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Can The Inflammatory Response Be Evaluated Using 18F-FDG Within Zones of Microvascular Obstruction Following Myocardial Infarction?

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Can The Inflammatory Response Be Evaluated Using 18F-FDG Within Zones of Microvascular Obstruction Following Myocardial Infarction?

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Short Running Title – ¹⁸F-FDG Uptake in Infarcted Myocardium
Abstract

Inflammation that occurs following acute myocardial infarction plays a pivotal role in "healing" by facilitating the creation of a supportive scar. $^{18}$F-FDG, which is taken up avidly by macrophages, has been proposed as a marker of cell-based inflammation. However, its reliability as an accurate indicator of inflammation has not been established, particularly in the early post infarction period when regional myocardial perfusion is often severely compromised.

Methods: Nine adult dogs underwent left anterior descending coronary occlusion with or without reperfusion. Animals were imaged between 7 to 21 days post infarction with Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI) following: a) bolus injection of Gd-DTPA, b) bolus injection of $^{18}$F-FDG, c) bolus injection of $^{99}$Tc-DTPA to simulate the distribution of Gd-DTPA (which represents its partition coefficient in well perfused tissue) and d) the injection of $^{111}$Indium-labeled white blood cells 24 hours earlier. Following sacrifice, myocardial tissue concentrations of $^{18}$F, $^{111}$In and $^{99}$Tc were determined in a well counter. Linear regression analysis evaluated the relationships between a) the concentrations of $^{111}$In vs $^{18}$F and b) the dependence of the ratio of $^{111}$In/$^{18}$F to the apparent distribution volume of $^{99m}$Tc-DTPA.

Results: In seven of the nine animals $^{111}$In increased as $^{18}$F increased with the other two animals showing weak negative slopes. With respect to the dependence
of $^{111}\text{In}/^{18}\text{F}$ with partition coefficient four animals showed no dependence and four showed a week positive slope with one animal showing a negative slope. Further, in regions of extensive microvascular obstruction, $^{18}\text{F}$ significantly underestimated the extent of the presence of $^{111}\text{In}$.

Conclusions: In the early post myocardial infarction period, PET $^{18}\text{F}-\text{FDG}$ imaging following a single bolus administration may underestimate the extent and degree of inflammation within regions of microvascular obstruction.

**Keywords**

Myocardial infarction, myocardial inflammation, PET/MRI, $^{18}\text{F}-\text{FDG}$, $^{111}\text{In}$ labelled white blood cells, late gadolinium enhancement (LGE)
There has been significant effort to develop non-invasive imaging methods to quantify in time and location the inflammatory response after myocardial infarction towards the goal of potentially intervening with therapies that may prevent or limit the degree of adverse left ventricular remodelling. The goal of understanding the role of the inflammatory response in the progression of myocardial remodelling is not new (1) but to date, the techniques have been crude, and limited in both spatial and temporal resolution.

Whereas the uptake of $^{18}$F-FDG in regions of recent myocardial infarction was found to be an unreliable indicator of myocardial viability, recent studies have suggested that the uptake of $^{18}$F-FDG by macrophages could be used to identify the degree and extent of myocardial inflammation in the early post-infarction period. Here we have focussed on validating the reliability of $^{18}$F-FDG as a marker of post-infarction inflammation, particularly in light of the markedly compromised flow in areas of recently infarcted myocardium. Adding another layer of complexity to the use of $^{18}$F-FDG in this setting is the need to suppress competing uptake in the normal myocardium and its non-specificity with respect to inflammation cell type (2,3). Despite these limitations, the combination of PET and MRI imaging in one device, hybrid PET/MRI, would allow one to serially track in three dimensions the relationships between scar and macrophage-based inflammation using late gadolinium enhancement (LGE) and $^{18}$F-FDG.
respectively. The potential role of this approach to assess myocardial scar and inflammation has already been shown in another disorder associated with inflammation (sarcoidosis (4)).

