King's Research Portal

DOI:
10.1016/j.ejrad.2016.02.026

Document Version
Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):

Citing this paper
Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights
Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the Research Portal

Take down policy
If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 28. Jul. 2023
Accepted Manuscript

Title: Relationships of body habitus and SUV indices with signal-to-noise ratio of hepatic 18F-FDG PET

Author: G. Keramida A. Dunford M. Siddique G.J. Cook A.M. Peters

PII: S0720-048X(16)30069-9
DOI: http://dx.doi.org/10.1016/j.ejrad.2016.02.026
Reference: EURR 7413

To appear in: European Journal of Radiology

Received date: 17-2-2016
Accepted date: 26-2-2016

Please cite this article as: Keramida G, Dunford A, Siddique M, Cook GJ, Peters A.M. Relationships of body habitus and SUV indices with signal-to-noise ratio of hepatic 18F-FDG PET. European Journal of Radiology http://dx.doi.org/10.1016/j.ejrad.2016.02.026

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Relationships of body habitus and SUV indices with signal-to-noise ratio of hepatic $^{18}$F-FDG PET

Relationships of body habitus and SUV indices with signal-to-noise ratio of hepatic $^{18}$F-FDG PET

1G Keramida, 2A Dunford, 3M Siddique, 3G J Cook, 4A M Peters

1Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, Brighton, UK
2Department of Nuclear Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK
3Imaging Sciences and Biomedical Engineering, King’s College, London, UK
4Division of Clinical and Laboratory Investigation, Brighton and Sussex Medical School, Brighton, UK.

Author for correspondence
Professor A Michael Peters
Department of Nuclear Medicine
Royal Sussex County Hospital
Eastern Road
Brighton
BN2 5BE
UK
Telephone: 0044(0)1273523360
Fax: 0044(0)1273533366
Email: a.m.peters@bsms.ac.uk

Short title: Body habitus and signal-to-noise ratio in obesity

ABSTRACT

Objective: Tissue accumulation of $^{18}$F-FDG is quantified as standardised uptake value (SUV), which may be expressed as the voxel maximum (SUV$_{\text{max}}$) or mean (SUV$_{\text{mean}}$). SUV$_{\text{max}}$/SUV$_{\text{mean}}$ may be a marker of hepatic steatosis, while the
coefficient of variation (CV) of SUV may be a marker of hepatic fat distribution heterogeneity (HFDH). Alternatively, they may reflect low signal-to-noise ratio (‘noise’) in obese persons in whom hepatic steatosis is common. The study aim was to compare the impact of body size on noise versus SUV and CT density (CTD).

**Methods:** Dynamic PET was performed (30x1 min frames) following FDG injection in 60 patients undergoing routine PET/CT. Hepatic FDG clearance was measured using Patlak-Rutland graphical analysis with abdominal aorta as input. Noise was quantified as the standard deviation (SD) of the plot residuals (ignoring the first 2 frames), normalised to the intercept (NRMSD). SUV$_{max}$, SUV$_{mean}$ and CTD were measured from 60 min whole body PET/CT. CV of SUV and SD of CTD were quantified in 28/60 patients using texture analysis.

**Results:** NRMSD correlated with weight ($r=0.49; p<0.0001$) and BMI ($r=0.48; p=0.0001$). SUV$_{max}$, SUV$_{mean}$, SUV$_{max}$/SUV$_{mean}$, CV of SUV, CTD, and SD of CTD all correlated strongly with weight and BMI ($p<0.0001$). However, they correlated weakly with NRMSD, the strongest being SUV$_{max}$ ($r=0.34; p=0.008$) and SD of CTD ($r=0.42; n=28; p=0.026$).

**Conclusions:** Noise is increased in overweight/obese persons but has little effect on SUV indices, CTD and their variabilities. SUV$_{max}$/SUV$_{mean}$ and CV of SUV are therefore, to some extent, markers of hepatic steatosis and HFDH, respectively.

