The Metabolic Activity of the Spleen and Bone Marrow in Patients with Acute Myocardial Infarction Evaluated by $^{18}$F-FDG PET Imaging

Kim et al.: Activation of the spleen and bone marrow in AMI

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Abstract

Background—Atherosclerosis is considered to be an inflammatory disease associated with the activation of hematopoietic and immune-related organs such as the bone marrow (BM) and spleen. We evaluated the metabolic activity of those organs and of the carotid artery with 18F-FDG PET in patients with coronary artery disease, including acute myocardial infarction (AMI).

Methods and Results—Whole-body combined 18F-FDG PET/CT was performed in 32 patients with AMI, 33 patients with chronic stable angina, and 25 control subjects. The mean standard uptake value (SUV) was calculated in the regions of interest in the spleen and the BM of lumbar vertebrae. The target-to-background ratio (TBR) of the SUVs of the carotid artery and jugular vein was also calculated. In patients with AMI, the SUVs of the BM (1.67±0.16) and spleen (2.57±0.39), as well as the TBR of the carotid artery (2.13±0.42), were significantly higher than the corresponding values of patients with angina (1.22±0.62; 2.03±0.35; 1.36±0.37, all p<0.001) and controls (0.80±0.44; 1.54±0.26; 1.22±0.22, all p<0.001) independent of traditional cardiovascular risk factors and high-sensitivity CRP (hsCRP). In all groups combined, the TBR of the carotid artery was significantly associated with the SUVs of the BM (r=0.535, p<0.001), spleen (r=0.663, p<0.001), and hsCRP (r=0.465, p<0.001).

Conclusions—The metabolic activity of the BM and spleen as well as of the carotid artery was highest in patients with AMI, intermediate in patients with angina, and lowest in control subjects. The activation of the BM and spleen was significantly associated with inflammatory activity of the carotid artery.

Keywords: spleen, bone marrow, coronary artery disease, positron emission tomography

Basic biological and clinical research supports the role of inflammation in the initiation, growth,
and rupture of atherosclerotic plaques. At every stage of atherosclerosis, monocyte-derived macrophages are the principal mediators of inflammation. Recent studies lend some clarity to the role of inflammation in driving the atherogenic response to hypercholesterolemia and suggest that this process is initiated in the bone marrow (BM) and spleen. In response to hypercholesterolemia, both the BM and spleen overproduce inflammatory monocytes that enter the circulation, accumulate in lesions, and differentiate into macrophages.

Acute myocardial ischemic injury and infarction (AMI) activate the sympathetic nervous system and trigger a cascade of hematopoietic stem and progenitor cell (HSPC) proliferation in the BM and emigration to the spleen, as well as peripheral monocytosis. In this process, the spleen acts as an extramedullary hematopoietic reservoir producing inflammatory monocytes that aggravate atherosclerosis. Thus, this inflammatory linkage between the BM, spleen and blood following an acute cardiac event may intensify the chronic inflammatory process involved in atherosclerosis, independently from the primary myocardial wound site. This mechanism of systemic inflammation in atherosclerotic disease initiated by the BM and spleen has been studied in animal models, but not in humans with coronary artery disease (CAD).

Activated inflammatory cells express high levels of glucose transporters and accumulate $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG). For this reason, $^{18}$F-FDG positron emission tomography (PET) is a useful noninvasive imaging technique to evaluate the inflammatory status of atherosclerotic plaques and periodontal disease. Theoretically, the metabolic activity of the BM and spleen can be also evaluated by PET using $^{18}$F-FDG.

This study has 3 objectives: (1) to determine whether the metabolic activation of the BM and spleen is associated with AMI; (2) whether the degree of metabolic activation of these organs is associated with inflammatory activity at carotid plaques remote from the coronary
arteries, and (3) whether the activity in the BM and spleen is higher in patients with chronic stable angina (CSA) than in control subjects. We measured $^{18}$F-FDG uptake in the spleen, BM, and carotid artery using whole-body $^{18}$F-FDG-PET/computed tomography (CT) in patients with AMI, CSA, and control subjects without a history of CAD.

