Measurement of ^{68}Ga -DOTATOC Uptake in the Thoracic Aorta and Its Correlation with Cardiovascular Risk

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Abstract

Purpose ^{68}Ga -labeled 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid-D-Phe¹-Tyr³-octreotide (^{68}Ga -DOTATOC) is taken up by activated macrophages, which accumulate in active inflammatory lesions. The purpose of this study was to investigate the feasibility of ^{68}Ga -DOTATOC PET/CT for assessment of vulnerable plaque, by evaluating correlation between aortic uptake of ^{68}Ga -DOTATOC and cardiovascular risk factors.

Methods Fifty patients with neuroendocrine tumors who underwent ^{68}Ga -DOTATOC PET/CT were retrospectively enrolled. The uptakes in the thoracic aorta were measured by two methods: multi-sample region-of-interest (ROI) method and single volume-of-interest (VOI) method. $\text{TBR}_{\text{max-avg}}$, $\text{TBR}_{\text{mean-avg}}$, $\text{TBR}_{\text{max-VOI}}$, and $\text{TBR}_{\text{mean-VOI}}$ were defined by maximum and mean target-to-background ratio (TBR) from the multi-sample ROI method and the single VOI method, respectively.

Results Framingham risk score (FRS) exhibited significant correlations with $\text{TBR}_{\text{max-avg}}$ and $\text{TBR}_{\text{mean-avg}}$, as well as $\text{TBR}_{\text{max-VOI}}$ ($r = 0.3389$ – 0.4593 , $P < 0.05$ for all). $\text{TBR}_{\text{max-avg}}$ and $\text{TBR}_{\text{max-VOI}}$ were significantly higher in high FRS group than in low FRS group (1.48 ± 0.21 vs. 1.70 ± 0.17 , $P < 0.001$ for $\text{TBR}_{\text{max-avg}}$ and 1.90 ± 0.33 vs. 2.25 ± 0.36 , $P = 0.002$ for $\text{TBR}_{\text{max-VOI}}$). TBR exhibited high correlations between the two measuring methods ($r = 0.9684$, $P < 0.001$ for $\text{TBR}_{\text{mean-avg}}$ and $\text{TBR}_{\text{mean-VOI}}$ and $r = 0.8681$, $P < 0.001$ for $\text{TBR}_{\text{max-avg}}$ and $\text{TBR}_{\text{max-VOI}}$).

Conclusions ^{68}Ga -DOTATOC uptake in the thoracic aorta exhibited a significant correlation with cardiovascular risk factors, which suggests the feasibility of ^{68}Ga -DOTATOC PET for vulnerable plaque imaging, with a simple measurement of the single VOI method that is comparable to the multi-sample ROI-based approach.

Keywords PET/CT · Atherosclerosis · ^{68}Ga -DOTATOC · Cardiovascular risk

Introduction

Atherosclerosis is one of leading causes of fatal morbidity and mortality in the world [1]. Critical cardiovascular events such as acute myocardial infarction or sudden cardiac death are caused by rupture of vulnerable atherosclerotic plaques. The most important feature of vulnerable plaque is active inflammation in vessel wall, which can be identified by extensive

macrophage accumulation [2]. Because vulnerable plaque is a direct diagnostic target for preventing critical events by atherosclerosis, there have been many attempts to find novel and noninvasive vascular imaging techniques to identify vascular inflammation, which cannot be detected using conventional imaging methods [3].

Since macrophage is a key player in every stage of atherogenesis, it can serve as a potential target for molecular imaging [4]. ^{68}Ga -labeled 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid-D-Phe¹-Tyr³-octreotide (^{68}Ga -DOTATOC), a selective radiotracer binding to somatostatin receptor subtype-2 (SSTR-2), has recently been suggested as a potential imaging agent to detect vascular inflammation, because it can be taken up by macrophages or monocytes that express SSTR-2 [5]. Although ^{18}F -2-fluoro-2-deoxyglucose (FDG) has been the most widely used imaging tracer for vulnerable plaque [6–9], FDG has a

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Fig. 1 Methods for drawing multi-sample ROI and single VOI. Multiple circular ROIs were drawn on every 5-mm axial images in the multi-sample ROI method (a), whereas a single VOI for the whole ascending thoracic aorta or descending thoracic aorta was drawn by stacking and interpolating ROIs that are drawn for the aorta (b). Upper row is axial and lower row is sagittal images

drawback that it is a non-specific metabolic imaging agent. In contrast, ^{68}Ga -DOTATOC may be a specific imaging tracer for macrophages or monocytes to detect the vascular inflammation because it is not taken up by other cells such as smooth muscle cells.

