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Feasibility of ^{68}Ga-FAPI-46 PET for Evaluating Active Fibrosis in Aortic Aneurysm

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Abstract

Aortic aneurysm (AA) is a disease where aortic wall loses its elasticity, showing fibrosis. Fibroblast activation protein (FAP) expression can be evaluated using radiolabeled FAP-inhibitor (FAPI) PET in fibrosis. We investigated FAP expression in AA and the feasibility of ^{68}Ga-FAPI PET for AA imaging.

Twenty AA patients who were planned for resection were prospectively enrolled. Nine lung cancer patients were used as control. Markers including FAP expression were assessed in AA and the remote aorta. Preoperative ^{68}Ga-FAPI-46 PET was evaluated visually and quantitatively using maximal standard uptake value (SUVmax), and were compared with the growth rate of AA.

FAP expression was increased in Western blotting ($P = 0.014$), both in intima and adventitia of AA. The SUVmax was significantly correlated with the FAP expression ($r = 0.678$, $P = 0.008$). The SUVmax of AA was significantly higher than the aortic SUVmax of the control ($P = 0.018$). The growth rate of AA was different between the uptake grade groups ($P = 0.029$), and correlated with SUVmax ($r = 0.625$, $P = 0.013$).

FAP expression is variably increased in AA and possibly related to the progression of AA. ^{68}Ga-FAPI PET can be a promising imaging for evaluating FAP expression of AA.

Key words: fibrosis, fibroblast activation protein, aortic aneurysm, FAPI, PET

Non-standard Abbreviations and Acronyms

Aortic aneurysm = AA

Computed tomography = CT

Fibroblast activation protein = FAP

Fibroblast activation protein inhibitor = FAPI

Immunohistochemistry = IHC

Magnetic resonance imaging = MRI

Positron emission tomography = PET

Smooth muscle actin = SMA

Standardized uptake value = SUV

Transforming growth factor = TGF

Introduction

Aortic aneurysm (AA) is localized dilatation of aortic wall that can result in fatal dissection or rupture.[1] Since AA is generally asymptomatic, most AA are detected incidentally during physical examination or imaging tests for other indications,[2] including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). At present, the most effective treatment for AA is open surgery or endovascular interventions.[3] A diameter greater than 5.5 cm is used as the criteria for the need of treatment. However, the cross-sectionally assessed diameter is not a direct marker of AA progression. Surgical referral is also considered when the aneurysm grows more than 1 cm per year, since the rapid growth is a key predictor for rupture of AA.[4] However, measurement of growth rate requires regular and serial image follow-up.

AA progression involves various biological processes, particularly the chronic infiltration of inflammatory cells into tunica adventitia and media.[5,6] In these processes, fibroblasts are one of the first activated cell types, primarily in the tunica adventitia.[7] Fibroblast is essential for maintenance of the structure of blood vessel wall in the normal arteries, by producing the extracellular matrix. Activated fibroblasts transform into myofibroblasts and induces perivascular fibrosis through remodeling of tunica adventitia and media.[8] Finally, the loss of elasticity of media leads to aneurysmal progression.[9]

Recently, activated fibroblast-targeted molecular imaging methods have been developed and used in clinical researches and

practices. Fibroblast activation protein (FAP) is a surface protein that is upregulated in the activated fibroblasts.[10] FAP-inhibitor (FAPI) is a group of small molecules that specifically binds to FAP, and various radiolabeled FAPIs have been developed as imaging tracers for positron emission tomography (PET). Among them, ^{68}Ga-labeled FAPIs have demonstrated favorable imaging features, with fast and stable accumulation in target lesions, and have been used in many diseases.[11]

We hypothesized that FAP expression is increased in active and progressive AA, and that the enhanced FAP expression can be imaged by ^{68}Ga-FAPI-46, one of the ^{68}Ga-labeled FAPIs. Our study aims to assess the FAP expression in surgically resected AA tissues, and correlate it with image findings on ^{68}Ga-FAPI-46 PET. Additionally, we evaluated the correlation between the image findings and the AA growth rate.

Methods

Subjects and Study Design

Consecutive patients with AA who were planned for aortic surgery in Seoul National University were prospectively enrolled. Patients underwent ^{68}Ga-FAPI-46 PET/CT before surgery. The aneurysmal portion of the aorta was resected and replaced with a vascular graft. During the surgery, aortic wall of the resected aneurysmal segment was sampled and used for pathological analysis. In two patients, the resection margin of the operated aorta was sampled as the non-aneurysmal remote aorta. Patients' demographic and clinical information were obtained from the hospital information system,[12] and serial enhanced CT images were reviewed from the picture achieving and communication system of our institution. For comparison, ^{68}Ga-FAPI-46 PET images of 9 lung cancer patients without known vascular disease were retrospectively reviewed. ^{68}Ga-FAPI-46 PET was performed in these patients during the same study period for cancer evaluation.