**Methods**

**Study Subjects**

Between June 2008 and March 2009, we prospectively recruited patients at Korea University Guro Hospital who were diagnosed with AMI or CSA. AMI was defined as typical changes in biochemical markers of myocardial necrosis along with at least 1 of the following: ischemic symptoms, electrocardiographic changes indicative of new ischemia, development of pathologic Q waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. CSA was defined as the presence of stable anginal symptoms for at least 6 months with at least 50% luminal narrowing in at least 1 major coronary artery on angiography. Criteria for exclusion from the control group were a history of cardiovascular disease (myocardial infarction, unstable angina, stroke, or cardiovascular revascularization), greater than stage 1 hypertension (resting blood pressure $\geq 160/100$ mmHg), uncontrolled diabetes mellitus (glycated hemoglobin $>9\%$), malignancy, or severe renal or hepatic disease. Subjects with a history of an inflammatory condition, or those taking inflammation-modulating medications within the prior 6 months, were excluded from the study. All participants provided written informed consent and the Korea University Institutional Review Board approved this study protocol.

The following clinical and demographic parameters were recorded: age, sex, body mass index, waist circumference, the presence of hypertension (defined as those taking
antihypertensive medications or ≥2 blood pressure recordings over 140/90 mmHg), the presence of diabetes mellitus (defined as those undergoing treatment with diet and/or medications or a fasting serum glucose >126 mg/dl), and dyslipidemia (defined as those taking lipid-lowering medications or a fasting serum total cholesterol ≥240 mg/dl, triglycerides ≥200 mg/dl, high density lipoprotein cholesterol <40 mg/dl, or low density lipoprotein cholesterol ≥160 mg/dl). Cardiac troponin T and creatine kinase-MB fraction (CK-MB) were measured using electrochemiluminescence immunoassays on the Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, Indiana, USA). Concentrations of troponin T >0.1 ng/mL and CK-MB >6.73 ng/mL in men or >3.77 ng/mL in women were used as cutoff values to diagnose AMI based on the manufacturer’s instructions.

18F-FDG PET/CT Imaging

18F-PET/CT was performed using the Gemini TF 16-Slice PET/CT scanner (Philips Medical Systems, Cleveland, Ohio, USA). Patients diagnosed with AMI, all of whom were successfully treated by primary percutaneous coronary intervention, underwent PET/CT within 10 days of the event when they were clinically stable (mean: 6.3 days; range: 1-10). The TF scanner is a new high-performance, time-of-flight-capable, fully 3-dimensional PET scanner that uses lutetium-yttrium oxyorthosilicate crystals.15 After at least 12 hours of fasting, FDG (5.19 MBq/kg) was injected intravenously, after which patients rested in a quiet room for 60 minutes. In diabetic patients, who may have a different blood clearance from nondiabetic patients, we determined blood glucose level before 18F-FDG administration and changed the PET schedule if it exceeded 180 mg/dl to reduce the metabolic effect on FDG uptake. Whole-body PET images (from below the cerebellum to the inguinal region) were acquired for 10 minutes (1 minute per bed position).
Analysis of Positron Emission Tomography Images

PET images were analyzed on a dedicated workstation (Extended Brilliance Workspace 3.5; Philips). Right carotid FDG uptake was measured along the length of the right carotid vessel, starting at the bifurcation and extending inferiorly and superiorly every 4 mm for a total of 8 consecutive PET/CT images for each subject. Arterial FDG uptake was quantified in the region of interest (ROI) around each artery on every slice of the co-registered transaxial fusion PET/CT images. The highest standard uptake values (SUVs) of the ROIs of all 8 slices within the right carotid artery were averaged together for each subject. Next, the arterial SUV was divided by the blood-pool SUV measured from the jugular vein for normalization. In this way, the arterial target-to-background ratio (TBR) was calculated for each subject. 18F-FDG uptake was measured in the spleen by placing an ROI around the organ on all transaxial slices. The highest SUVs from all transaxial slices were recorded and their average was used as the mean SUV for the entire organ. BM 18F-FDG uptake was calculated under CT-guided anatomical reference from the third to fifth lumbar vertebrae, and the average of the highest SUVs was used as the mean SUV for analysis. To determine the variability of the mean SUV measurements, images from 20 subjects were analyzed twice, several weeks apart, by 2 readers who were unaware of the subjects’ clinical histories. The intra- and inter-observer correlation coefficient values of the mean SUV measurements were greater than 0.9.