In positron emission tomography (PET)/computed tomography (CT) for vascular inflammation, several methods have been suggested to quantify the inflammatory activity and burden. While the maximal uptake is often used for tumor imaging as a representative value for the most malignant tissue component, inflammatory burden is also important in vascular inflammation imaging. Thus, some researchers suggested multiple sampling of region-of-interest (ROI) to measure inflammatory activity of multiple areas of large arteries [10]. However, the method requires drawing of ROIs on many slices of images, which is quite time-consuming and laborious. A single volume-of-interest (VOI) is relatively easy, although it may not show overall inflammatory burden.

The purpose of this study was to investigate the feasibility of ^{68}Ga -DOTATOC PET/CT for assessment of vulnerable plaque, by evaluating correlation between aortic uptake of ^{68}Ga -DOTATOC and cardiovascular risk factors. Additionally, aortic uptake was measured by two methods of the multi-sample ROI and the single VOI methods, to compare efficacy of measurement indexes in terms of cardiovascular risk factors.

Materials and Methods

Patients

Patients who underwent ^{68}Ga -DOTATOC PET/CT for staging workup of suspected or known neuroendocrine tumors between April 2015 and October 2016 were retrospectively enrolled in this study. Medical records were reviewed to evaluate cardiovascular risk of patients based on Framingham risk

Table 1 Characteristics of patients

Characteristics	Value
Sex	
Male	23
Female	27
Age	55.8 ± 14.6
Previous history of CAD	3 (6%)
Hypertension	22 (44%)
Diabetes	11 (22%)
BMI	23.8 ± 3.3
Smoking	
Never smoker	40 (80%)
Ex-smoker	2 (4%)
Current smoker	8 (16%)

CAD coronary artery disease

Table 2 PET indexes according to the FRS groups (mean $\pm$ SD)

FRS group	No.	TBR _{max-avg}	TBR _{mean-avg}	TBR _{max-VOI}	TBR _{mean-VOI}
< 10%	26	1.43 $\pm$ 0.19	0.99 $\pm$ 0.11	1.84 $\pm$ 0.30	1.01 $\pm$ 0.11
10–20%	9	1.62 $\pm$ 0.22	1.11 $\pm$ 0.10	2.07 $\pm$ 0.38	1.13 $\pm$ 0.10
20–30%	6	1.64 $\pm$ 0.13	1.26 $\pm$ 0.12	2.06 $\pm$ 0.26	1.09 $\pm$ 0.11
$\geq$ 30%	9	1.72 $\pm$ 0.19	1.09 $\pm$ 0.09	2.34 $\pm$ 0.37	1.09 $\pm$ 0.10

FRS Framingham risk score

score (FRS), age, sex, body mass index (BMI), smoking habits, diabetes, and arterial hypertension. FRS, predicting the 10-year risk for cardiovascular disease, was calculated by the previously reported method [11] and used for correlation analysis with various ^{68}Ga -DOTATOC PET parameters.

The study design was approved and informed consent from each patient was waived by the Institutional Review Board of Seoul National University Hospital (H-1711-112-901).

Imaging Technique

Patients were intravenously injected with ^{68}Ga -DOTATOC (185 MBq), and PET/CT was performed 60 min after injection using dedicated PET/CT scanners (Biograph mCT40 or mCT64, Siemens Healthcare). A low-dose CT scan (120 kVp, 50 mAs) was acquired first for attenuation correction and anatomical localization. CT images were reconstructed into 5-mm-thick slices. Afterwards, PET images from the

vertex to the proximal thigh were obtained for 2 min per bed position (6–7 bed positions for a patient), and images were reconstructed by an iterative algorithm (ordered subset expectation maximization, iteration 2, subset 21).

Image Analysis

PET images were reviewed by two experienced nuclear medicine specialists who were unaware of patient and clinical information. As a quantitative value, standardized uptake value (SUV) was measured from an ROI or a VOI, using an analysis toolkit (MIM, MIM Software Inc., Cleveland, USA). The uptakes in the ascending thoracic aorta (ATA; from the aortic root to the beginning of the aortic arch), the descending thoracic aorta (DTA; from the end of aortic arch to the diaphragm), and the overall thoracic aorta (merging of ATA and DTA) were measured by the two methods.