The study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 2207-016-1338). All procedures were performed in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consents were obtained from all the patients.

Image Acquisition and Analysis

^{68}Ga-FAPI-46 PET/CT were performed using a single PET/CT scanner (Biograph mCT40, Siemens Medical Solutions, Erlangen, Germany), 60 minutes after injecting ^{68}Ga-FAPI-46 (185 MBq). CT scan was obtained first for attenuation correction and lesion localization (120 kVp, 80 mA, slice thickness of 5 mm), and PET scans were obtained from the vertex to the pelvis area for 2 minutes per bed position. PET images were reconstructed by an iterative algorithm (ordered subset expectation maximization) with CT-based attenuation correction.

PET images were analyzed by consensus of two image specialists (H.Y.S. and J.C.P.) using analysis software packages (Syngo.via, Siemens Medical Solutions, Erlangen, Germany, https://www.siemens-healthineers.com/digital-health-solutions/syngovia; and MIM v7.3.5, MIM Software Inc., Cleveland, OH, USA, https://www.mimsoftware.com/). Initially, the uptake of ^{68}Ga-FAPI-46 in the aortic aneurysmal wall was visually graded as 1 (not discernible from blood pool), 2 (discernible but mild uptake), and 3 (marked uptake). Afterward, a volume-of-interest was manually drawn to encompass the AA lesion and standardized uptake value (SUV) was measured from the volume-of-interest. In the control group, aortic uptake was measured in the descending thoracic aorta.

The maximum diameter of AA was measured using serial contrast-enhanced CT scans. The annual growth rate of AA was calculated based on measurements from the two CT scans, which were obtained with intervals of at least 6 months.

Pathological Analysis of Aortic Specimens

For immunohistochemistry (IHC) and histological analysis, tissues were fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned. H&E staining was performed to assess overall tissue morphology and pathological changes, and Masson's trichrome staining was applied to evaluate fibrosis. IHC staining was performed for FAP, transforming growth factor (TGF)-β1, and α-smooth muscle actin (SMA) expression using primary antibodies (anti-FAP [ab227703], anti-TGF-β1, and α-SMA; Abcam).

For quantitative Western blot analysis, total protein was extracted from the AA tissue using a lysis buffer for 30 minutes. Lysates were centrifuged at 12,000 G for 20 minutes at 4°C, and protein concentrations were determined using the BCA protein assay kit (Thermo Fisher Scientific, Waltham, MA, USA). Equal amounts of protein were resolved on 10% SDS-PAGE gels, transferred to PVDF membranes using the iBlot 2 Dry Blotting System (Thermo Fisher Scientific), and blocked with 5% skim milk in TBST for 2 hours. Membranes were incubated overnight at 4 °C with primary antibodies (anti-FAP [ab53066], anti-TGF-β1 [ab215715], and α-SMA [ab5694]; Abcam, Cambridge, UK) in EveryBlot Blocking Buffer (Bio-Rad, Hercules, CA, USA). HRP-conjugated secondary antibodies were applied, and bands were visualized using the Clarity Western ECL Substrate (Bio-Rad) on the Amersham 680 Imaging System (GE Healthcare, Chicago, IL, USA). Band intensities were analyzed with ImageJ software (ImageJ v1.54g, National Institutes of

Health, Bethesda, MD, USA, https://imagej.nih.gov/ij/) and normalized to β-actin levels.

To evaluate the uptake of ^{68}Ga-FAPI-46 in the aortic tissue, autoradiography was performed using paraffin-embedded sections. After 30-minute incubation with ^{68}Ga-FAPI-46 (30 μCi/0.1 mL) at room temperature, the sections were air-dried and exposed to an imaging plate (FUJIFILM BAS-IP SR2040). The imaging plates were scanned using a phosphor imager (Typhoon FLA 9500, GE Healthcare, Chicago, IL, USA) and the images were analyzed using a vendor-supplied software package (ImageQuant TL v8.1, GE Healthcare Life Sciences, Uppsala, Sweden, https://www.cytivalifesciences.com).

