Role of FDG PET-CT in Takayasu Arteritis
Sensitive Detection of Recurrences

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OBJECTIVES The aim of this study was to investigate whether the maximum standardized uptake value (max SUV) of $^{18}$F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) provides a quantitative indication of disease activity in Takayasu arteritis (TA) cases.

BACKGROUND The clinical value of FDG-PET for assessing TA has been investigated. Clinical evaluation of disease activity is often difficult, because most patients develop recurrent inflammation while receiving corticosteroid treatment.

METHODS Thirty-nine TA patients underwent FDG-PET/CT at Tokyo Medical and Dental University from 2006 to 2010 (35 women and 4 men; median age, 30 years). Disease activity was defined according to National Institutes of Health criteria. Biomarkers including C-reactive protein and erythrocyte sedimentation rate were measured. Forty subjects without vasculitis served as control subjects.

RESULTS The max SUV was significantly higher in active than in inactive cases and control subjects (active [n=27], median value, 2.7 vs. inactive [n=12], 1.9; control [n=40], 1.8; p<0.001 each). Given a max SUV cutoff of 2.1, sensitivity for active-phase TA was 92.6%, specificity 91.7%, positive predictive value 96.2%, and negative predictive value 84.6%. In receiver-operating characteristic curves comparison, max SUV was superior to C-reactive protein (p<0.05) and erythrocyte sedimentation rate (p<0.05). Max SUV was significantly higher in relapsing on treatment cases (n=17) than in stable on treatment cases (n=12) (median value, 2.6 vs. 1.9; p<0.001).

CONCLUSIONS FDG-PET/CT is useful for detection of active inflammation not only in patients with active TA before treatment but also in relapsing patients receiving immunosuppressive agents. The max SUV is useful for assessing subtle activity of TA with high sensitivity. (J Am Coll Cardiol Img 2012; 5:422–9) © 2012 by the American College of Cardiology Foundation
Takayasu arteritis (TA) is a chronic vasculitis, mainly involving large vessels, including the aorta, pulmonary artery, and their major branches (1). Major diagnostic criteria used by the American College of Rheumatology include clinical symptoms caused by inflammatory or stenotic lesions in these arteries (2). Another important aspect of TA is the chronic inflammatory nature of this disease. Disease activity is assessed with National Institutes of Health (NIH) criteria on the basis of 4 elements of clinical status (3).

Even in patients receiving corticosteroid treatment, recurrences are common. Estimation of disease activity in TA patients, particularly those receiving treatments, is a significant clinical management issue. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the biological markers generally used to assess disease activity in TA patients. However, these markers do not allow differentiation between active and inactive TA, because they are nonspecific inflammatory markers (4).

Research has focused particularly on the diagnostic role of 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) in patients with TA, because this modality can estimate the degree as well as the site of inflammation (5,6). Meller et al. (7) reported that FDG-PET is more reliable than magnetic resonance (MR) imaging for monitoring disease activity during immunosuppressive therapy. In addition, the maximum standardized uptake value (max SUV) increases as inflammatory reactions spread, and max SUV can thus serve as a quantitative marker of FDG uptake. However, problems with studies using FDG-PET include study designs for determining activity in TA and low sensitivity for diagnosing TA (8).

Thus, the diagnostic utility of max SUV from FDG-PET has not been established. Therefore, we investigated whether max SUV, as a quantitative marker, can be used to determine TA activity in a relatively large number of patients in a single center.

The first aim of this study was to compare the accuracies of max SUV, CRP, and ESR for assessing disease activity in TA. The second aim was to investigate whether max SUV of FDG-PET/computed tomography (CT) can serve as an activity marker in patients with recurrent TA being treated with steroids or other immunosuppressants.

METHODS

Study patients. The consecutive TA cases that underwent FDG-PET/CT at Tokyo Medical and Dental University from 2006 to 2010 were retrospectively reviewed. Forty TA patients and 40 control subjects without vasculitis were enrolled. One TA patient was excluded, because infectious disease was noted when FDG-PET/CT was performed. The 39 TA cases (35 women, 4 men; median age, 30 years; range, 13 to 71 years) underwent FDG-PET/CT for diagnosis or clinical needs with suspicion of recurrence. The TA had been diagnosed with American College of Rheumatology criteria in all cases (2). We also diagnosed patients with the Guideline for Management of Vasculitis Syndromes (Japanese Circulation Society 2008) (9), including the criteria of the Ministry of Health, Labour and Welfare of Japan. We generally used the latter criteria in clinical diagnosis. In this study, we confirmed TA patients satisfied with both of the 2 diagnostic criteria. The 40 control subjects (36 women, 4 men; median age, 38 years; range, 13 to 70 years) were selected by sex and age as a case-matched study population. Thirty-one control subjects had malignant diseases in remission after therapy and underwent FDG-PET/CT to assess recurrence. The other 9 subjects were healthy and underwent FDG-PET/CT for cancer screening. All of these subjects showed no evidence of inflammation or vasculitis, and FDG-PET showed negative study.

