosclerotic carotid, coronary or large artery plaques.

Clearly, standardization and protocol harmonization of PET in atherosclerotic imaging is required in order to facilitate future direct comparison of results from different institutions.

In order 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 minimize 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 SUVmax. For a small size lesion, despite the bias, the SUVmax appeared to be still useful for representing plaque activity. When both the size and the activity were decreased, the measured SUVmax decreased as well, similar to what has been observed with atherosclerotic plaque assessment in
the literature. Even if the measurement was not perfectly accurate, SUVmax conveyed information regarding the features of the lesion, representing both the activity and lesion size. These phantom studies of simulated atherosclerotic lesions demonstrated that optimized protocols may significantly reduce the SUVmax measurement errors in wall activity estimates.

What about TBR: Target-to-Blood Pool Ratio?

Variability in the measured components of TBR in relation to blood pool activity: 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 SUVmax leading to maximum TBR (TBRmax), or from SUVmean over a region of interest drawn around a plaque and venous blood pool, leading to mean TBR (TBRmean). In some papers, TBRmeanofmax is also used by averaging the TBRmax 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 FDG, TBR is thought to represent plaque inflammation. Indeed, vascular wall plaque TBR on FDG PET/CT has been shown to correlate well with plaque macrophage density (6) and one study showed that intra- and inter-reader agreement of TBR measurement within 2 weeks was high (7). However, reproducibility of a measurement does not equate to accuracy. In order to determine whether TBR is close to the quantity's actual (true) value, we need to examine next all variables that may impact 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) is measured. The venous blood pool SUV is obtained from the superior venal cava, inferior venal cava, jugular vein, or right atrium, which is variable in the published studies. Blood activity of the radiotracer from pre- to post-therapeutic studies can be variable both for biological reasons (e.g. differential clearance from the kidneys or hepatobiliary pathway) as well as 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.

FDG clearance from the blood pool is fast with only small amount of the radiotracer persisting in the blood, approximately 1 hour after injection, when 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 FDG can be affected by many factors including: 1) time of PET imaging after FDG injection, which may range from 45 min to 90 min or longer, 2) variability in blood cell uptake, blood cell density, the rate of blood flow in veins along with time-dependent decrease in SUV in the superior vena cava and jugular vein (8), 3) significant negative correlation between estimated glomerular filtration rate (eGFR) and the blood pool SUV for FDG and positive correlation between the eGFR and TBR in the same subjects (9). In spite of these variables, no corrections have been attempted or implemented in the published studies to adjust for these factors on TBR for plaque quantification.
What is the scientific and/or biologic reasoning behind the derivation of TBR and what does it exactly represent? Despite the broad application of TBR in the literature, particularly in the field of atherosclerosis PET imaging, its biological significance and physiologic or mathematical 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 point out that blood activity adds to vascular wall activity due the spatial blurring of PET images (imperfect spatial resolution) and to the tissue fraction effect. They applied a mathematical model that incorporates observed wall activity (reflecting the summation of real wall activity plus blood activity) adjusted by weighting factors that take into consideration the spill-out of wall activity in neighboring regions. They argue 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.

In order 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 two measured values, as is done in TBR. The fact that the clearance of FDG from the venous blood pool can be quite variable from subject to subject, depending on their renal clearance, metabolic milieu, diabetes mellitus, 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.

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.

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*J Nucl Med.*
Published online: February 26, 2015.
Doi: 10.2967/jnumed.115.154385

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