**Key words:** signal-to-noise ratio; FDG; PET/CT; standardised uptake value; obesity

**INTRODUCTION**

There have been several studies on the advantages and disadvantages of different ways of quantifying tissue $^{18}$F-FDG accumulation on PET/CT, including glucose
utilization rate (MRglu) [1-3], FDG clearance [4-6] and standardized uptake value (SUV) [7-9]. The most widely used parameter is SUV, which is the tissue FDG concentration per unit of administered FDG. It is multiplied by a metric of whole body size, usually body weight, to account for the dilution of FDG throughout its whole body distribution volume. SUV can be expressed as the mean of voxel values in a region of interest (SUV\text{ave}) or as the maximum voxel value (SUV\text{max}).

There has been recent interest in FDG accumulation in the liver. The liver is used as a reference region for the quantification of tumour FDG uptake, especially adrenal glands [10] and lymphoma [11] and the validity of the liver for this, especially when it is pathologically fatty, has been studied [12-15]. There is also interest in the use of FDG for studying glucose metabolism in hepatic steatosis [16] and for diagnosing hepatic inflammation, such as in steatohepatitis [15].

SUV faces problems with respect to the liver as a result of spurious correlations arising from multiple inter-correlations that exist between hepatic steatosis, blood glucose level and body habitus because patients with hepatic steatosis tend to have high blood glucose and be obese [17,18]. Moreover, it has been suggested that SUV calculated using weight is overestimated in obese persons because comparatively little FDG enters adipose tissue and lean body mass (LBM) has been proposed as a better alternative [19,20]. Hepatic SUV also correlates with blood glucose in a rather complex non-linear fashion [21].

Another concern is that signal-to-noise ratio may be reduced in obese persons. It is thought that SUV\text{max} is particularly susceptible to noise because it is based on a single
voxel, while $\text{SUV}_{\text{mean}}$ is less susceptible [9,22]. This implies that $\text{SUV}_{\text{max}}/\text{SUV}_{\text{mean}}$, which has been proposed to be a marker of hepatic fat [17], would also be susceptible to noise. The regional variability of SUV has been proposed as a possible marker of hepatic fat heterogeneity but again may also simply be determined by noise [23].

The aim of this study, therefore, was to examine the associations of CT density and SUV indices, and their regional variabilities, with signal-to-noise ratio in FDG PET/CT.

**METHODS**

**Patients**

Sixty patients having routine clinically indicated FDG PET/CT for the management of cancer agreed to undergo dynamic imaging in addition to their routine clinical study. Patients with focal liver pathology identified on PET/CT were excluded. Body mass index (BMI) was calculated as weight/height$^2$ and LBM from height, weight and gender using the equations of Boer [24].

All patients gave informed consent for the dynamic study, which is not part of our routine scanning protocol, and for use of their routine 60 min data. The study was approved by a local institutional review board.
Imaging

Whole body imaging

All patients had routine whole-body PET/CT 60 min post-injection of ~400 MBq FDG. Patients fasted for 6 h before FDG injection. Blood glucose was measured using a glucometer (ACCU-CHEK Performa; Inform ll strips; USA).

A Siemens Biograph 64-slice PET scanner, with immediate non-enhanced CT scanning (120 Kvp/50 mA - Care dose 4D; slice 5 mm; pitch 0.8; rotational speed 0.5/sec), was used to cover the area from the orbital margin to the lower trochanters. Arms were up, as arms down may result in artificial elevation of the liver FDG signal due to beam-hardening effects. 3D emission data were then acquired at 3 min per bed position (PET reconstruction: 4 iterations; subset 8; Gaussian pre-filter; FWHM 5 mm; matrix size 168x168; zoom 1).

Dynamic imaging

In addition to their routine imaging, patients consented to additional dynamic imaging at one frame per min for 30 min starting immediately following FDG injection in a single bed position with detectors over the torso. CT was switched off so that there was no additional radiation dose over and above that indicated for the routine clinical study.