Here, using both in vivo imaging, and ex vivo tissue analysis, we have investigated in a well characterized canine model of myocardial infarction the uptake of $^{18}$F-FDG into infarcted myocardium and its distribution into the central core areas of microvascular obstruction (MO) in comparison to the distribution of $^{111}$Indium-labeled white blood cells.

**MATERIALS AND METHODS**

**Animals and Surgical Preparation**

The study was approved by the Animal Care Committee of the University of Western Ontario (Animal Use Protocol 2011-67).

Nine 19 – 24 kg adult female bred-for-research hounds were used. Anesthesia was induced using Propofol and maintained with isoflurane (2%). Following a left thoracotomy, a myocardial infarction was induced by placing a snare ligature around the left anterior descending coronary artery. In five animals, this snare was released after 3 hours while in four it was left in place for the duration of the study. Animals underwent PET/MRI imaging at a single imaging session in both the occlusion reperfusion group (OR) at 7, 7, 13, 14 and 20 days
and the permanent occlusion group (PO), at 7, 8, 13 and 13 days. The imaging protocol involved simultaneous cardiac magnetic resonance (CMR) and PET.

\textbf{\textsuperscript{18}F-FDG PET Imaging}

Suppression of normal myocardial uptake of FDG was accomplished by modification of the techniques used to highlight inflamed coronary plaques, and for imaging patients with suspected sarcoidosis (4-8). An infusion of 20% lipid (Intralipid, Baxter Healthcare Corporation) at a rate of 0.25 ml/min/kg was administered intravenously over a 50 minute period, beginning 20 minutes prior to FDG injection. In addition, 2000 units of heparin were given intravenously immediately prior to the lipid infusion to further suppress glycolysis and the animals fasted between 16 and 21h before the start of imaging (7,8). All dogs were fed a normal diet. This myocardial suppression protocol was validated prior to the current study in three non-infarcted animals. These were compared with and without intralipid with either a normal diet or a high fat diet. Measurements of Standardized Uptake Values (SUV) max were taken in the left ventricular wall. Significance was tested using a one-tailed paired t-test with p set at 0.05.

Animals were anesthetized and transferred to the PET/MRI (Biograph mMR (Siemens AG,)). An intravenous injection of \textsuperscript{18}F-FDG (250-300 MBq) was given and data collected for 70 min in list mode. Attenuation correction was
performed using segmentation of images obtained with a 2-point Dixon MRI pulse sequence. In the last 10 min of this $^{18}$F-FDG acquisition three-dimensional (3D) LGE MRI data was acquired. Retrospective binning of data was done to 6 cardiac phases. PET data was reconstructed using an iterative 3D ordered subset expectation maximization (OSEM) method using 3 iterations and 21 subsets, a zoom factor of 2.5, 344 x344 x127 matrix size and a 2mm Gaussian smoothing filter. Voxel size with these parameters was 0.83mm x 0.83mm x 2.03mm. After the animal was euthanized while in the scanner, and without being moved, a further 10 minute PET acquisition was collected.

**CMR Imaging**

CMR was initiated at the start of the intralipid infusion. Using Siemens works-in-progress software, a single slice multi echo T2* map was acquired to estimate the presence of hemorrhage (single breath hold, ECG-triggered, multi-echo gradient echo (GRE) sequence, 8 images per slice with echo times (TE) of 2.5, 4.8, 7.1, 9.5, 11.8, 14.2, 16.5 and 18.9 ms, TR = 467 ms, 2 averages, 3.5 mm slice thickness, 192 x 156 matrix resulting in the voxel size of 1.35 mm x 1.35 mm in plane x 3.5mm nominal slice thickness). Due to cardiac motion only the first 5 echoes were used to estimate presence of susceptibility which is consistent with hemorrhage. A bolus of 0.2 mmol/kg gadolinium contrast (Magnevist®, Bayer Inc.,) was infused at 0.3 ml/sec followed by a 40 ml saline infusion. Twenty minutes following the bolus infusion, a respiratory and cardiac gated 3D
whole heart inversion recovery gradient echo pulse sequence was acquired as previously described (4,9) using an integrated parallel acquisition technique fat supressed isotropic/voxel size 1 x 1 x 1 mm, (TE= 1.3ms, 20° flip angle, and variable inversion times to suppress signal in non-infarcted myocardium). The animal was then euthanized and the whole heart inversion recovery gradient echo sequence was repeated while the 3D 10 min $^{18}$F-FDG images were acquired.