Statistical analysis

All data were expressed in mean ± standard deviation. Mann-Whitney test was used to evaluate the difference of quantitative indexes between the two groups. Kruskal-Wallis test was used to compare the differences of imaging indexes between different visual grade groups. Correlation between indexes was evaluated using Spearman's rank correlation coefficient. All data were analyzed by a commercial statistical software package (MedCalc v15.8, MedCalc Software Ltd., Ostend, Belgium, https://www.medcalc.org/en/), and a *P*-value < 0.05 was considered statistically significant.

Results

Patients

Twenty patients with AA (8 men and 12 women; age 67.7 ± 11.5 y) were prospectively enrolled in this study; 9 with ascending aorta aneurysms, 5 with arch or descending thoracic aorta aneurysms, 1 with thoracoabdominal aorta aneurysms, and 5 abdominal aorta aneurysms. Patients' demographic and clinical characteristics are summarized in Table 1. ^{68}Ga-FAPI-46 PET images of 9 patients with lung cancer (3 men and 6 women; age 63.2 ± 5.6 y) were retrospectively reviewed as a control group. There were no significant differences between the AA and control patients in clinical characteristics related to AA; sex, age, body mass index, blood pressure, C-reactive protein, underlying related diseases, and family history (P = n.s. for all, Table 1).

FAP Expression in Aortic Aneurysm

AA tissue was obtained from 14 patients, excluding cases in which the harvested aortic tissues were not available for western blotting. Additionally, the remote aorta tissue was collected from 3 AA patients.

In the quantitative Western blot analysis (Fig. 1A), FAP/β-actin ratio was significantly higher in the AA tissue (n = 14, median 0.85, range 0.22 – 2.09), compared with the remote aorta (n = 3, median 0.17, range 0.03–0.28) (P = 0.014, Fig. 1B). Similarly, TGF-β/β-actin ratio was also significantly higher in the AA tissue (median 0.67, range 0.10–2.27) than in the remote aorta (median 0.05, range 0.03–0.28) (P = 0.012, Fig. 1C).

However, α-SMA/ β-actin ratio was not significantly different between the two groups (P = 0.900, Fig. 1D).

In the H&E and Masson's trichrome staining of the remote aorta, collagen fibers were observed mostly in the adventitia, whereas the AA tissue showed collagen fibers both in the intima-media layer and the adventitia layer (Fig. 2). In the IHC, significant FAP expression was not observed in the remote aorta. However, the AA tissue showed high FAP expression in both the intima-media and adventitia layers. TGF-β showed a similar expression pattern to that of FAP.

In the autoradiographic analysis, ^{68}Ga-FAPI-46 uptake was diffusely increased in the aortic aneurysm tissue compared with the remote aorta (Fig. 3).

^{68}Ga-FAPI-46 PET

In the visual analysis, ^{68}Ga-FAPI-46 uptake in the AA sites was variable (n = 11 in grade 1, n = 5 in grade 2, and n = 4 in grade 3), whereas all control group patients had low uptake and was in grade 1. Representative images are shown in Fig. 4. When the uptake was quantitatively measured, SUVmax showed significant differences according to the visual grading (2.04 ± 0.20 in grade 1, 2.65 ± 0.31 in grade 2, and 3.16 ± 0.26 in grade 3, Fig. 5A), suggesting relevance of semiquantitative analyses. The SUVmax of ^{68}Ga-FAPI-46 uptake also showed a significant positive correlation with the FAP/β-actin ratio (n = 14, r = 0.678, P = 0.008, Fig. 5B). In the comparison between AA (n =

20) and control groups (n = 9), the SUVmax of ^{68}Ga-FAPI-46 uptake was significantly higher in the AA group (2.42 ± 0.51 *vs*. 1.99 ± 0.36, P = 0.018, Fig. 5C).

Correlation of ^{68}Ga-FAPI-46 Uptake with Growth Rate of AA

The growth rate of AA was measured in 15 patients for whom adequate contrast-enhanced CT images were available (n = 7 in grade 1, n = 5 in grade 2, and n = 3 in grade 3). In overall group, the growth rate of AA was not so high (median 0.07, range -0.77–3.01 cm/year). The growth rate of AA was significantly higher in the high visual uptake group, compared with the low visual uptake group (P = 0.029, Fig. 6A). Also, SUVmax of AA showed a significant correlation with the growth rate (r = 0.625, P = 0.013, Fig. 6B).