Image analysis

Whole body imaging

SUV\text{max}, SUV\text{mean} and CT density were measured from a 3 cm region of interest over the right lobe of the liver. In 28 of the 60 patients, texture analysis of the liver was
performed on the routine 60 min PET and CT scans from large volumes of interest (ranging from 160 – 1300 voxels) using in-house software implemented under MATLAB (The MathWorks Inc.) for measurement of the coefficient of variation (CV) of SUV and the standard deviation (SD) of CTD.

*Dynamic imaging*

Images were analysed using *HERMES* software. Hepatic FDG clearance was measured using Patlak-Rutland graphical analysis [5,25]. Hepatic activity was summed from regions of interest (ROI) of 3.0 cm diameter over the right lobe on about 20 transaxial images. Blood pool activity was obtained similarly from ROIs of 1.6 cm diameter on about 20 transaxial images of the abdominal aorta.

The gradient of the Patlak-Rutland plot, which reflects the rate of FDG phosphorylation, is proportional to FDG clearance. The intercept is proportional to the distribution volume of FDG [4,25] with identical proportionality constants relating slope to clearance. The first 2 frame values, during which mixing of tracer between blood and hepatic tissue distribution volume was assumed to take place, were not included in the analysis.

The correlation coefficient of the Patlak-Rutland plot (R\textsubscript{P-R}) was recorded. ‘Noise’ was quantified from the Patlak-Rutland plot as the standard deviation (SD) of the residuals of the points and calculated from the following equation.

\[
\text{SD} = \left(\frac{\sum \text{residual}^2}{[28-1]}\right)^{0.5}
\] (12.1)
where the residual is the y value at any time, t, minus the regression line y value at the same time (Fig 1). The SD was then normalised by dividing it by the intercept of the plot to give the ‘normalised root mean standard deviation’ (NRMSD) or ‘noise’. Examples of Patlak-Rutland plots with high noise and low noise are shown in Fig 1.

RESULTS

1. Correlations of NRMSD with whole body metrics, $R_{P-R}$ and administered activity

Mean NRMSD was 0.081 (SD 0.032). NRMSD correlated with weight ($r = 0.49; p < 0.0001$), BMI ($r = 0.48; p = 0.0001$) and LBM ($r = 0.41; p = 0.001$) (Table 1), suggesting that noise is increased in large persons. NRMSD showed no significant correlation with administered activity ($r = -0.02$) or $R_{P-R}$ ($r = -0.08$). Dividing weight by administered activity did not increase its correlation with NRMSD ($r = 0.47$). $R_{P-R}$ did not correlate with weight ($r = 0.14$) or BMI ($r = -0.07$).

2. Correlations of SUV indices and CT density with whole body size metrics

$SUV_{max}/SUV_{mean}$ correlated with CT density ($r = 0.42; n = 60; p = 0.008$), suggesting that it is a measure of hepatic fat, as suggested previously [21]. The CV of SUV correlated with CT density ($r = 0.46; n = 28; p = 0.014$). It also correlated strongly with the SD of CT density ($r = 0.75; p < 0.0001$), suggesting that both these variabilities may be markers of hepatic fat distribution heterogeneity [23]. $SUV_{max}/SUV_{mean}$, CT density, CV of SUV and SD of CT density all correlated strongly with weight, BMI and LBM (Table 1). The correlations of $SUV_{max}$ and $SUV_{mean}$ with weight were also both strong ($r = 0.69$ and 0.50 [$p < 0.0001$], respectively; Table 2), but this would be expected as both are calculated using weight.
3. Correlations of NRMSD with SUV indices and CT density

In contrast to their correlations with whole body size metrics, SUV_{max}/SUV_{mean} (r = 0.24; p = 0.045), CT density (r = -0.24; p = 0.065), CV of SUV (r = 0.33; n = 28; p = 0.086) and SD of CT density (r = 0.42; n = 28; p = 0.026) all showed weak or insignificant correlations with NRMSD (Table 2). SUV_{max} correlated more strongly with NRMSD (r = 0.34; p = 0.008) than SUV_{mean}, which showed a weak correlation with NRMSD (r = 0.26; p = 0.045), consistent with the notion that SUV_{max} is more susceptible to noise than SUV_{mean}.

