Accuracy of arterial [^{18}F]-Fluorodeoxyglucose uptake quantification: A kinetic modeling study

Jakub Toczek, PhD,[a,b] Jing Wu, PhD,[c,d] Ansel T. Hillmer, PhD,[c,d,e] Jinah Han, PhD,[a,b] Irina Esterlis, PhD,[b,d,e] Kelly P. Cosgrove, PhD,[c,d,e] Chi Liu, PhD,[c,d] and Mehran M. Sadeghi, MD[a,b,f]

[a] Cardiovascular Molecular Imaging Laboratory, Section of Cardiovascular Medicine and Yale Cardiovascular Research Center, Yale University School of Medicine, New Haven, CT
[b] Veterans Affairs Connecticut Healthcare System, West Haven, CT
[c] Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT
[d] Yale PET Center, Yale University School of Medicine, New Haven, CT, United States
[e] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States
[f] Yale Cardiovascular Research Center, New Haven, CT

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Abstract. **2-deoxy-2- [^{18}F] fluoro-D-glucose (FDG) PET is commonly used for the assessment of vessel wall inflammation. Guidelines for analysis of arterial wall FDG signal recommend the use of the average of maximal standardized uptake value (mean SUV_{max}) and target-to-blood (mean TBR_{max}) ratio. However, these methods have not been validated against a gold standard such as tissue activity ex vivo or net uptake rate of FDG (K_i) obtained using kinetic modeling. We sought to evaluate the accuracy of mean SUV_{max} and mean TBR_{max} for aortic wall FDG signal quantification in comparison with the net uptake rate of FDG.**

Methods. **Dynamic PET data from 13 subjects without prior history of cardiovascular disease who enrolled in a study of vascular inflammation were used for this analysis. Ex vivo measurement of plasma activity was used as the input function and voxel-by-voxel Patlak analysis was performed with t^* = 20 minute to obtain the K_i image. The FDG signal in the ascending aortic wall was quantified on PET images following recent guidelines for vascular imaging to determine mean SUV_{max} and mean TBR_{max}.**

Results. **The K_i in the ascending aortic wall did not correlate with mean SUV_{max} (r = 0.10, P = NS), but correlated with mean TBR_{max} (r = 0.82, P < 0.001) (Figure 1B). K_i and K_{i_max} strongly correlated (R = 0.96, P < 0.0001) and similar to K_i, K_{i_max} did not correlate with mean SUV_{max} (r = 0.17, P = NS), but correlated with mean TBR_{max} (r = 0.83, P < 0.001).**

Conclusions. **Kinetic modeling supports the use of mean TBR_{max} as a surrogate for the net uptake rate of FDG in the arterial wall. These results are relevant to any PET imaging agent, regardless of the biological significance of the tracer uptake in the vessel wall. (J Nucl Cardiol 2020;27:1578–81.)**

Key Words: PET • FDG • Vascular imaging • Inflammation • Image analysis

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Jakub Toczek and Jing Wu have contributed equally to this work.

Reprint requests: Mehran M. Sadeghi, MD, Yale Cardiovascular Research Center, 300 George Street, #770G, New Haven, CT 06511; *mehran.sadeghi@yale.edu*

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Abbreviations	
CT	Computed tomography
FDG	^{18}F-fluorodeoxyglucose, 2-deoxy-2-[^{18}F] fluoro-D-glucose
PET	Positron emission tomography
SUV	Standardized uptake value
TBR	Target-to-background ratio

INTRODUCTION

2-deoxy-2- [^{18}F] fluoro-D-glucose (FDG), a glucose analog used for positron emission tomography (PET) imaging, accumulates in cells with high glucose metabolic activity, such as inflammatory cells.[1] Recently, the use of FDG PET for assessment of vessel wall inflammation has become a common practice. Guidelines for analysis of arterial wall FDG signal were recently published, and recommend the use of the average of maximal standardized uptake value (mean SUV_{max}) and target-to-blood (mean TBR_{max}) ratio, i.e., the ratio of SUV_{max} to blood activity measured as SUV_{mean} inside large venous structures, such as the superior vena cava.[2] However, these methods have not been validated against a gold standard such as tissue activity ex vivo, which cannot be determined in humans, or net uptake rate of FDG (K_i), which can be obtained using kinetic modeling. The objective of this study was to evaluate the accuracy of mean SUV_{max} and mean TBR_{max} for aortic wall FDG signal quantification in comparison with the net uptake rate of FDG using dynamic imaging and kinetic modeling.