Statistical Analysis

Baseline characteristics of the participants were analyzed according to the 3 main study groups. Frequencies and proportions were reported for categorical variables, and either mean ± standard deviation or median with interquartile range were reported for continuous variables based on normality of distribution. The Pearson chi-squared test, Fisher’s exact test, one-way analysis of
variance (ANOVA), and the Kruskal-Wallis test were used to compare variables between groups. Subsequent comparisons were performed by Bonferroni’s post-hoc test, or the Mann-Whitney U-test or Fisher’s exact test with Bonferroni corrected p values. The SUVs of the BM and spleen and the TBRs of the carotid artery were compared between the 3 groups using analysis of covariance (ANCOVA) with Bonferroni multiple comparisons, in which the possible confounding effects of sex, waist circumference, hypertension, diabetes, dyslipidemia, smoking, statin use, and high-sensitivity C-reactive protein (hsCRP) were taken into account by including them in the model as covariates. Spearman correlation analysis was performed to identify the relationship between $^{18}$F-FDG uptake in multiple organs and hsCRP. Multiple linear regression analyses using the TBR of the carotid artery as a dependent variable were also performed to investigate whether there was an independent relationship between $^{18}$F-FDG uptake in each organ and uptake in the carotid artery. Data were analyzed using SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). P-values less than 0.05 were considered statistically significant.

Results

Clinical and laboratory characteristics

The subjects included 51 men (56.7%) and 39 women (43.3%). Women comprised the majority of the control group, while men comprised the majority of the CSA and AMI groups. The mean age of subjects was 57.7±10.1 years, and did not differ significantly between groups. Compared to the control group, most of the traditional cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, and smoking, were more prevalent in the CSA and AMI groups. The prevalence of those risk factors was not significantly different between the CAD groups. Subjects taking statins comprised nearly a third of total subjects in both CAD groups upon initial presentation. There were significant stepwise increases in white blood cell count and hsCRP
from the control group to the AMI group (Table 1).

Comparison of FDG uptake in the bone marrow, spleen, and carotid artery between groups

The mean maximum SUV levels in the spleen and BM were incrementally and significantly higher in the AMI and CSA groups compared to the control group (Table 1, Figure 1A, Figure 2A, and Figure 2B). The AMI group had higher carotid artery TBRs than did the CSA and control groups (Table 1, Figure 1B, and Figure 2C). Although the carotid artery TBR of the CSA and control groups did not differ significantly (Table 1 and Figure 2C), it reached statistical significance after adjusting for sex, waist circumference, hypertension, diabetes, dyslipidemia, smoking, statin use, and hsCRP in ANCOVA analysis (for the carotid artery TBR, AMI vs. CSA group, p<0.001; CSA vs. control group, p=0.038). The SUVs of the spleen and BM were also significantly different between groups after the same adjustments (for spleen SUV, AMI vs. CSA group, p<0.001; CSA vs. control group, p<0.001, for BM SUV, AMI vs. CSA group, p=0.003; CSA vs. control group, p=0.017).

Correlation between high-sensitivity C-reactive protein and FDG uptake in the bone marrow, spleen, and carotid artery

The TBR of the carotid artery and SUVs of the BM and spleen correlated significantly with each other in study subjects overall. Without adjustment, the TBR of the carotid artery was most highly correlated with the SUV of the spleen. HsCRP was also significantly correlated with FDG uptake in the BM, spleen, and carotid artery (Table 2). In the AMI group, there was no correlation between peak serum CK-MB and troponin-T levels and FDG uptake in the BM, spleen, or carotid artery (data not shown).
Relationship between carotid artery target-to-background ratio and bone marrow FDG uptake, spleen FDG uptake, and high-sensitivity C-reactive protein

Multiple linear regression analysis of the overall study population, which included age, sex, waist circumference, hypertension, diabetes, dyslipidemia, smoking, and statin use as covariates, revealed an independent relationship between carotid artery TBR, the SUVs of the spleen and BM, and hsCRP. The SUVs of the spleen and BM were significantly associated with carotid artery TBR even after further adjustment for hsCRP. In contrast, hsCRP did not maintain a significant association with carotid artery TBR when the SUV of the BM or spleen was entered into the model as an independent variable (Table 3).