DISCUSSION

Body habitus has a significant association with the signal-to-noise ratio expressed in terms of the scatter of data points around the regression line of the Patlak-Rutland suggesting that signal-to-noise ratio is decreased in large persons.

There are several patient-related issues that could influence signal-to-noise ratio. The first is the administered activity of FDG. Surprisingly this did not correlate with NRMSD, perhaps because the range of administered activities was quite narrow. The second is body size and more specifically the whole body volume throughout which FDG is distributed and diluted. There is evidence to suggest that the distribution space is closer to LBM than body weight [19]. Thirdly, the size of the individual determines the mean path length of photons from the aorta and liver to the detector. Thus, photon attenuation will be greater in large individuals. The distance in water over which 511 keV photons lose 50% of counts by attenuation (‘half distance’, analogous to half life) is 7.3 cm. So increased abdominal girth could have a significant impact on the count
density. Fourthly, patient movement would also decrease signal-to-noise ratio but would not be expected to correlate with body size indices so should play no role in determining the influence of body size on NRMSD.

With regard to the interpretation of the correlations of NRMSD with SUV indices and CT density and their variabilities, a critical assumption in this study is that if there is increased noise in the dynamic study, there will also be increased noise in the static study. This is a reasonable assumption if the principal determinant of noise is body size and is supported by the finding of a significant correlation between SUV$_{\text{max}}$ and NRMSD. Thus, as it is based on a single voxel, SUV$_{\text{max}}$ is thought to be more susceptible to noise than SUV$_{\text{mean}}$. The correlation of noise with SUV$_{\text{max}}$, however, may be the result of the respective correlations of weight with SUV indices (which are calculated using weight) and NRMSD with weight, except a non-significant correlation was seen between SUV$_{\text{mean}}$ and NRMSD.

Previous studies have shown that SUV$_{\text{max}}$/SUV$_{\text{mean}}$ correlates with CT density [21,23]. Presumably FDG does not enter hepatic fat so SUV$_{\text{max}}$ will be based on a relatively fat-free voxel in contrast to SUV$_{\text{mean}}$, which will be ‘diluted’ by hepatic fat. It was therefore suggested that the ratio is a measure of hepatic fat [21]. An alternative explanation for the correlation of SUV$_{\text{max}}$/SUV$_{\text{mean}}$ with CT density is low signal-to-noise ratio in patients with fatty liver who tend to be large. Accordingly, SUV$_{\text{max}}$/SUV$_{\text{mean}}$ correlated moderately strongly with weight. However, it correlated weakly with NRMSD. If the correlation of the ratio with weight was the result of patient-related noise, it would have been expected to correlate more strongly with NRMSD.
A previous study raised the possibility that the variabilities of SUV\textsubscript{max}/SUV\textsubscript{mean} and CT density are markers of hepatic fat heterogeneity [23]. The close correlations between CV of SUV and SD of CT density and between both of these variabilities and body size metrics is consistent with this claim, although, as with SUV\textsubscript{max}/SUV\textsubscript{mean}, these correlations may be the result of high body size. But again, as with SUV\textsubscript{max}/SUV\textsubscript{mean}, if they were the result of patient-related noise, they would be expected to correlate more closely with NRMSD. The correlation between CV of SUV and mean CT density is therefore likely, at least partly, to be the result of hepatic fat heterogeneity in hepatic steatosis.

The absence of correlation between NRMSD and R\textsubscript{P-R} can be explained by the fact that unlike R\textsubscript{P-R}, NRMSD is not influenced by the gradient of a regression. In contrast, R\textsubscript{P-R} tends to increase with regression slope gradient. For example, with a gradient of zero, the correlation coefficient will be zero. If all the residuals were all zero, then NRMSD would also be zero.