Fig. 2 Correlations between PET indexes and FRS. TBR_{max-avg} (a), TBR_{mean-avg} (b), and TBR_{max-VOI} (c) of the overall thoracic aorta exhibited significant correlations with FRS. TBR_{mean-VOI} exhibited a correlation with FRS, with a borderline significance (d)

In the multi-sample ROI method, circular ROIs for ATA or DTA were drawn on every 5-mm axial image (Fig. 1a). Maximum SUV and mean SUV were measured in each ROI and averaged as representative values. Additionally, mean SUV of blood pool was measured in the superior vena cava as a reference value, to yield a target-to-background ratio (TBR). $TBR_{\text{max-avg}}$ and $TBR_{\text{mean-avg}}$ were defined as averaged maximum and mean SUV divided by mean SUV of blood pool, respectively. In the single VOI method, a single VOI for whole ATA or DTA was made by stacking and interpolating circular ROIs that were drawn for the aorta (Fig. 1b). In this VOI, maximum and mean SUV were measured. TBR was calculated by the same method described above and defined as $TBR_{\text{max-VOI}}$ and $TBR_{\text{mean-VOI}}$, respectively.

Calcium volume score (CVS) of the left anterior descending coronary artery was measured by using a dedicated image processing software (Osirix, Pixmeo, Geneva, Switzerland) [12].

Statistical Analysis

The values were expressed as mean $\pm$ standard deviation (SD). The Bland-Altman plot was used for comparing the two measurement methods. Correlations between FRS and PET indexes were assessed using Pearson's correlation coefficients. Student's *t* test was used to compare data between two groups. Intraclass correlation coefficients (ICCs) with 95% confidence interval (CI) were calculated to test the inter-reader agreement for PET index measurements. Data were analyzed using a commercial statistics software package (SPSS version 21.0, IBM Software, Chicago, IL, USA), and *P* values less than 0.05 were regarded as statistically significant.

Results

Patients

During the study period, 60 patients underwent ^{68}Ga -DOTATOC PET/CT. Among them, 10 patients were excluded

due to imaging errors or incomplete clinical data for calculating FRS. Finally, 50 patients (M/F = 23:27, age 55.8 ± 14.6 years, range 23–77 years) were included in the final analysis. Overall FRS of the patients was $17.5 \pm 19.3\%$. Clinical characteristics of patients are summarized in Table 1.

Correlation Between FRS and PET Indexes

FRS was calculated in 50 patients; 26 patients (52%) had risk of cardiovascular disease less than 10%, 9 (18%) had risk of 10–20%, 6 (12%) had risk of 20–30%, and 9 (18%) had risk greater than 30%. PET values according to the FRS subgroups are shown in Table 2.

FRS exhibited significant correlations with $TBR_{\text{max-avg}}$ and $TBR_{\text{mean-avg}}$, as well as $TBR_{\text{max-VOI}}$ ($r = 0.3389$ – 0.4593 , $P < 0.05$ for all; Fig. 2a–c). However, $TBR_{\text{mean-VOI}}$ exhibited a borderline negative significance ($r = 0.2531$, $P = 0.076$; Fig. 2d). Higher correlation coefficients and significances were observed with maximum values ($TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$) than with mean values ($TBR_{\text{mean-avg}}$ and $TBR_{\text{mean-VOI}}$) (Table 3). Similar results were obtained in the subgroup analyses; when indexes from the ATA or DTA only were analyzed, all indexes except $TBR_{\text{mean-VOI}}$ of the DTA exhibited significant correlations with FRS (Table 3). The highest correlation coefficient was observed with $TBR_{\text{max-avg}}$ obtained from the ATA.

In the correlation analysis between CVS and PET indexes, CVS showed a significant correlation with FRS, whereas no significant correlation was found between CVS and PET indexes (Supplemental Table 1).

Comparison of PET Indexes Between High and Low FRS Groups

When patients were classified into high ($> 20\%$) and low ($\leq 20\%$) FRS groups, $TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$ were significantly higher in high FRS group than in low FRS group (1.48 ± 0.21 vs. 1.70 ± 0.17 , $P < 0.001$ for $TBR_{\text{max-avg}}$ and 1.90 ± 0.33 vs. 2.25 ± 0.36 , $P = 0.002$ for $TBR_{\text{max-VOI}}$; Fig. 3a). In the subgroup analyses, $TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$ of the ATA exhibited significant differences between the two risk groups (Fig. 3b), and those of the DTA also exhibited significant differences (Fig. 3c). Representative cases of high and low FRS patients whose images show different uptake pattern in the ATA are shown in Fig. 4.

