^{18}F-FDG Uptake to Assess Eosinophilic Inflammation in Asthma: Would SUV at Late Imaging Be Relevant?

TO THE EDITOR: We read with great interest the article by Harris et al. (*1*) demonstrating that ^{18}F-FDG uptake rate (K_i, min^{-1}) precisely predicts the degree of eosinophilic inflammatory response in the lungs of asthmatic patients undergoing an allergen challenge. Any result in this field is of tremendous interest because it may provide complementary quantitative insight into the severity of the inflammatory response in asthma and thus may be used for testing innovative therapies. The study of Harris et al. used the gold standard graphical method of Patlak et al. involving dynamic acquisition until about 60 min after injection and venous blood sampling (*2,3*), allowing determination of the ratio of K_i in allergen-challenged and diluent-control lobe, which was compared with that of eosinophil counts obtained with bronchoalveolar lavage.

Because we have proposed an adapted estimation of ^{18}F-FDG metabolism that can be used for lung examination in clinical practice (*4*), we suggest that the standardized uptake value (SUV) assessed at late imaging may be used to estimate eosinophilic inflammation in asthma. Let us consider SUV at a late imaging time of $t > 60$ min:

$$SUV(t) = A_{Trap}(t)W/A_{Inj}, \qquad \textbf{Eq. 1}$$

where $A_{Trap}(t)$ ($kBq \cdot mL^{-1}$) is the trapped ^{18}F-FDG activity per tissue unit volume for free tracer in blood and interstitial volume can be neglected at late imaging (*5*), A_{Inj} is the injected activity, and W is the patient's weight. The former activity can also be derived from a compartmental model analysis as (*4*):

$$A_{Trap}(t) = K_i\, A_{Inj}\, f(t), \qquad \textbf{Eq. 2}$$

where f(t) is a function involving ^{18}F-FDG input function parameters. Therefore, combining Equations 1 and 2 provides the following expression for SUV that now involves K_i:

$$SUV(t) = Ki\ f(t)\ W, \qquad \textbf{Eq. 3}$$

As a consequence, the ratio of SUV and K_i in allergen-challenged and diluent-control lobe (subscripts 1 and 2, respectively) is the same because f(t) and W are the same:

$$SUV_1(t)/SUV_2(t) = K_{i1}/K_{i2}. \qquad \textbf{Eq. 4}$$

Harris et al. (*1*) found that the latter ratio was strongly correlated with eosinophil count ratio ($P < 0.001$). Furthermore, it should be emphasized, first, that correction for ^{18}F physical decay usually applied to SUV is cancelled out in the former ratio; second, that the use of mean SUV over lung lobe area (or volume) reduces variability in comparison with that of maximal SUV; and importantly, third, that assessing SUV ratio instead of K_i ratio avoids a time-consuming dynamic acquisition and invasive blood sampling.

In conclusion, the method of Harris et al. (*1*) clearly demonstrates that PET of ^{18}F-FDG uptake rate K_i may serve as a reliable biomarker of eosinophilic inflammation and its functional effects in asthma. In that framework, the current model analysis further suggests that simple SUV may play a similar role when assessed at late imaging. Analysis of SUV data obtained from the last dynamic frames in the study of Harris et al. would give some indication as to whether this suggestion may be tested in a clinical study.

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Published online Jun. 1, 2012.
DOI: 10.2967/jnumed.112.102822

REPLY: We appreciate Drs. Laffon and Marthan's interest in our article relating with high precision the allergen-to-diluent ratio of the ^{18}F-FDG uptake rate (K_i) to the allergen-to-eosinophil count. They wonder if the ratio of late SUV might also closely correlate with the ratio of eosinophil count. To examine this possibility, we reanalyzed our data using the last 10-min frame of our dynamic acquisition to calculate both a mean and a peak standardized uptake value (SUV) in the regions of interest for the right middle lobe (allergen) and right upper lobe (diluent). We plotted the allergen-to-diluent ratio of mean and peak SUV against the ratio of eosinophil counts and found coefficients of determination of 0.3944 ($P = 0.18$) and 0.0015 ($P = 0.94$), respectively, compared with 0.9917 ($P < 0.001$) for the ^{18}F-FDG K_i ratio (*1*).

The reason for the marked difference in performance between SUV and K_i is unclear but may be due to the assumption that plasma activity is low in relation to tissue activity when SUV is calculated. Since SUV is the sum of both plasma activity and uptake, the ratio of SUV in the allergen-to-diluent regions of interest can closely approximate the ratio of K_i only when plasma activity is low relative to activity taken up by the tissue. In most organs, plasma

volume is low compared with tissue volume, and this assumption is reasonable. However, in the lung, plasma volume is nearly equal to tissue volume, and plasma activity could be a substantial fraction of total activity in a region of interest, even late during imaging. This consideration may be particularly problematic in regions with slow uptake, such as the diluent lobe in our experiment, for which the error may be magnified when SUV is used.