Discussion

Activated fibroblast plays a key role in inflammation and tissue repair.[13] In the development of AA, inflammation is a hallmark of biological processes, accompanied by the gradual loss of smooth muscle cells and disruption of extracellular matrix.[14] Activated fibroblast may directly cause amplification of inflammation and disruption of extracellular matrix by secreting matrix metalloproteinase.[5] In this study, we evaluated FAP expression as a surrogate marker for activated fibroblasts, in surgically resected AA tissues and preoperative ^{68}Ga-FAPI-46 PET images. The results demonstrated high FAP expression, which was well correlated with increased uptake of ^{68}Ga-FAPI-46 in AA tissues. Additionally, we observed a weak but significant correlation between ^{68}Ga-FAPI-46 uptake and the growth rate of AA.

The efficacy of FAPI PET has been widely investigated in cancers, where FAP expression is increased in cancer-associated fibroblasts, leading to high uptake on FAPI PET.[15] FAP overexpression has also been linked to poor prognosis in cancer.[16] While the exact function of FAP in cancer remains unclear, numerous clinical studies have reported high sensitivity of FAPI PET for cancers,[17] in association with activated cancer-associated fibroblasts. Activation of fibroblasts occurs not only in the tumor microenvironment but also in the nonmalignant conditions such as wound healing, inflammation, or atherosclerosis.[18,19] Recent studies have reported the application of FAPI PET in cardiovascular disorders such as myocardial infarction, hypertension, and heart

failure.[20-22] Based on this background, ^{68}Ga-FAPI-46 PET was applied to AA in this study.

In the pathological specimens, FAP was evaluated alongside other key markers of AA, including TGF-β and α-SMA. TGF-β is a well-known mediator in the progression of AA despite its controversial role.[14,23] TGF-β is deemed to promote apoptosis of smooth muscle cells and matrix degradation. In a previous study, high expression of TGF-β was observed in the aneurysmal tissues of both syndromic and non-syndromic AA,[24] which is consistent with our results that the aneurysmal specimen exhibited elevated TGF-β expression in the adventitia layer. α-SMA, a marker for smooth muscle of the aorta, has been reported to be downregulated in AA, primarily in the early phase.[25] In our study, there was no difference in α-SMA expression between the AA and the remote aorta tissues, which may be related to relative stable phase and potential sampling limitations, including spatial heterogeneity and limited tissue availability.

In our study, FAP expression was significantly increased in the AA tissues, despite a wide variation. FAP expression was observed in both the intima-media and adventitia layers, matched with collagen fibers. In contrast, FAP expression was not observed in the remote aorta, even in the adventitia layer where collagen fiber was observed. The FAP expression measured on quantitative Western blotting was well correlated with the SUVmax measured on ^{68}Ga-FAPI-46 PET, suggesting that the PET imaging can be a promising non-invasive method for

evaluating FAP expression in the AA tissues. In a recent study, pilot human imaging was performed in 6 AA patients using ^{68}Ga-FAPI-04 PET, in combination with comprehensive animal experiments.[26] In this study, the uptake pattern in the aneurysmal wall was reported similar to that of our study.

The key factor in deciding on surgical intervention in AA is the risk of progression and rupture, which is currently based solely on the structural factors, current size of AA and its growth rate. Serial measurement of the AA size and the calculated growth rate can be the gold standard to determine AA progression. However, this approach requires serial and periodic CT follow-up, making it unsuitable for assessing immediate risk. Thus, we compared the growth rate with the AA uptake measured on ^{68}Ga-FAPI-46 PET. Both the visual grading and SUVmax exhibited significant associations with the growth rate. However, the overall growth rates were low, reflecting relatively stable AA in most patients, and substantial inter-individual variability was observed. Accordingly, the observed correlation was modest. Although patients with SUVmax below 2.5 tended to exhibit minimal growth, it should be regarded as exploratory, given the high variability in growth rates.

If the FAP expression in aneurysmal wall serves as a marker for inflammatory activity, vulnerability and progression risk of AA, ^{68}Ga-FAPI-46 and other FAPI PET may represent a promising imaging method for evaluating AA. It can be used for non-invasive evaluation of AA

patients, in terms of the current disease activity and immediate risk of rupture. Although increased ^{68}Ga-FAPI-46 uptake was observed predominantly in AA, low or focal ^{68}Ga-FAPI-46 uptake was also detected in aortic walls without AA. This finding may reflect that ^{68}Ga-FAPI-46 uptake shows a spectrum of vascular remodeling related to fibroblast-activated inflammation rather than being strictly aneurysm-specific. Moreover, FAPI PET could be used in drug development to evaluate the treatment efficacy for stabilizing the disease activity. Thus, further studies are required with a large cohort of patients who have varying disease activity of AA, to validate the efficacy of ^{68}Ga-FAPI-46 PET in evaluating AA patients.