Table 3 Correlations of FRS with PET indexes

PET indexes	Overall thoracic aorta		ATA		DTA	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
$TBR_{\text{max-avg}}$	0.4593	<0.001	0.4562	<0.001	0.3922	0.005
$TBR_{\text{mean-avg}}$	0.3389	0.016	0.3636	0.010	0.2824	0.047
$TBR_{\text{max-VOI}}$	0.4466	0.001	0.3960	0.004	0.3933	0.005
$TBR_{\text{mean-VOI}}$	0.2531	0.076	0.3004	0.034	0.1863	0.195

ATA ascending thoracic aorta, DTA descending thoracic aorta

Fig. 3 Comparison of PET indexes between high and low FRS groups. $TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$ of the overall thoracic aorta (a) were significantly higher in high FRS group than in low FRS group. $TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$ of the ATA (b) and $TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$ of DTA (c) also exhibited significant differences between the two risk groups

Fig. 4 A representative case of ^{68}Ga -DOTATOC PET/CT images. Axial PET/CT images from a 49-year-old man with FRS of 47.9 (high FRSs group) show a focal uptake in the ascending thoracic aorta (**a**, arrows). On the other hand, images from a 30-year-old woman with FRS 0.9 (low FRS group) did not show any focal uptake in the ascending thoracic aorta (**b**)

Comparison of Indexes for Aortic Uptake Between the Two Methods

TBR exhibited high correlations between the multi-sample ROI method and single VOI method. $\text{TBR}_{\text{mean-avg}}$ and $\text{TBR}_{\text{mean-VOI}}$ exhibited a significant correlation ($r=0.9684$, $P<0.001$) with each other, and the range of ± 1.96 SD was 0.11 (Fig. 5a, b). $\text{TBR}_{\text{max-avg}}$ and $\text{TBR}_{\text{max-VOI}}$ also exhibited a significant correlation ($r=0.8681$, $P<0.001$) and the range of ± 1.96 SD was 0.82 (Fig. 5c, d). However, a tendency was observed that $\text{TBR}_{\text{max-VOI}}$ was higher than $\text{TBR}_{\text{max-avg}}$, particularly in high value range (Fig. 5d). Equivalent results were seen in subgroup analyses conducted with indexes from ATA or DTA, respectively (Supplemental Figs. 1 and 2). The inter-reader ICCs for PET index measurement were greater than 0.9 for all indexes by both methods (Supplemental Table 2).

Discussion

The current study was aimed to test the feasibility of ^{68}Ga -DOTATOC PET/CT for the assessment of vulnerable plaque, by using correlation analysis between aortic uptake of ^{68}Ga -

DOTATOC and cardiovascular risk factors, and to compare two different measurement methods: multi-sample ROI and single VOI methods.

There have been many studies in which nuclear molecular imaging was applied to vulnerable plaque by using various radiotracers targeting inflammatory cells (e.g., ^{18}F -FDG, $^{99\text{m}}\text{Tc}$ -HYNIC-IL-2, ^{64}Cu -DOTA-vMIP-II, ^{111}In -EC0800, ^{11}C -PK11195), endothelial activation (e.g., ^{64}Cu -anti-P-selectin Ab, $^{99\text{m}}\text{Tc}$ -cAbVCAM1-5), proteolysis (e.g., $^{99\text{m}}\text{Tc}$ -RP805), neoangiogenesis (e.g., ^{68}Ga -NOTA-RGD), hypoxia (e.g., ^{18}F -FMISO), and calcification (e.g., ^{18}F -fluoride) [13]. However, it was recently documented that the uptake of ^{18}F -FDG and ^{68}Ga -DOTATATE in large arteries did not co-localize in atherosclerotic lesions [14]. Since DOTATOC binds only to the macrophages which express the SSTR in atherosclerotic plaque, it is expected to be a more specific tracer than FDG in atherosclerosis. A significant correlation of ^{68}Ga -DOTATOC uptake with risk factors of cardiovascular disease was observed in this study, and the result corresponds well with earlier studies [14–18].

To the best of our knowledge, this is the first study to suggest that the uptake of ^{68}Ga -DOATATOC significantly correlate with FRS. Recently, Malmberg et al. reported that uptake of ^{68}Ga -DOTATOC in arteries is not correlated with

Fig. 5 Correlations of indexes between the multi-sample ROI and the single VOI methods. The correlation between $TBR_{\text{mean-avg}}$ and $TBR_{\text{mean-VOI}}$ was excellent (a) and ± 1.96 SD on the Bland-Altman plot was 0.11 (b). The correlation between $TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$ was also significant (c) and ± 1.96 SD on the Bland-Altman plot was 0.82 (d)

FRS [16], whereas uptake of ^{64}Cu -DOTATATE shows a significant correlation with FRS. They analyzed uptake from the aortic arch which was not included in the current study because of its complex geometry hampering reproducibility [10] and semi-automatization for making a single VOI. In addition, they did not include the uptake from ATA, which exhibited the most significant correlation with FRS in the current study. These differences might account for the disagreement between the two studies.