The study protocol was approved by the institutional ethics review committee of Tokyo Medical and Dental University. All patients provided informed consent and agreed to the use of their data for this study.

Disease activity. We assessed disease activity by adopting NIH criteria (3), which define clinical status on the basis of 4 elements: systemic features, elevated ESR, vascular ischemia, and angiographic changes. The active phase is defined as new onset or worsening of 2 or more of these features. The NIH criteria were scored within 1 month before or after FDG-PET/CT.

In all 39 cases, serum CRP and ESR levels were measured and recorded within 3 days of FDG-PET/CT. We divided active cases into 2 groups: untreated cases, and relapsing on treatment cases. Untreated cases were defined as active TA patients without previous treatment with steroid or immunosuppressant. Relapsing on treatment cases were...
Table 1. Characteristics of TA Patients

<table>
<thead>
<tr>
<th></th>
<th>Active (n = 27)</th>
<th>Inactive (n = 12)</th>
<th>Control (n = 40)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>23</td>
<td>12</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Median age, yrs</td>
<td>27 (19–40)</td>
<td>51 (28–59)</td>
<td>38 (28–47)</td>
<td>NS</td>
</tr>
<tr>
<td>NIH score</td>
<td>3.0 (2–4)</td>
<td>1 (1–1)</td>
<td>n/a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>89 (84–95)</td>
<td>98 (89–109)</td>
<td>91 (83–98)</td>
<td>NS</td>
</tr>
<tr>
<td>Circulation time, min</td>
<td>62 (60–65)</td>
<td>63 (60–70)</td>
<td>67 (60–74)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean SUV in IVC</td>
<td>1.6 (1.3–1.8)</td>
<td>1.5 (1.5–1.7)</td>
<td>1.5 (1.3–1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial max SUV</td>
<td>2.7 (2.3–3.2)</td>
<td>1.9 (1.8–1.9)</td>
<td>1.8 (1.6–2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>1.0 (0.4–5.6)</td>
<td>0.1 (0.1–0.4)</td>
<td>n/a</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>40 (18–70)</td>
<td>19 (9–30)</td>
<td>n/a</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are median (25th to 75th percentile).

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IVC = inferior vena cava; max = maximum; NIH = National Institutes of Health; SUV = standardized uptake value; TA = Takayasu arteritis.

defined as those showing clinical worsening of 2 or more NIH criteria while receiving therapy and diagnosed as recurrence. All of the inactive cases were defined as stable on treatment cases in this analysis.

To determine the angiographic features for the NIH criteria, we assessed the findings of stenosis or dilation by MR angiography. If MR angiography data had not been obtained, computed tomography angiography (CTA) findings were used. Imaging data were assessed within 1 month before or after FDG-PET/CT. Imaging data at diagnosis was used for the scoring of untreated cases. We performed imaging tests more than twice, and the data were compared in patients with relapsing on treatment cases and stable on treatment cases.

FDG-PET/CT. All FDG-PET/CT scans were performed with Aquiduo (Toshiba Medical, Tokyo, Japan). The CT data were obtained in 2-mm slices with a 15° helical pitch, at 120 kV and 50 to 100 mA. Imaging data from CT comprised a matrix of 512 × 512 pixels. Patients were fasted more than 4 h, and their oral hydration and bladder emptying were completed before collecting PET/CT data. The CT data for attenuation correction and anatomical co-registration were obtained during expiratory breath-holding. Contrast media were not used. After CT scanning, patients were intravenously injected with 3.7 MBq/kg of FDG. A whole-body scan was performed on all patients 60 min after FDG injection. The PET data were obtained in 3-dimensional mode for 2 min in each bed position, for a total of 14 to 16 min. The PET data consisted of a matrix of 128 × 128 pixels.