The timing of the entire experimental protocol is shown in Figure 1.

**Image Processing**

The 3D LGE images taken in the live animal following the Gd-DTPA injection were processed for the size in grams of the region of MO. Sequential short axis LGE images underwent signal-threshold based quantification to total hyper enhance volume reported in grams using a Signal Threshold versus Reference Mean technique (9).

**In Vitro Tissue Counting**

After euthanasia, the hearts were excised and cut into 7 slices (base to apex). The slices were washed and visually examined for evidence of hemorrhage and scored them as 4 for severe to 1 for non-existent. With the post mortem 3D $^{18}$F-FDG and LGE images used as a guide, the myocardial tissue was segmented into an average of 107 (range 93 to 123) samples with average weight of 0.71g (SD = 0.18g).
Blood samples were taken; the white blood cells isolated and then labelled with $^{111}$In-Oxine (Cardinal Health) using standard methods (10). Labelled cells were injected between 21 and 28 hours prior to the start of imaging.

Six minutes after the bolus injection of Gd-DTPA, a bolus injection of $^{99m}$Tc-DTPA was given to allow for ex vivo measurement of the concentration of a tracer that would simulate the tissue distribution of Gd-DTPA (11). Upon euthanasia, ten one ml blood samples were taken so that partition coefficients for $^{99m}$Tc-DTPA for heart tissue could be calculated as $^{99m}$Tc activity per gram of myocardium divided by $^{99m}$Tc activity per ml of blood. That the partition coefficients ($\lambda$) of $^{99m}$Tc-DTPA and Gd-DTPA (Magnevist) are related in heart tissue (11):

$$\lambda_{Gd-DTPA} = 1.094 \times \lambda_{^{99m}Tc-DTPA}$$

Eq. 1

Tissue and blood samples were counted for $^{18}$F, $^{99m}$Tc and $^{111}$In in a high purity germanium well counter having an active volume of 190cc, an efficiency of greater than 10% and a spectral resolution of less than 2 keV over the range of energies (140 to 511 keV) being detected. Each sample was counted for 2 min with counts corrected for detector dead time and radioisotope decay. The tissue samples were separated into two groups. Group 2 corresponded to tissue with concentration at least 1SD below the mean $^{18}$F concentration. These tissue
samples generally had been taken from regions where MO was demonstrated on
the Gd-DTPA enhanced images. For all other samples it was assumed they came
from tissue that was not so affected. Results for each sample were tabulated as
$^{111}\text{In (cps/g)}$ vs. $^{18}\text{F (cps/g)}$ and as the ratio of $^{111}\text{In}$ to $^{18}\text{F}$ as a function of

$\lambda^{\text{heart}}_{\text{Tc-DTPA}}$.

**Statistical Analysis**

The results from the tissue counting for group 1 were fit by linear
regression (SigmaPlot© 13 by Systat Software Inc.). For each dog’s data two
regressions were fit for the non-microvascular obstruction data one to $^{111}\text{In (cps/g)}$
vs. $^{18}\text{F (cps/g)}$ and one to the ratio of $^{111}\text{In}$ to $^{18}\text{F}$ vs. $\lambda^{\text{heart}}_{\text{Tc-DTPA}}$.