Discussion

This study revealed significant associations between CAD, the metabolic activity of the spleen and BM, and the inflammatory activity of the carotid artery independent of traditional cardiovascular risk factors and hsCRP level. Those activities were highest in patients with AMI, intermediate in patients with CSA, and lowest in the control group. The $^{18}$F-FDG uptake in the carotid artery was significantly associated with the metabolic activity of the spleen and BM as well as with hsCRP level.

Most studies that support the association between inflammation and CAD have been based on epidemiologic analysis of circulating biomarkers$^{17-19}$ and animal experiments.$^{20-23}$ Recent studies have identified that the role of the spleen and BM in chronic and acute inflammation in atherosclerotic disease. In chronic inflammation of atherosclerosis, both the BM and spleen are involved. HSPCs progressively relocate from the BM to the splenic red pulp, where they clonally expand with granulocyte macrophage colony-stimulating factor and interleukin-3 and differentiate into inflammatory monocytes.$^{5}$ Monocytes born in the spleen
intravasate, circulate, and accumulate into atherosclerotic lesions in murine models.\textsuperscript{5} Our findings are consistent with this knowledge, in that significantly higher activity was found in the BM, spleen, and carotid artery in the CSA group than in the control group.

Using \textsuperscript{18}F-FDG PET, Assmus et al. found significantly higher metabolic activity in the BM and significantly larger populations of hematopoietic CD34\textsuperscript{+} and CD133\textsuperscript{+} cells in BM aspirates from patients within 7 days after AMI than in patients with chronic post-ischemic heart failure.\textsuperscript{24} The same authors reported that AMI induced by ligating a coronary artery or application of other stressors can activate stem cells in the BM in non-atherosclerotic mice.\textsuperscript{24} It has also been reported that acute ischemic myocardial injury triggers emergency hematopoiesis in the BM and spleen,\textsuperscript{7} and that AMI liberates HSPCs from BM niches via signals from the sympathetic nervous system.\textsuperscript{9} The progenitors then seed the spleen and yield a sustained boost in monocyte production to meet demand in the infarcted myocardium.\textsuperscript{7, 9} This process, however, may have unintended consequences, such as acceleration of underlying atherosclerosis triggering reinfarction or stroke.\textsuperscript{2, 9} Dutta et al. found that in ApoE-/- mice, AMI accelerates underlying aortic atherosclerosis.\textsuperscript{9}

In light of these findings, our AMI group indeed demonstrated higher metabolic activity in the spleen and BM than the CSA group. The greater inflammatory activity in the carotid arteries of the AMI group compared to the CSA group may be evidence of this damaging accumulation of monocytes in atherosclerotic lesions. Moreover, we found that the metabolic activity of the carotid artery was closely associated with that of the spleen and BM as well as with the level of hsCRP in the overall patient population. These findings suggest that the inflammatory status of atherosclerosis is influenced by systemic inflammation modulated by the spleen and BM.
Metabolic activation of the major organs that harbor inflammatory cells such as the spleen,\(^8\) or that participate in inflammatory cell production, such as the BM and spleen,\(^5,9\) has been revealed using \(^{18}\)F-FDG-PET in a variety of systemic conditions, including infection,\(^25\) cancer,\(^16\) connective tissue diseases\(^26\) and systemic autoimmune disorders.\(^27\) However, few studies have demonstrated the metabolic activation of the BM and spleen in humans with CAD. To the best of our knowledge, this is the first \textit{in vivo} human study showing the metabolic activity of the spleen and BM in patients with CAD using a molecular imaging tool.

In our study, the metabolic activity of the spleen and BM was high in patients with AMI even after a mean of 6.3 days from the event. Inflammatory monocytes, which have been found to be chronically expanded in the blood pool of atherosclerotic apoE-/- mice, impair infarct healing through prolonged presence in the infarct and deregulated resolution of inflammation.\(^28\) This result suggests that patients with AMI who have underlying inflammation associated with atherosclerosis may have prolonged activation of the organs involved in inflammation. Further studies are needed to determine the time period during which activation of the spleen and BM persists after AMI in humans.