Visual qualitative and semi-quantitative analyses of PET images. Data from FDG-PET/CT were analyzed by 2 nuclear medical radiologists blinded to the clinical data. The radiologists assessed focal uptake in the arterial wall as an inflammatory lesion of active TA. A region of interest was measured in the lesion, and max SUV was defined as the highest value in this area. Finally, highest max SUV in the arteries was defined in each case. In cases without significant uptake of FDG, arterial max SUV was defined as the highest value in a slice-by-slice analysis of the entire aorta. Blood pooling in the lumen was excluded when measuring uptake in the region of interest. Mean SUV was measured in the center of the inferior vena cava in all cases, and target/background ratio was calculated as max SUV in arterial wall/mean SUV in inferior vena cava.

Statistical analysis. Categorical data are presented as numbers (percentages), and continuous data are presented as median value and quartile (25% to 75%). We performed Kruskal–Wallis 1-way analysis of variance for comparison among 3 groups. Moreover, nonparametric statistics by Mann–Whitney–Wilcoxon with Holm correction was used to compare 2 groups. The 95% confidence intervals were calculated, and values of p < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS software (version 11.0.1J, SPSS, Inc., Chicago, Illinois). Area under the curve (AUC) was calculated for the receiver-operating characteristic (ROC) curve to determine optimal cutoff values and to compare the markers. With drawing ROC curve, the point that is closest to the point of 100% sensitivity and 100% specificity on the ROC curve defines cutoff value according to the standard method. MedCalc software (version 11.4, MedCalc Software, Mariakerke, Belgium) was used for statistical comparisons of ROC curves. Sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) were determined for the relevant cutoff values. Statistical correlation was determined by nonparametric analysis.

Table 2. Comparisons of Therapy Among the 3 TA Groups

<table>
<thead>
<tr>
<th></th>
<th>Untreated (n = 10)</th>
<th>Relapsing on Treatment (n = 17)</th>
<th>Stable on Treatment (n = 12)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>8</td>
<td>15</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Prednisolone dose (mg)</td>
<td>n/a</td>
<td>10 (6–16)</td>
<td>8 (2–15)</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>n/a</td>
<td>29.4%</td>
<td>25%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values of prednisolone dose are presented as median (25th to 75th percentile).

TA = Takayasu arteritis.
RESULTS

Twenty-seven cases were classified as active, and 12 were classified as inactive (Tables 1, 2, and 3). The max SUV was significantly higher in active than in inactive cases \((p < 0.001)\) (Table 1) and control subjects (median value, 1.8; \(p < 0.001\)) (Fig. 1, left). The target/background ratio was also significantly higher in active (median value, 1.7 [1.3 to 1.9]) than in inactive cases (median value, 1.1 [1.0 to 1.1]; \(p < 0.001\)) and control subjects (median value, 1.1 [0.9 to 1.2], \(p < 0.001\)) (Fig. 1, right). Inactive and control cases did not differ significantly in terms of either max SUV in arterial wall and target/background ratio.

Levels of CRP and ESR were significantly higher in the active than in the inactive cases (Table 1).

Imaging data were obtained in 37 cases by MR angiography and in 2 cases by CTA. Progression of stenosis or dilation of vessels was observed in the majority of relapsing cases with these modalities. No inactive cases showed any significant changes.

Comparisons among utilities of max SUV, CRP, and ESR for determining active phase TA. With ROC curve, we determined the cutoff value for these markers (max SUV = 2.1; CRP = 0.2 mg/dl; ESR = 19 mm/h). With this cutoff for max SUV, SE for active-phase TA was 92.6%, SP was 91.7%, PPV was 96.2%, and NPV was 84.6%. As for CRP, SE for active-phase TA was 81.5%, SP was 66.7%, PPV was 84.6%, and NPV was 61.5%. As for ESR, SE for active-phase TA was 74.1%, SP was 58.3%, PPV was 80%, and NPV was 50%.

Comparisons of ROC curves showed AUC to be 95.4% for max SUV, 84.7% for CRP, and 72.7% for ESR. Max SUV was superior to CRP \((p = 0.0283)\) and ESR \((p = 0.0033)\) in terms of ROC curve analysis for determining active phase disease with statistical significance (Fig. 2, left).

Comparisons among untreated, relapsing on treatment, and stable on treatment TA patients. The 27 active cases were divided into 10 untreated cases and 17 cases with relapsing on treatment. Prednisolone dose and the number of cases using immunosuppressants were not different between relapsing and stable cases (Table 2). Immunosuppressants were cyclophosphamide in 1 case, cyclosporine in 3 cases, methotrexate in 2 cases, and azathioprine in 2 cases.