In addition to the characteristics of the patient cohort, our study has several limitations. First, although the patients were prospectively enrolled in consecutive manner, the sample size was small. Additionally, pathological data were unavailable for some patients, and due to surgical concerns, remote aorta tissue was obtained from only 3 patients. Second, CT follow-up data were not obtained from 5 patients due to unavailable CT scans or insufficient follow-up periods. Moreover, the study cohort included aneurysms involving various aortic segments, each characterized by distinct pathophysiological mechanisms. This anatomical heterogeneity may affect the ^{68}Ga-FAPI-46 uptake. In addition, although images were independently evaluated by two experienced readers and reached consensus, formal quantitative assessment of interobserver agreement for visual analysis was not

performed. Furthermore, the control group does not represent a truly healthy vascular population and should be considered a potential confounding factor. Because cancer patients may have systemic inflammation or vascular remodeling that can influence ^{68}Ga-FAPI-46 uptake, the findings should be interpreted considering this limitation. Despite the statistical significance of the key findings, further studies with larger sample sizes, location-specific cohorts, including healthy volunteers, and comprehensive long-term follow-up data are required.

Conclusions

FAP expression is overall increased in AA tissues despite a wide variation. The uptake measured on ^{68}Ga-FAPI-46 PET is well correlated with the FAP expression on AA tissue, and exhibits significantly high uptake in AA. Also, the uptake is related to the progression of AA. Thus, ^{68}Ga-FAPI-46 PET can be a promising, non-invasive imaging method for evaluating AA. Further studies are warranted to validate clinical implication of FAP activity in the AA.

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Author contributions

JCP and JWC designed the study. JWC and JWB acquired data. HYS and JCP analyzed data and drafted the manuscript. SPL and JWC participated in discussion and revision. All authors read and approved the final manuscript.

Data availability statement

The datasets used in this study are available from the corresponding authors on reasonable request.

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Conflict of interests

The authors declare no conflict of interest.

Ethical approval

All the proceduring during this study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 2207-016-1338) in accordance with the 1964 Helsinki declaration, and informed consents were obtained from all the patients.

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We would like to thank all participants for the contribution to this study. We would also like to thank all the study nurses and technical assistants for their study support.