Our study has several limitations. First, its cross-sectional design, small sample size, and significant differences between subjects and controls may have introduced various levels of bias. Although we attempted to adjust for these differences and the small sample size, our model may not be sufficiently powered to support the results. Second, we did not perform coronary angiography in the control group to confirm the presence of coronary atherosclerosis and this may have affected our results. Third, we did not perform histopathological analysis of tissue samples from the spleen or BM. However, it is already known that \(^{18}\)F-FDG accumulates in tissue macrophages and its intensity correlates with the staining density of tissue macrophages in
corresponding histological sections of specimens.\textsuperscript{10, 11} Fourth, the patients with AMI may have had elevated levels of catecholamines and endogenous steroids associated with stress in addition to their underlying inflammatory state. However, we were not able to control for all factors affecting glucose metabolism and FDG uptake, including levels of insulin, catecholamines, steroids, and other substrates in plasma, which may have affected our results. Fifth, we did not control for other factors affecting systemic inflammation, such as life style habits, low-grade chronic infections, and genetic predisposition. Finally, we did not measure the biomarkers of HSPC in the BM or monocyte subsets in the peripheral blood. In short, this study was not designed to definitively prove an etiological hypothesis, but was an observational study designed to measure metabolic activity of the spleen and BM in patients with CAD as an indirect probe into a previously established condition.

In conclusion, the metabolic activity of the BM and spleen as well as of the carotid artery was highest in patients with AMI, intermediate in patients with CSA, and lowest in controls. The relationship between those parameters and CAD status was independent of traditional cardiovascular risk factors. Activation of the BM and spleen was closely associated with the activity in the carotid artery. Our results offer insights into risk stratification, monitoring of therapy, and physiological changes in the early stages of atherosclerosis, when intervention may be most effective.

**Sources of Funding**

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Disclosures

None.

References

Table 1. Baseline characteristics of study subjects.

<table>
<thead>
<tr>
<th></th>
<th>AMI (n=32)</th>
<th>CSA (n=33)</th>
<th>Control (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56.9±11.6</td>
<td>61.2±11.5</td>
<td>57.1±7.5</td>
<td>0.206</td>
</tr>
<tr>
<td>Men</td>
<td>21 (65.6)</td>
<td>24 (72.7)</td>
<td>6 (24.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6±2.6</td>
<td>26.0±4.0</td>
<td>23.5±2.9</td>
<td>0.022</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>83.4±16.3</td>
<td>92.3±11.4</td>
<td>80.9±7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (46.9)</td>
<td>19 (57.6)</td>
<td>1 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (40.6)</td>
<td>13 (39.4)</td>
<td>2 (8.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>19 (59.4)</td>
<td>16 (48.5)</td>
<td>2 (8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (40.6)</td>
<td>13 (39.4)</td>
<td>2 (8.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Statin use</td>
<td>9 (28.1)</td>
<td>11 (33.3)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>187±44</td>
<td>156±35</td>
<td>189±25</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>137±14       a,b</td>
<td>160±100 a</td>
<td>87±44 b</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>88 (58-168)</td>
<td>113 (85-254)</td>
<td>68 (56-122)</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>45±12 a</td>
<td>49±15 a</td>
<td>59±16</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>124±42 a</td>
<td>92±30</td>
<td>115±24 a</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.9±2.1 a</td>
<td>7.0±1.6 a</td>
<td>5.7±0.4</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>6.1 (5.7-7.8)</td>
<td>6.6 (5.7-7.5)</td>
<td>5.6 (5.4-5.9)</td>
<td></td>
</tr>
<tr>
<td>WBC, x10³/uL</td>
<td>10.9±3.3</td>
<td>6.5±1.2</td>
<td>5.0±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>10.6 (8.4-12.6)</td>
<td>6.5 (5.5-7.7)</td>
<td>5.0 (3.9-6.3)</td>
<td></td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>3.48±3.10</td>
<td>1.53±1.55</td>
<td>0.55±0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.88 (1.05-5.97)</td>
<td>1.16 (0.32-2.49)</td>
<td>0.41 (0.17-0.82)</td>
<td></td>
</tr>
<tr>
<td>peak CK-MB, ng/mL</td>
<td>145.6±127.3</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>peak troponin-T, ng/mL</td>
<td>3.66±4.64</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>TBR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid artery</td>
<td>2.13±0.42</td>
<td>1.36±0.37 a</td>
<td>1.16±0.09 a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.57±0.39</td>
<td>2.03±0.35</td>
<td>1.54±0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>1.67±0.16</td>
<td>1.22±0.62</td>
<td>0.80±0.44</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD; median with interquartile range in parenthesis; or number with percentage in parentheses.