METHODS AND RESULTS

We used the data from 13 subjects [median age 32 (range 28 to 45), median body mass index 31 (range 22 to 38 kg/m^2)] without prior history of cardiovascular disease who enrolled in a study of vascular inflammation performed under protocols approved by Yale University and VA Connecticut Healthcare System Institutional Review Board committees.[3] Informed consent was obtained from all individual participants included in the study. The subjects were asked to follow a standard low carbohydrate diet to reduce myocardial FDG uptake. At the time of the study, the blood glucose level was $\leq$ 106 mg·dL^{-1} for all subjects. After a low dose non-contrast attenuation correction computed tomography scan, the subjects were administrated 344 ± 30 MBq of FDG and a 2-hour dynamic PET acquisition was performed on a Biograph mCT PET/CT scanner. During the 2-hour dynamic PET acquisition, the subjects first underwent a 6-minute dynamic single-bed scan over the heart (binned into 4 × 0.25 min, 4 × 0.5 min, 3 × 1 min) and then 18 continuous-bed-motion passes from head to pelvis (4 × 2 min, 13 × 5 min, and 1 × 30 min). Serial blood samples were collected throughout image acquisition and used to determine *ex vivo* whole blood and plasma activity. Dynamic PET images were reconstructed using ordered subset expectation-maximization algorithm (21 subsets, 2 iterations) incorporating point spread function and time-of-flight information with corrections for attenuation, scatter, random coincidences, and decay. The voxel size of the reconstructed image was 2.036 × 2.036 × 2 mm^3. *Ex vivo* measured plasma time activity curve was fitted with sum of exponentials and used as the input function and voxel-by-voxel Patlak analysis was performed with t^* = 20 min to obtain the K_i image. The FDG signal in the ascending aortic wall was quantified on PET images reconstructed from the final 30 minutes of acquisition, following recent guidelines for vascular imaging.[2] Briefly, the SUV_{max} was measured on consecutive axial slices in the ascending aorta and averaged to obtain mean SUV_{max}; the mean TBR_{max} was calculated as the ratio of aortic mean SUV_{max} to blood pool activity measured in the superior vena cava and expressed as mean SUV.[3] The mean K_i value in the entire ascending aortic wall was quantified on the K_i images using a population-based thresholding method. First, the mean and the standard deviation of blood K_i in the ascending aorta were calculated using data from all subjects. Then the mean K_i value in the ascending aortic wall was calculated for each subject using the voxels with K_i values above the threshold of mean plus 1.5-fold standard deviation of blood K_i. The mean K_{i_max} was determined on K_i images using the methodology recommended for determining the mean SUV_{max}.[2] Statistical analyses were performed using GraphPad Prism 7. Pearson correlation was used to evaluate the relation between different variables. A P value less than 0.05 was considered significant.

Examples of SUV and K_i images are shown in Figure 1A. The mean K_i value in the ascending aortic wall was 4.57 ± 0.39 μL/min/cm^3 and the mean SUV_{max} and mean TBR_{max} values measured on images from the last 30 min of image acquisition were 3.42 ± 0.37 g·cm^{-3} and 2.34 ± 0.29, respectively. The K_i in the ascending aortic wall did not correlate with mean SUV_{max} (r = 0.10, P = NS) but correlated with mean TBR_{max} (r = 0.82, $P < 0.001$) (Figure 1B). K_i and mean K_{i_max} strongly correlated (R = 0.96, $P < 0.0001$), with mean K_{i_max} being 1.78 ± 0.19-fold higher compared to mean K_i. Similar to K_i, mean K_{i_max} did not correlate