The present study also documented that FRS is more strongly correlated with maximum values ($TBR_{\text{max-avg}}$ and $TBR_{\text{max-VOI}}$) than with mean values ($TBR_{\text{mean-avg}}$ and $TBR_{\text{mean-VOI}}$). The maximum values represent the highest inflammation activity, while the mean values are averaged activity. Rudd et al. [19] have compared the two methods of ^{18}F -FDG uptake measurement, mean, and maximum TBR. They suggested that mean TBR is appropriate for trials of systemic therapies, whereas the maximum TBR is appropriate for tracking local and plaque-based therapy. The clinical meaning of maximum and mean TBR might be different from each other, and our study suggests that the highest vascular inflammation activity is responsible for overall cardiovascular risk.

The correlation between ^{68}Ga -DOTATOC uptake and FRS exhibited higher statistical significance in ATA than in DTA (Table 3). In a previous study, the presence of plaques in ATA had the highest specificity for predicting coronary artery disease, compared to that in DTA or aortic arch [20]. Furthermore, ATA is the recommended site for measuring

^{18}F -FDG uptake to evaluate atherosclerotic change due to its excellent reproducibility [10]. These previous results are in accordance with the findings of this study.

If there are only a small number of inflammatory foci in the aorta, a single value of maximum uptake may overestimate the atherogenic activity of the whole artery. Thus, multi-sample ROI method has been suggested, in which maximum uptake is measured in each of multiple ROIs and averaged to a single value. While this method is much laborious, the single VOI method in the current study measures maximum and mean uptake by simply drawing a VOI for the whole aorta. The maximal value from this method ($TBR_{\text{max-VOI}}$) represents the highest inflammatory lesion in the entire vessel. $TBR_{\text{max-avg}}$ also showed a significant correlation with FRS, and thus, it is suggested that the uptake of aorta could be measured more simply. In comparison of the two methods, the Bland-Altman plot showed a tendency that the difference of $TBR_{\text{max-VOI}}$ is higher than that of $TBR_{\text{max-avg}}$, particularly in high value range. Because ^{68}Ga -DOTATOC uptake in the aorta is usually very low, it is reasonable that a single maximal value is larger than averaged one and the difference is larger in high value range than in low value range.

The current study has several limitations. First, aortic plaque or inflammation was not directly evaluated and the correlation between aortic ^{68}Ga -DOTATOC uptake and plaque vulnerability was not assessed. Second, the study was retrospectively designed with neuroendocrine tumor patients, and most patients had low cardiovascular risk. Also, the

number of patients was relatively small. Based on the current study, further studies are warranted with a prospective design and larger case numbers.

Conclusion

^{68}Ga -DOTATOC uptake in the thoracic aorta has a significant correlation with cardiovascular risk factors, which suggests that ^{68}Ga -DOTATOC uptake may be a potential predictor for cardiovascular events and biomarker for assessment of vulnerable plaque. Among various indexes, $\text{TBR}_{\text{max-avg}}$ or $\text{TBR}_{\text{max-VOI}}$ of ATA may be used as simple and effective representative indexes. Simple measurement from the single VOI method is comparable to multi-sample ROI-based approach in terms of agreement and correlation with risk factors. Further studies are warranted regarding clinical efficacy of ^{68}Ga -DOTATOC PET/CT in atherosclerosis and its correlation with cardiovascular events using these PET indexes.

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Compliance with Ethical Standards

Conflict of Interest Lee Reeree, Jihyun Kim, Jin Chul Paeng, Jung Woo Byun, Gi Jeong Cheon, Dong Soo Lee, June-Key Chung, and Keon Wook Kang declare that they have no conflict of interest.

Ethical Approval All procedures followed were performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The study design was approved by the Institutional Review Board of the Seoul National University Hospital (H-1711-112-901).

This manuscript has not been published before or is not under consideration for publication anywhere else and has been approved by all co-authors.

Informed Consent The study design of the retrospective analysis and exemption of informed consent were approved by the Institutional Review Board of the Seoul National University Hospital.

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