The max SUV was higher in untreated (median value, 2.8 [2.4 to 3.2]) and relapsing on treatment cases (median value, 2.6 [2.3 to 3.3]) than in stable on treatment cases (median value, 1.9; \(p = 0.004\) vs. untreated; \(p < 0.001\) vs. relapsing) (Fig. 3). The CRP levels and ESR showed same differences among groups, but ESR did not show difference between relapsing and stable cases (Fig. 4, right).

Correlations between max SUV and CRP or ESR \((r = 0.646; p < 0.001\) vs. CRP, \(r = 0.378; p = 0.018\) vs. ESR) were significant (Fig. 5).

**Table 3. Arteries of Highest Maximum Standardized Uptake Value**

<table>
<thead>
<tr>
<th>Arteries</th>
<th>Active Number of Cases</th>
<th>Active %</th>
<th>Inactive Number of Cases</th>
<th>Inactive %</th>
<th>Control Number of Cases</th>
<th>Control %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending aorta</td>
<td>5</td>
<td>18.5</td>
<td>1</td>
<td>8.3</td>
<td>18</td>
<td>45.0</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>10</td>
<td>37.0</td>
<td>6</td>
<td>50.0</td>
<td>19</td>
<td>47.5</td>
</tr>
<tr>
<td>Descending aorta</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>Left carotid artery</td>
<td>4</td>
<td>14.8</td>
<td>2</td>
<td>16.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Left subclavian artery</td>
<td>4</td>
<td>14.8</td>
<td>2</td>
<td>16.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Brachioccephalic artery</td>
<td>1</td>
<td>3.7</td>
<td>1</td>
<td>8.3</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Right carotid artery</td>
<td>1</td>
<td>3.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Right subclavian artery</td>
<td>1</td>
<td>3.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Left renal artery</td>
<td>1</td>
<td>3.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Figure 1. Comparisons of Max SUV and TBR Among Active, Inactive, and Control Cases**

The maximum standardized uptake value (max SUV) (left) and target to background ratio (TBR) (right) in active cases were statistically higher than those in inactive and control cases.
Correlation coefficient between max SUV and ESR was relatively low.

Comparisons of ROC curves between relapsing and stable cases showed AUC to be 94.1% for max SUV, 79.4% for CRP, and 63.2% for ESR. Max SUV showed significant superiority to both CRP \( (p = 0.0331) \) and ESR \( (p = 0.0022) \) in ROC curve analysis for determining recurrence (Fig. 2, right).

Representative cases of untreated and relapsing cases are shown in Figures 6 and 7.

**DISCUSSION**

We used FDG-PET/CT to assess TA disease activity, because this modality can identify sites of accelerated metabolism indicative of an inflammatory reaction, and max SUV can be used to quantitatively represent the degree of inflammation. Our present results thus support the concept that max SUV provides a valid means of comparing patients with active and inactive TA. We examined whether changes in blood glucose levels and venous mean SUV would impact the validity of our arterial max SUV data but found that these data did not differ between active and inactive TA.

Webb et al. (5) were the first to report the diagnostic accuracy of FDG-PET in 18 TA cases. Their SE was 92%, and SP was 100%. Disease activity was determined by a combination of clinical symptoms of TA in this report. Kobayashi et al. (10) were the first to establish a cutoff for max SUV in their study of 14 TA patients. Their SE was 90.9%, and SP was 88.8%, but they defined active disease as a clinical requirement for prednisolone. Walter et al. (6) described the qualitative utility of FDG-PET in 26 cases with giant cell arteritis (n =...
20) or TA (n = 6), and the visual grade of FDG uptake (grades I to III) correlated significantly with both CRP and ESR. The SE for pathological FDG uptake in large vessels was 60.0%, and SP was 99.8%, but disease activity was not assessed. We obtained higher SE (92.6%) and SP (91.7%) in a larger number (39) of TA patients, compared with these previous studies. In addition, our first study aim was to analyze ROC curves and thereby demonstrate diagnostic utility with a max SUV cutoff of 2.1 (AUC: 95.4%). The optimal max SUV cutoff for assessing TA activity remains to be determined. In a previous study (10), the cutoff was lower than ours, because the definition of active cases differed from that used in our study. Herein, we propose a cutoff of 2.1 for max SUV on the basis of our clinical study employing a subjective definition of TA activity.