**RESULTS**

In the preliminary experiments evaluating myocardial suppression of $^{18}\text{F}$-
FDG uptake there was a significant drop in SUV max when intralipid was
administered independent of diet ($p=0.02$) and when animals were given a normal
diet ($p=0.0084$) but no significant effect of intralipid when a high fat diet was
given ($p=0.24$). Hence it was decided to use intralipid infusion and not to use a
high fat diet. Note for all these experiments animals were injected with 2,000 IU
of heparin (7) as others have demonstrated the combination of heparin and
intralipid as effective (8).

The experimental parameters, except for $^{111}\text{In}$ labelling efficiency, were
consistent for all the animals while the variation of extensiveness of myocardial
injury varied from mild to severe (Table 1). The linear regression analysis shows an expected relationship between $^{111}\text{In}/g$ vs. $^{18}\text{F}/g$ consistent with $^{18}\text{F}$-FDG representing inflammation in seven of the nine dogs however in only four of these seven was the relationship independent of the partition coefficient (Table 2). Subject OR4 (14 day) images showed a sub-endocardial infarct without evidence of MO and limited evidence of hemorrhage (Figure 2). The tissue analysis for this animal (Figure 3) demonstrates that there was a significant positive slope between $^{111}\text{In}$ and $^{18}\text{F}$ concentrations. Also, the ratio of $^{111}\text{In}$ to $^{18}\text{F}$ was constant (that is independent) of the $^{99m}\text{Tc}$-DTPA partition coefficient. Images for PO1 (7 day) show a large area of microvascular obstruction (Figure 4) with the corresponding tissue analysis (Figure 5) showing a significant negative slope of $^{111}\text{In}$ to $^{18}\text{F}$ and that the ratio of $^{111}\text{In}$ to $^{18}\text{F}$ significantly increases as the partition coefficient increases.

Single slice T2* weighted images for OR4 (Figure 6) show little to no hemorrhage although visual evaluation of excised heart slices showed mild hemorrhage present (Table 1). T2* weighted images for PO1 (Figure 7) provide evidence of significant hemorrhage supported by visual inspection of the excised heart (Table 1). Results for the other 7 animals fall between what is seen in these two animals which represent the extremes. In all of the other animals but one (OR5; at 20 days) the concentration of $^{111}\text{In}$ increased as $^{18}\text{F}$ increased. With respect to the dependence of $^{111}\text{In}/^{18}\text{F}$ to partition coefficient three were similar to
OR4 (Fig. 3) with zero slope while four showed a significant positive slope and one showed a significant negative slope.

DISCUSSION

If $^{18}$F-FDG was strictly a measure of inflammation it is expected that there would be a) a strong positive linear regression between the tissue concentration of $^{111}$In and $^{18}$F and b) that there would be no dependence on the ratio of $^{111}$In/$^{18}$F to the partition coefficient of DTPA. As seen for subject PO1 in Figures 4 and 5 this clearly cannot be assumed in tissue with MO. At the minimum values of the partition coefficient, this ratio increases seven fold suggesting that in the region of MO (reduced apparent partition coefficient), there were $^{111}$In labelled white blood cells but little $^{18}$F consistent with the post mortem images of $^{18}$F distribution. Furthermore the pattern shown in Fig 3, which is the desired pattern if $^{18}$F-FDG represents inflammation in the cardiac supressed tissue post MI, is not necessarily the pattern seen even in tissue that is reasonably well perfused i.e. that does not have evidence of MO. Our results are mixed with clear evidence that the uptake of $^{18}$F-FDG may be at variance with the degree of inflammation as measured with $^{111}$In labelled white blood cells after myocardial infarction.

In 7 of the 9 animals $^{111}$In cps/g increased linearly as the $^{18}$F cps/g increased, suggesting that in these animals, $^{18}$F-FDG was increasing as the number of white blood cells was increasing. However in only four of these animals were the $^{111}$In/$^{18}$F ratio independent of the partition coefficient in non-
MO tissue. In the other three animals the slope was significantly positive in two and negative in one; indicating that although $^{18}$F was increasing as $^{111}$In the ration was not independent of $\lambda^{heart}_{99mTc-DTPA}$. That is, $^{18}$F-FDG was underestimating in two and overestimating in one the number of inflammatory cells.