In conclusion, we have used scatter in the Patlak-Rutland plot to assess signal-to-noise ratio, which appears to be increased in heavy persons. The study supports the notion that SUV\textsubscript{max}/SUV\textsubscript{mean} is a marker of hepatic fat. Although CV of SUV and SD of CT density are susceptible to noise, they are at least partly markers of hepatic fat distribution heterogeneity. Correcting them for the effects of noise would nevertheless be desirable if they were to be used as such markers.

**CONFLICT OF INTEREST**

All authors declare no conflicts of interest
REFERENCES


20. Tahari AK, Chien D, Azadi JR, Wahl RL. Optimum lean body formulation for
Sep;55(9):1481-4

associated with increased hepatic FDG uptake. Eur J Radiol 2014;83:751-5

22. Vanderhoek M, Perlman SB, Jeraj R. Impact of the definition of peak
standardized uptake value on quantification of treatment response. J Nucl Med
2012;53:4-11

23. Keramida G, Hunter J, Dizdarevic S, Peters AM. Heterogeneity of intrahepatic
fat distribution determined by $^{18}$F-FDG PET and CT. Ann Nucl Med (in press)

24. Boer P. Estimated lean body mass as an index for normalization of body fluid

Figure 1. Examples of Patlak-Rutland plots showing high signal-to-noise ratio (upper panel, NRSMD = 0.125; R_{P-R} = 0.63) and low signal-to-noise ratio (lower panel; NRSMD = 0.035; R_{P-R} = 0.95). Vertical lines illustrate residuals.
**TABLES**

**Table 1.** Correlation coefficients (p) of relationships of NRMSD, SUV indices and CT density with metrics of whole body size.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Weight</th>
<th>BMI</th>
<th>LBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRMSD</td>
<td>60</td>
<td>0.49</td>
<td>0.48 (0.0001)</td>
<td>0.41 (0.001)</td>
</tr>
<tr>
<td>SUV_mean</td>
<td>60</td>
<td>0.50</td>
<td>0.59</td>
<td>0.27 (0.04)</td>
</tr>
<tr>
<td>SUV_max</td>
<td>60</td>
<td>0.69</td>
<td>0.76</td>
<td>0.47 (0.0002)</td>
</tr>
<tr>
<td>SUV_max/SUV_mean</td>
<td>60</td>
<td>0.55</td>
<td>0.56</td>
<td>0.48</td>
</tr>
<tr>
<td>CT density</td>
<td>60</td>
<td>0.52</td>
<td>0.40 (0.002)</td>
<td>0.49</td>
</tr>
<tr>
<td>CV SUV</td>
<td>28</td>
<td>0.85</td>
<td>0.78</td>
<td>0.80</td>
</tr>
<tr>
<td>SD CT density</td>
<td>28</td>
<td>0.67 (&lt;0.0001)</td>
<td>0.71</td>
<td>0.56 (0.002)</td>
</tr>
</tbody>
</table>

**Table 2.** Correlation coefficients (p) of relationships of SUV indices and CT density with NRMSD

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>NRMSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV_mean</td>
<td>60</td>
<td>0.26 (0.045)</td>
</tr>
<tr>
<td>SUV_max</td>
<td>60</td>
<td>0.34 (0.008)</td>
</tr>
<tr>
<td>SUV_max/SUV_mean</td>
<td>60</td>
<td>0.24 (0.065)</td>
</tr>
<tr>
<td>CT density</td>
<td>60</td>
<td>0.24 (0.065)</td>
</tr>
<tr>
<td>CV of SUV</td>
<td>28</td>
<td>0.33 (0.086)</td>
</tr>
<tr>
<td>SD of CT density</td>
<td>28</td>
<td>0.42 (0.026)</td>
</tr>
</tbody>
</table>