P-values represent overall differences across groups as determined by ANOVA or the Kruskal-Wallis test for continuous variables and Pearson’s chi-squared test or Fisher’s exact test for categorical variables.

a,b The same letters indicate no statistical significance based on Bonferroni’s post-hoc test, or the Mann-Whitney U-test and, or separate Pearson’s chi-squared test or Fisher’s exact test with Bonferroni corrected p values.

AMI, acute myocardial infarction; BMI, body mass index; CSA, chronic stable angina; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; SUV, standard uptake value; TBR, target-to-background ratio; WBC, white blood cell; WC, waist circumference.
Table 2. Spearman correlation analysis between hsCRP level and FDG uptake in the carotid artery, spleen, and BM in the overall study population.

<table>
<thead>
<tr>
<th></th>
<th>SUV of BM</th>
<th>SUV of Spleen</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBR of Carotid artery</td>
<td>0.535*</td>
<td>0.663*</td>
<td>0.465*</td>
</tr>
<tr>
<td>SUV of BM</td>
<td>-</td>
<td>0.637*</td>
<td>0.525*</td>
</tr>
<tr>
<td>SUV of Spleen</td>
<td>0.637*</td>
<td>-</td>
<td>0.458*</td>
</tr>
</tbody>
</table>

* *p<0.001
BM, bone marrow; hsCRP, high sensitivity C-reactive protein; SUV, standard uptake value; TBR, target-to-background ratio.
Table 3. Multiple linear regression analysis using the carotid artery TBR as a dependent variable.

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>p</th>
<th>R²</th>
<th>R² adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV, bone marrow*</td>
<td>0.438</td>
<td>&lt;0.001</td>
<td>0.329</td>
<td>0.245</td>
</tr>
<tr>
<td>SUV, bone marrow †</td>
<td>0.395</td>
<td>&lt;0.001</td>
<td>0.378</td>
<td>0.288</td>
</tr>
<tr>
<td>SUV, spleen*</td>
<td>0.688</td>
<td>&lt;0.001</td>
<td>0.461</td>
<td>0.394</td>
</tr>
<tr>
<td>SUV, spleen †</td>
<td>0.644</td>
<td>&lt;0.001</td>
<td>0.486</td>
<td>0.412</td>
</tr>
<tr>
<td>hsCRP*</td>
<td>0.011</td>
<td>0.040</td>
<td>0.192</td>
<td>0.088</td>
</tr>
</tbody>
</table>

*The association with the carotid artery TBR after adjustment for age, sex, waist circumference, hypertension, diabetes, dyslipidemia, smoking, and statin use.
†The association with the carotid artery TBR after adjustment for the above covariates and hsCRP.

R² adjusted = 1 – (1 - R²)(N-1)/(N-P-1), where R² = sample R-square, p = number of predictors, N = total sample size.

hsCRP, high sensitivity C-reactive protein; SUV, standard uptake value; TBR, target-to-background ratio.
**Figure Legends**

Figure 1. A. Representative examples of maximum-intensity-projection $^{18}$F-FDG PET images showing highly increased uptake and moderately increased uptake throughout the bone marrow and spleen in patients with acute myocardial infarction (AMI) and chronic stable angina (CSA), respectively. B. Axial fusion images at the carotid artery level from the same scan showing diffuse intense uptake of $^{18}$F-FDG in the carotid arteries of patients with AMI (arrow) and moderate uptake in patients with CSA.

Figure 2. Mean differences in spleen SUV (A), BM SUV (B), and the carotid artery TBR (C) between the 3 study groups. Error bars show 95% confidence intervals of means.

AMI, acute myocardial infarction; BM, bone marrow; CSA, chronic stable angina; SUV, standard uptake value; TBR, target-to-background ratio.
Figure: SUV of BM

- AMI: p<0.001
- CSA: P=0.002

Legend:
- AMI
- CSA
- Control
The Metabolic Activity of the Spleen and Bone Marrow in Patients with Acute Myocardial Infarction Evaluated by $^{18}$F-FDG PET Imaging

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