The potential explanations for this disconnect between Indium concentrations, reflective of the presence of inflammatory cells injected back into circulation one day earlier, and the $^{18}$F-FDG concentrations in myocardial tissue may be due to the markedly compromised perfusion to the MO zone reducing the availability of $^{18}$F-FDG to inflammatory cells. Following a single bolus injection, the concentration of $^{18}$F-FDG rapidly declines. In the setting of markedly reduced flow, there may have been insufficient opportunity for inflammatory cells to take up the tracer, whereas Indium-labelled white blood cells had been circulating between 21 and 28 hours prior to animal sacrifice and tissue harvesting. In contrast, in areas of infarction where perfusion is not severely compromised, our results indicate that although $^{18}$F-FDG accumulation increases as $^{111}$In increases it may not increase proportionately hence suggesting that the use of $^{18}$F-FDG imaging in these areas must be interpreted as a non-quantitative indicator of the degree of inflammatory cell activity.

One potential limitation of our study relates to the validity of the measurement of $\lambda^{heart}_{99mTc-DTPA}$ as an indication of the value of $\lambda^{heart}_{Gd-DTPA}$. This is
because the $^{99m}$Tc-DTPA injection into the live animal was on average 6 min (range 5 – 7 min) after the Gd-DTPA injection. Hence $^{99m}$Tc-DTPA had 6 min less time to penetrate areas of MO. This could have resulted in an underestimation of the partition coefficient in some infarcted tissue samples.

A limitation of our work relates to the interpretation of the results given the potential difference between the nature of the white blood cells labelled with $^{111}$In that accumulate in the infarct region and normal myocardium versus those that take up $^{18}$F-FDG. There is evidence in dogs that neutrophil density peaks in reperfused infarcted myocardium within one day with very low concentrations by day 7 whereas macrophage concentration peaks around 7 days post infarction (12). As in blood the number of neutrophils exceeds the number of monocytes by a factor of approximately ten it is difficult to conclude what fraction of the labelled white blood cells in the infarcted myocardium are $^{111}$In labelled neutrophils and/or $^{111}$In labelled monocytes. This is further confounded as it is generally assumed that monocytes are transformed to macrophage (2) and then replicate and accumulate in the infarct region. These transformed monocytes, even if still labelled with $^{111}$In, would have the amount of label per cell diluted during replication. In addition we do not know to what extent neutrophils within the region of MO would be labelled by $^{18}$F-FDG as well as macrophages. Adding to this is the growing evidence that an appreciable fraction of the macrophages
that accumulate in the infarcted region may not be transformed monocytes but rather resident macrophages in the myocardium \((13,14)\).

The study design could have been improved by measuring blood flow using microspheres in the tissue samples. However the absence of MRI contrast after a bolus injection has become an accepted, albeit qualitative, standard. Note that we have characterized tissue blood flow in these two animal models using microspheres in the past \((15,16)\).

Although we have followed in detail \(^{111}\)In-Oxine labelling of white blood cells \((10)\) we achieved lower than normal labelling efficiencies. As the greatest discrepancy between the \(^{111}\)In counts and \(^{18}\)F counts were in subject PO1 which had the highest labelling efficiency of 83% we do not believe that the low labelling efficiencies affected the conclusions drawn from our results.

**CONCLUSION**

Our results suggest some limitations regarding the use of a bolus injection of \(^{18}\)F-FDG to study the inflammatory process after myocardial infarction even when active uptake of \(^{18}\)F-FDG in normal myocardial tissue is suppressed. In the presence of large regions of MO, \(^{18}\)F-FDG may not reliably and accurately represent the degree of inflammatory cell activity possibly due to compromised delivery. Further, even in areas of infarction without MO, the degree of
inflammation may be underestimated or even overestimated the reasons of which remain, at this time, unknown.