The major challenge in therapeutic management of TA is recurrence, because even if corticosteroid therapy is effective, 72% of cases suffer multiple recurrences within 6 months (11). Conventional inflammatory markers such as ESR and CRP, which reflect systemic inflammation, are nonspecific for TA, and immunomodulatory agents can modify these parameters. We focused on 2 groups of acute TA patients: untreated, and relapsing on treatment. In our evaluation of relapsing cases, ROC curves revealed that ESR and CRP underestimate TA activity in patients receiving steroid treatment. Conversely, max SUV from FDG-PET/CT showed a stronger correlation with clinical activity even in relapsing on treatment cases, probably because FDG-PET/CT can detect local inflammatory lesions in vessels. In addition, our representative relapsing patient (Case 2) showed that

![Figure 4. Comparisons of CRP and ESR Among Patients With Untreated, Relapsing on Treatment, and Stable on Treatment of Takayasu Arteritis](image)

C-reactive protein (CRP) was statistically different among untreated, relapsing, and stable cases (left). Erythrocyte sedimentation rate (ESR) in relapsing and stable cases was not statistically different (right).

![Figure 5. Correlation With Max SUV to CRP and ESR](image)

Correlation with max SUV to CRP and ESR is shown. Max SUV showed good correlation to CRP but not to ESR. Abbreviations as in Figure 2.
Figure 6. Representative Case #1 (Untreated Takayasu Arteritis)

A 20-year-old woman presented with left arm pain. The CRP and ESR were elevated to 11.04 mg/dl and 132 mm/h, respectively. Magnetic resonance (MR) angiography (top, middle) showed stenosis in the bilateral carotid and left subclavian arteries and diagnosed as Takayasu arteritis. The $^{18}$F-fluorodeoxyglucose uptake was seen in the same lesions and the aortic arch (bottom). She was classified as untreated in this study. The measured max SUV in the aortic arch was highest level. She was administered corticosteroids. CT – computed tomography; PET – positron emission tomography; other abbreviations as in Figure 2.

Figure 7. Representative Case #2 (Relapsing on Treatment Takayasu Arteritis)

A 23-year-old woman with Takayasu arteritis was taking corticosteroids at a dose of 5 mg/day. The ESR was 18 mm/h, but she had left arm pain with slight CRP elevation up to 1.1 mg/dl. The $^{18}$F-fluorodeoxyglucose-PET/CT imaging showed uptake in the left subclavian artery, and max SUV was elevated (left). After increasing dose of prednisolone to 30 mg/day, the uptake disappeared, and max SUV was decreased (right). Strong $^{18}$F-fluorodeoxyglucose uptake on her right side is uptake due to an artificial graft, from the right axial artery to the right external iliac artery. Abbreviations as in Figures 2 and 6.
max SUV clearly represents therapeutic effectiveness before versus after steroid treatment.

On the basis of these results, we recommend imaging by FDG-PET for diagnosis of TA or detection of its recurrence but not for routine observation. This imaging could be useful, especially if the assessment of recurrence is difficult due to absence or low levels of CRP or ESR elevation.

**Study limitations.** We performed FDG-PET/CT and MR angiography or CTA not by prospective protocol but by clinical needs in each case. The data acquisition of the biomarkers was within 3 days of FDG-PET/CT but not at the same time. Our protocol of FDG-PET was not optimized for measuring vascular SUV, because of a relatively lower dose of tracer and a shorter circulation time. The wall imaging is important for diagnosing TA; however, we did not perform wall imaging by MR in all patients in this series. Comparisons of PET imaging and MR wall imaging are a future issue of investigation.

**CONCLUSIONS**

Max SUV obtained with FDG-PET/CT had high SE and SP for detecting subtle TA activity, and our ROC curve indicated this approach to be superior to both ESR and CRP, with statistical significance. The diagnostic accuracy of max SUV was also shown in relapsing TA cases. This technology would allow differentiation of not only active TA but also relapsing TA while receiving steroid therapy from stable TA. In addition, FDG-PET/CT is useful for localization of inflammation in TA.

We propose a max SUV cutoff of 2.1 for detecting active inflammation of TA in untreated and relapsing cases. The max SUV from FDG-PET/CT allows sensitive assessment of clinical state and facilitates selecting the optimal therapy for TA patients.

**Key Words:** FDG-PET • max SUV • Takayasu arteritis.