Figures

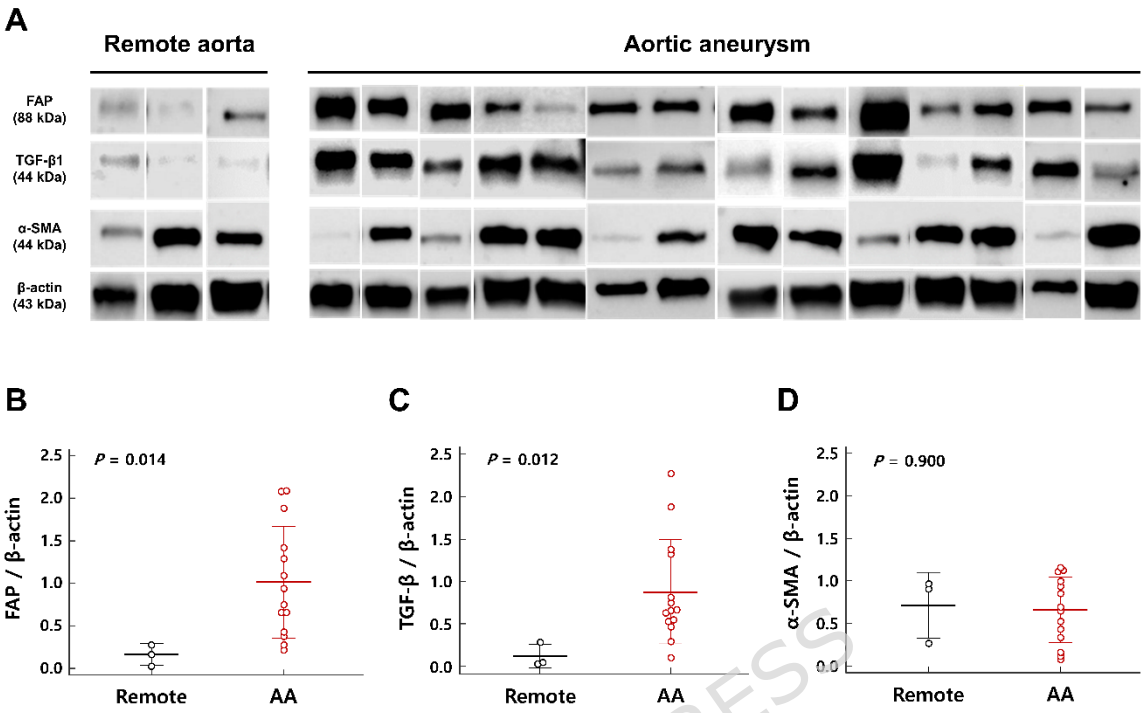

Figure 1. Quantitative Western blotting of the resected aneurysm. The aneurysm tissue showed high expression of FAP and TGF-β (A). In the quantitative analysis, the expressions of FAP and TGF-β normalized to β-actin expression were significantly higher than the remote aortic tissues (B and C), whereas the expression of α-SMA was not (D). Samples were originated from the same experiment and were processed in parallel. The results have been cropped and the original Western blotting is presented in Supplementary Figure 1. FAP = fibroblast activation protein; TGF = transforming growth factor; SMA = smooth muscle actin; AA = aortic aneurysm.

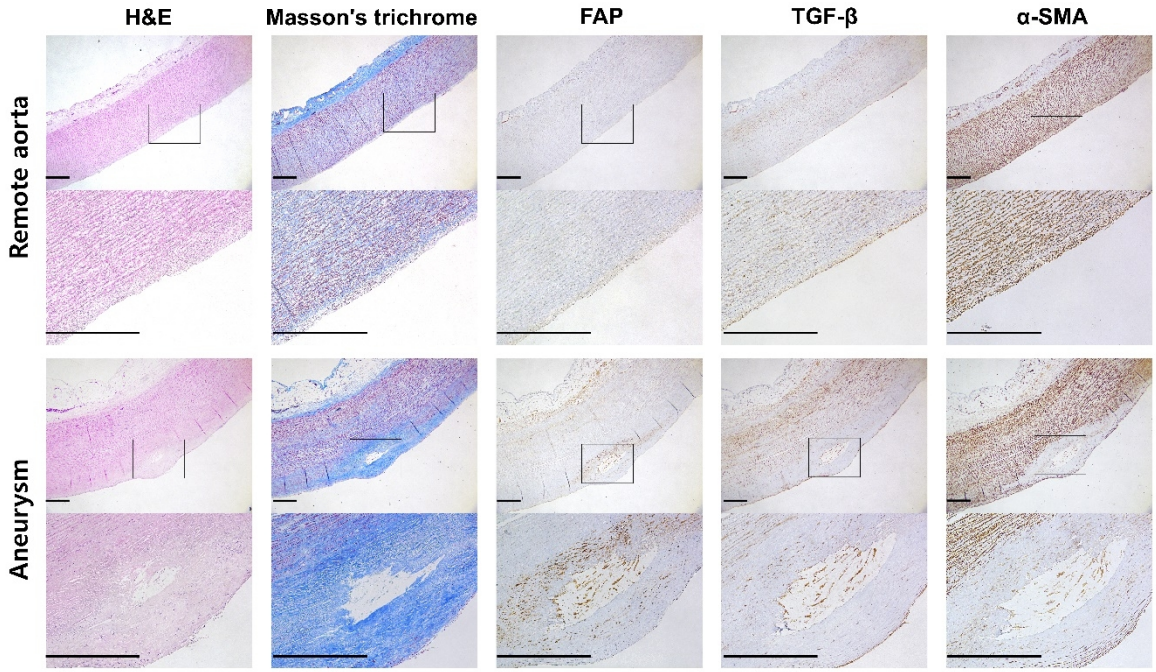

Figure 2. Pathological images. On Masson's trichrome staining, collagen fibers were observed in both the intima-media and adventitia layer (box) in the aneurysm tissue, while it was observed only in adventitia layer in the remote aorta. However, FAP expression was not observed in the adventitia layer of the remote aorta, in contrast to the high expression in both the intima-media and adventitia layers of the aneurysm. FAP = fibroblast activation protein; TGF = transforming growth factor; SMA = smooth muscle actin.