Using dynamic ^{18}F-FDG scans rather than late, static PET scans is more complicated, as it requires a rapid, smooth injection; multiple blood draws; and a single–bed-position acquisition. However, our laboratory has developed a method to reduce the number of arterial samples to derive an input function (*2*). With this method, we can take as few as 2 venous samples (we often take 5 or 6 in case of problems with sampling), which are used to "calibrate" an input function measured with PET from a region of interest defined over the right heart or the aorta. Granted, we still have to image continuously during injection, thus reducing the imaging field to a single bed position. Newer scanners are able to acquire larger fields of view, or alternatively, one can move the subject back and forth between 2 or 3 bed positions in order to acquire dynamic datasets.

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Published online Jun. 4, 2012.
DOI: 10.2967/jnumed.112.104018

Differentiated Thyroid Carcinoma: Is There Any Evidence for the Use of Recombinant Human TSH in Thyroid Hormone–Secreting Metastasis?

TO THE EDITOR: We are thankful for the interesting and highly relevant article by Douglas Van Nostrand and colleagues, published in the March 2012 issue (*1*). The objective of this study was to compare administration of recombinant human thyroid-stimulating hormone (rhTSH) versus thyroid hormone withdrawal for the identification of metastasis in differentiated thyroid cancer (DTC) on ^{131}I planar whole-body imaging and ^{124}I PET. The authors observed that ^{131}I planar whole-body scans and ^{124}I PET scans identified significantly more foci of metastasis in patients after preparation with thyroid hormone withdrawal than with rhTSH injections. The conclusion drawn by the authors that "physicians should be cautious in using rhTSH for patient preparation before diagnostic scanning for the detection of DTC or treating distant metastasis secondary to DTC with ^{131}I" appears well founded on the data presented. Furthermore, such a study is important, because recently there has been a shift toward the use of rhTSH in increasing numbers of indications in patients with DTC.

However, we have several concerns regarding the authors' conclusion that "the use of rhTSH is appropriate for patients. . .[to] increase their endogenous TSH because their metastases are producing significant thyroid hormone." First, none of the patients in the evaluated study cohort was identified as a patient with thyroid hormone–secreting metastasis. Second, there is no corresponding discussion to support this conclusion. Furthermore, DTC with thyroid hormone–secreting metastases is exceedingly rare. Only a few cases have been reported since the first patient with adenocarcinoma of the thyroid with thyroid hormone–secreting metastasis and postoperative thyrotoxicosis was described by Leiter et al. in 1946 (*2*). Because of the small number of cases reported so far, patients with hormone-producing metastasis represent a challenge for the further treatment of DTC. Recently, we reported the case of a patient with thyroid hormone–secreting metastasis leading to persistent TSH suppression after thyroidectomy and radioiodine remnant ablation. As suggested by Van Nostrand et al., we assumed that rhTSH was the appropriate preparation to elevate the TSH level before ^{131}I whole-body imaging. However, we observed that when applied before the second radioiodine treatment, rhTSH increased the ^{131}I uptake into the thyroid hormone–secreting metastasis and prolonged the effective half-life of ^{131}I in relation to measurements from the first radioiodine therapy without rhTSH (*3*). Compared with the original therapy without rhTSH, the ^{131}I uptake after rhTSH increased from 8.4% to 39% and the effective half-life increased from 2.2 to 4.1 d. Subsequent radiation exposure caused bone marrow toxicity with myelosuppression. To prevent grade IV neutropenia, the patient was successfully treated with pegfilgrastim, a long-acting granulocyte-stimulating growth factor.

On the basis of the data presented by van Nostrand et al. and our own experience, we cannot agree with their recommendation regarding the use of rhTSH in the subgroup of patients with thyroid hormone–secreting metastasis. We would propose adding the following clarifications to the article: rhTSH might not be necessary for diagnostic ^{131}I whole-body imaging in patients with TSH suppression due to thyroid hormone–secreting metastasis, because thyroid hormone–secreting metastases generally show a high ^{131}I uptake. Furthermore, in patients undergoing ^{131}I treatment, the use of rhTSH needs to be handled carefully as it can increase ^{131}I uptake and prolong the effective half-life of ^{131}I, leading to an increased exposure to radiation and bone marrow toxicity. Because this subgroup of patients is extremely rare, further studies regarding their optimal diagnostic work-up and treatment should be performed before any general recommendation is given.

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