DISCLOSURES

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References


Fig. 1: The timing of the entire experimental protocol.
Figure 2

**Fig. 2:** Post mortem MRI (A), PET (B) and PET/MRI (C) images of subject OR4 14 days. The MR image demonstrates an antero-apical subendocardial infarct. The increased activity of 18F-FDG in the chest wall in the PET image is at the site of surgery.
Figure 3

Fig. 3. Quantitative analysis of the tissue samples for the same subject as shown in Fig. 2 (i.e. OR4). The regression of $^{111}$In vs. $^{18}$F was strong and the slope significantly positive (A – upper). The regression of $^{111}$I/$^{18}$F vs. the $\lambda_{99mTc-DTPA}$ was very weak and the slope was not significant indicating that $^{111}$I/$^{18}$F ratio was independent of $\lambda_{99mTc-DTPA}$ (B – lower).
Fig. 4: Post mortem PET/MRI images of subject PO1 (7 days). The antero-apical infarct is transmural with a large central MO that is void in both $^{18}$F-FDG and Gd-DTPA but is surrounded by a zone of increased $^{18}$F-FDG and Gd-DTPA.
Figure 5

**A.**

Quantitative analysis of the tissue samples for the same subject as shown in Fig. 4 (i.e. PO1) the regression analysis excluded samples estimated to be from MO tissue (designated as group 2). The regression of $^{111}$In vs. $^{18}$F in A is modest but the negative slope significant. The regression of $^{111}$In/$^{18}$F vs. $^{99m}$Tc-DTPA in B is significant and indicates that as the partition coefficient increases $^{111}$In increases more quickly than $^{18}$F. Note that this ratio is much higher in the MO zone which suggests that $^{18}$F-FDG significantly underestimated the extent of inflammation in this zone.
Figure 6

**Fig. 6**: Gradient echo images (i.e. T2* imaging) of subject OR4 (also featured in Figs. 2 and 3) at echo times of 2.5 ms (A), 9.5 ms (B) and a matched LGE image (C). No evidence of hemorrhage was identified. The white arrow indicates a sub-endocardial infarction. Examination of the tissue and assessment of the LGE images showed no evidence of MO while examination of tissue (Table 1) suggested mild hemorrhage.
Figure 7

**Fig. 7:** Gradient echo images (i.e. T2* imaging) of subject PO1 (also featured in Figs. 3 and 4) at echo times of 2.5 ms (A), 9.5 ms (B) and a matched LGE image (C). The white arrow on B indicates susceptibility indicative of hemorrhage. The white arrow on C indicates a transmural infarct and an associated region of MO. Examination of tissue (see Table 2) from this region indicated significant hemorrhage.
Table 1 – Experimental details and tissue characterization

<table>
<thead>
<tr>
<th>Subject</th>
<th>Imaging Day</th>
<th>PGL MBq</th>
<th>$^{18}$F-FDG MBq</th>
<th>$^{111}$In MBq</th>
<th>$^{111}$In LE</th>
<th>$^{99m}$Tc-DTPA MBq</th>
<th>MO Tissue</th>
<th>MO Volume Images g+*</th>
<th>Hemorrhage**</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR1</td>
<td>7</td>
<td>3.1</td>
<td>259</td>
<td>3.7</td>
<td>13</td>
<td>28</td>
<td>3</td>
<td>5.6</td>
<td>4</td>
</tr>
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<td>OR2</td>
<td>7</td>
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<td>211</td>
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<td>2</td>
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<td>37</td>
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<td>26</td>
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<tr>
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<td>3</td>
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<td>1</td>
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<td>16</td>
<td>52</td>
<td>41</td>
<td>2</td>
<td>1.0</td>
<td>4</td>
</tr>
</tbody>
</table>

PGL = arterial plasma glucose concentration in mmol/L; LE = $^{111}$In white blood cell labelling efficiency; MO = Microvascular obstruction rated from an examination of the post mortem DGE images as large (4), medium (3), small (2) or non-existent (1).