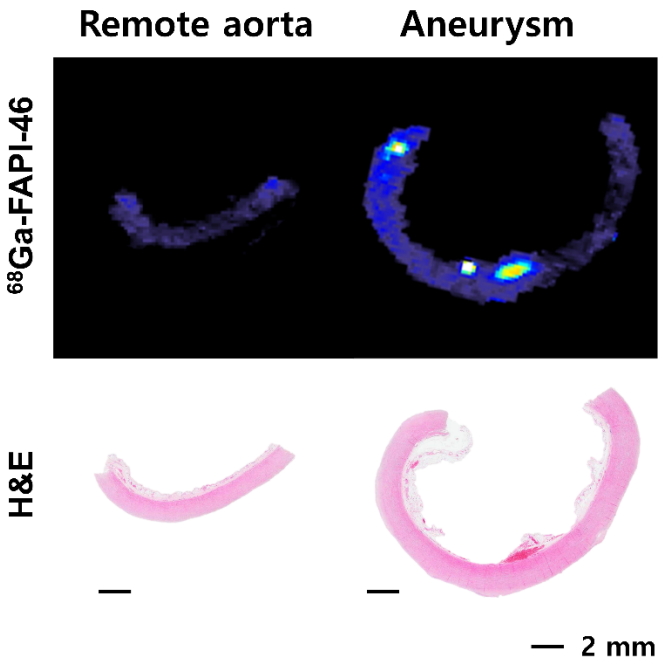

Figure 3. Autoradiographic images. Diffuse ^{68}Ga-FAPI-46 uptake was shown in aneurysm tissue relative to the remote aorta. FAP = fibroblast activation protein.

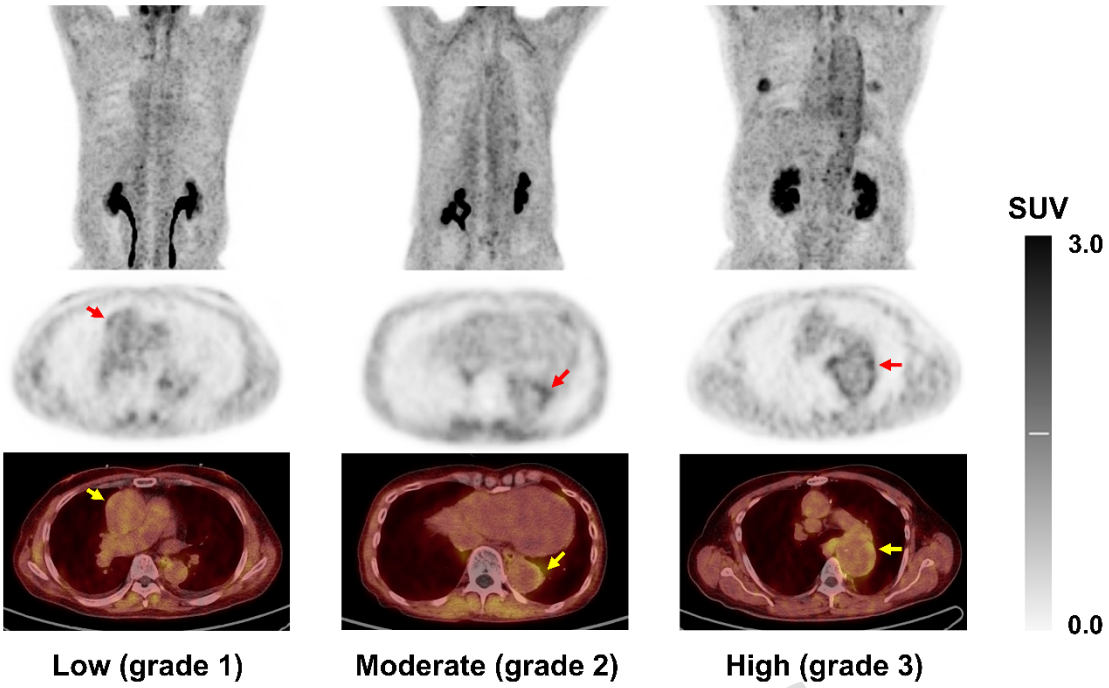

Figure 4. Representative cases of ^{68}Ga-FAPI-46 PET. An uptake indiscernible from the blood pool activity was classified as grade 1. Discernible but mild uptake, and prominent uptake were classified as grade 2 and 3, respectively. Arrows show uptakes in the aortic aneurysm. SUV = standardized uptake value.