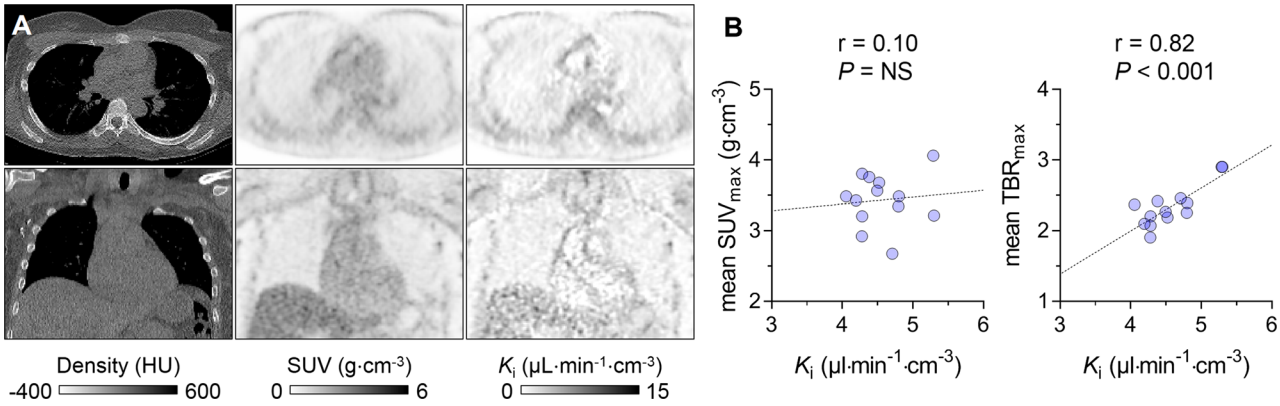

Figure 1. Comparison of PET images with the net uptake rate of FDG in the ascending aorta. **A** Examples of attenuation-corrected CT (left) and FDG PET images at 90 to 120 minute post-injection (middle) with corresponding K_i images (right). **B** Correlation between K_i and mean SUV_{max} (left) and mean TBR_{max} (right). The two highest data points on the mean TBR_{max} graph overlap, appearing as a darker circle.

with mean SUV_{max} ($r = 0.17$, P = NS) but correlated with mean TBR_{max} ($r = 0.83$, $P < 0.001$).

DISCUSSION

Recent guidelines recommend the use of both mean SUV_{max} or mean TBR_{max} for analysis of FDG signal in the arterial wall.[2] We used kinetic modeling to evaluate the net uptake rate of FDG in the arterial wall in a cohort of subjects without history of cardiovascular disease. Our study demonstrates that the net uptake rate of FDG in the arterial wall correlates with mean TBR_{max} but not mean SUV_{max}, supporting the use of TBR_{max} to evaluate FDG uptake in the arterial wall. These results are in accordance with similar analyses performed in other tissues[4,5] or conceptualized on a theoretical level.[6]

The ability of PET imaging to provide quantitative measurement of tissue activity over time can be leveraged to assess radiotracers behavior via kinetic modeling. When FDG concentration is at a steady-state equilibrium between a reversible compartment and the plasma, the net influx rate (K_i) of FDG, assumed to be irreversibly trapped within the cellular compartment following its phosphorylation, can be estimated using Patlak analysis.[7] K_i relates to a relevant physiological parameter in the tissue, i.e., the glucose metabolic rate.[8] The direct measurement of FDG tissue concentration *ex vivo* is not feasible in most clinical studies. The alternative, i.e., the determination of FDG tissue concentration on PET images and its normalization as SUV (or TBR) introduces a number of confounding factors to consider[9]; some of which shared with image-derived K_i determinations. The use of SUV_{max} (and TBR_{max}) to quantify FDG signal in the arterial wall suffers from the challenges associated with the small size of the arterial wall. Indeed, the normal ascending aorta wall thickness is $\sim$ 1.5 mm,[10] while the spatial resolution of clinical PET scanners is at best about 5 mm.[11] The resulting partial volume effect results in an underestimation of the activity in the structure with higher activity (i.e., aortic wall) compared to the surrounding areas of lower activity.[12] In this study, we used a thresholding method on K_i images to generate a VOI corresponding to the ascending aortic wall, based on a volume defined around the ascending aorta, with the assumption that, in this restricted volume, the aortic wall is the structure with the higher metabolic rate. Since kinetic modeling was performed on images subject to partial volume effect, the presented mean K_i value may also represent an underestimation of the metabolic rate of FDG in the aortic wall.

In this relatively young population with minimal cardiovascular risk factors, we did not evaluate the extent of atherosclerosis, and thus the source of FDG signal cannot be ascertained. Indeed, while vessel wall inflammation is often evaluated by FDG PET, a significant portion of the arterial wall FDG signal cannot be attributed to the presence of macrophages.[13] Regardless of the cellular source of the signal, the arterial FDG signal in our dataset spanned the range of previously reported data,[14] supporting broader validity of the correlations.

In conclusion, we show that mean TBR_{max} is superior to mean SUV_{max} as a surrogate of the net uptake rate of FDG in the arterial wall. These results are relevant to any PET imaging agent, regardless of the biological significance of the tracer uptake in the vessel wall.

NEW KNOWLEDGE GAINED

Mean TBR_{max} is superior to mean SUV_{max} as a surrogate of the net uptake rate of FDG in the arterial wall.

Disclosure

Mehran M. Sadeghi is a consultant for Bracco Research USA. Jakub Toczek, Jing Wu, Ansel T. Hillmer, Jinah Han, Irina Esterlis, Kelly P. Cosgrove and Chi Liu have no conflict of interest to disclose.

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