+ Subjects are listed as occlusion type (OR for occlusion reperfusion or PO for permanent occlusion) and day of sacrifice under Imaging Day.

** Sliced excised heart tissue was visually examined to confirm presence or absence of hemorrhage and scored as severe (4) to non-existent (1).

+* The extent of MO in grams was also assessed from the LGE in vivo 3D image.
Table 2

**Regression equations for non-microvascular obstructed tissue** *

<table>
<thead>
<tr>
<th>Subject</th>
<th>$^{111}\text{In}/g$ vs. $^{18}\text{F}/g$</th>
<th>$^{111}\text{In}/^{18}\text{F}$ vs. $\lambda_{99mTc-DTPA}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR1</td>
<td>Slope up + 0.0072 ± 0.0012, R² = 0.279, p &lt; 0.0001</td>
<td>No slope - 0.0027 ± 0.0044, R² = 0.023, p = 0.54</td>
</tr>
<tr>
<td>OR2</td>
<td>Slope up + 0.0064 ± 0.0008, R² = 0.46, p &lt; 0.0001</td>
<td>Slope up + 0.0043 ± 0.0007, R² = 0.31, p &lt; 0.0001</td>
</tr>
<tr>
<td>OR3</td>
<td>Slope up + 0.0029 ± 0.0007, R² = 0.1611, p &lt; 0.0001</td>
<td>No slope + 0.0015 ± 0.0011, R² = 0.02, p = 0.19</td>
</tr>
<tr>
<td>OR4</td>
<td>Slope up + 0.0257 ± 0.0017, R² = 0.724, p &lt; 0.01</td>
<td>No slope - 0.017 ± 0.0022, R² = 0.006, p &gt; 0.05</td>
</tr>
<tr>
<td>OR5</td>
<td>No slope - 0.0001 ± 0.0004, R² = 0.0009, p = 0.78</td>
<td>Slope up + 0.0026 ± 0.0011, R² = 0.06, p = 0.024</td>
</tr>
<tr>
<td>PO1</td>
<td>Slope down - 0.024 ± 0.011, R² = 0.046, p = 0.78</td>
<td>Slope up + 0.047 ± 0.012, R² = 0.141, p &lt; 0.0001</td>
</tr>
<tr>
<td>PO2</td>
<td>Slope up + 0.0182 ± 0.0024, R² = 0.37, p &lt; 0.0001</td>
<td>Slope up + 0.0077 ± 0.0009, R² = 0.39, p &lt; 0.0001</td>
</tr>
<tr>
<td>PO3</td>
<td>Slope up + 0.0186 ± 0.0034, R² = 0.28, p &lt; 0.0001</td>
<td>No slope + 0.0024 ± 0.01, R² = 0.43, p = 0.82</td>
</tr>
<tr>
<td>PO4</td>
<td>Slope up + 0.0819 ± 0.0097, R² = 0.44, p &lt; 0.0001</td>
<td>Slope down - 0.198 ± 0.0164, R² = 0.622, p &lt; 0.0001</td>
</tr>
</tbody>
</table>

* The slope, plus/minus the slope standard error, the square of the correlation coefficient and the significance of the slope obtained from the linear regression analysis is given.

+ “Slope up” indicates that there was significant positive slope. “No slope” indicates the p value for the slope was greater than 0.05. “Slope down” indicates a significant negative slope.
Can The Inflammatory Response Be Evaluated Using $^{18}$F-FDG Within Zones of Microvascular Obstruction Following Myocardial Infarction?

Frank S. Prato, John Butler, Jane Sykes, Lynn Keenliside, Kimberley J. Blackwood, R. Terry Thompson, James A. White, Yoko Mikami, Jonathan D. Thiessen and Gerald Wisenberg

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