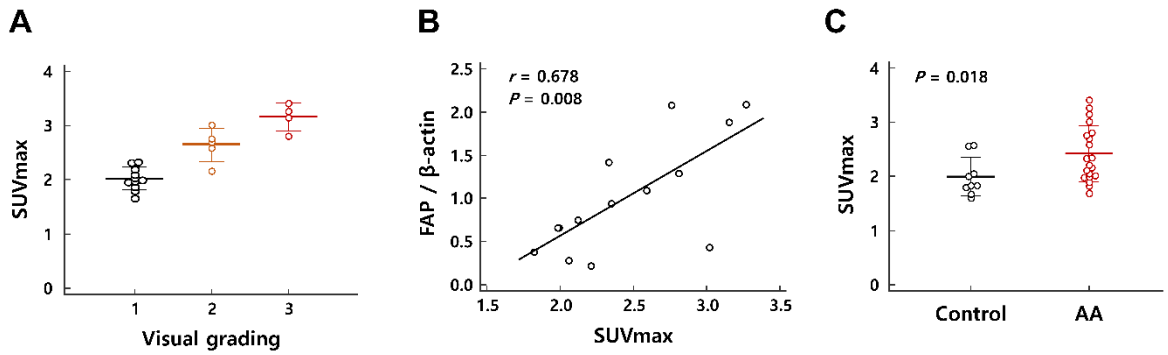

Figure 5. Uptake of ^{68}Ga-FAPI-46 on PET imaging. (A) SUVmax showed differences according to the visual grading. (B) SUVmax of the aortic aneurysm demonstrated significant correlation with the FAP expression on quantitative Western blotting. (C) SUVmax was significantly higher in the aortic aneurysm than the aorta of the control group. FAP = fibroblast activation protein; SUV = standardized uptake value; AA = aortic aneurysm.

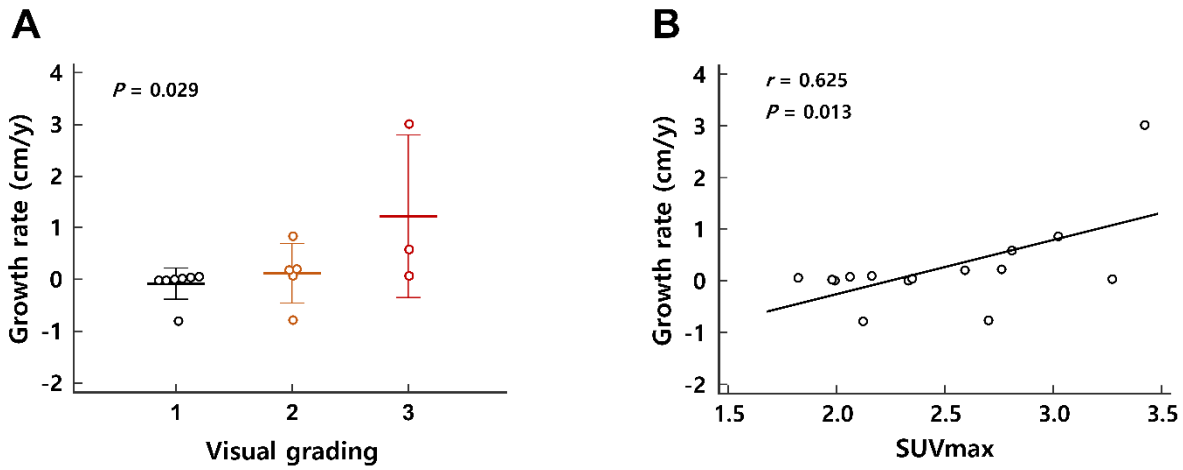

Figure 6. Growth rate of aortic aneurysm according to uptake of ^{68}Ga-FAPI-46. The growth rate of the aortic aneurysm showed significant association with visual grading (A) and correlation with SUVmax (B). SUV = standardized uptake value.

Table

Table 1. Clinical characteristics of the 20 aortic aneurysm patients and 9 control

Variable	Control	Aortic aneurysm	*P*
Sex (Male : Female)	3 : 6	8 : 12	0.945
Age (year)	63.2 ± 5.6	67.7 ± 11.5	0.114
BMI (kg/m^2)	24.2 ± 6.0	26.4 ± 4.7	0.167
Systolic blood pressure (mmHg)	125.3 ± 28.2	127. 5 ± 20.6	0.358
Diastolic blood pressure (mmHg)	74. 8 ± 7.9	75.4 ± 13.4	0.850
C-reactive protein (mg/dL)	0.88 ± 2.13	0.30 ± 0.50	0.981
Hypertension	3 (33%)	13 (65%)	0.236
Diabetes mellitus	3 (33%)	4 (20%)	0.760
Dyslipidemia	2 (22%)	7 (35%)	0.798
Smoking history	3 (33%)	5 (25%)	0.989
Family history of AA	0	2 (10%)	0.848

BMI = body mass index; AA = aortic aneurysm.