International Journal of Cardiology 283 (2019) 171–177

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Positron emission tomography/computed tomography detection of increased ^{18}F-fluorodeoxyglucose uptake in the cardiac atria of patients with atrial fibrillation☆

Emiri Watanabe [a,*], Masao Miyagawa [a], Teruyoshi Uetani [b], Masaki Kinoshita [b], Riko Kitazawa [c], Mie Kurata [d], Hayato Ishimura [a], Takuya Matsuda [a], Yuki Tanabe [a], Tomoyuki Kido [a], Teruhito Kido [a], Akira Kurata [a], Teruhito Mochizuki [a]

[a] Department of Radiology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan
[b] Department of Cardiology, Pulmonology, Hypertension & Nephrology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan
[c] Department of Molecular Pathology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan
[d] Department of Pathology, Ehime University Graduate School of Medicine and Proteo-Science Center, Toon, Ehime, Japan

ARTICLE INFO

Article history:
Received 2 August 2018
Received in revised form 4 October 2018
Accepted 29 October 2018
Available online 31 October 2018

Keywords:
Atrial fibrillation
^{18}F-FDG
Inflammation
PET/CT

ABSTRACT

Background: Direct evidence of inflammatory activity in the atria of patients with atrial fibrillation (AF) is scarce. We assessed the capability of positron-emission tomography/computed tomography (PET/CT) to diagnose AF based on fluorodeoxyglucose (FDG) uptake in the atrial wall.

Methods and results: Among 8233 patients who underwent FDG-PET/CT as work-up for malignancies, we identified 180 consecutive patients with AF (2.2%). Of those, we selected 137 patients who had fasted >12 h before FDG injection for inclusion in the experimental group (88 men and 49 women; age: 72.7 ± 8.9 years). Controls were 62 age- and sex-matched patients without AF. For visual analysis, we used a 4-point grading system. For quantitative analysis, we used the maximum standard uptake value (SUVmax) in the left (LA) and right atrial (RA) myocardium and the target-to-background ratio (TBR) of SUVmax to blood pool activity. The sensitivity, specificity, and positive-predictive value for detecting AF visually were 54.0%, 95.2%, and 96.1%, respectively; for quantitative analysis, the respective values were 65.7%, 75.8%, and 85.7%. Multivariable analysis of 11 clinical and imaging variables showed significant associations with RA SUVmax (odds ratio [OR]: 14.353, $P = 0.026$) and LA volume (OR: 1.371, $P = 0.0001$). The RA TBR was greater in cases with persistent AF than in those with paroxysmal AF ($P < 0.0001$). Pathological investigation of 4 autopsy hearts confirmed infiltration of extravascular macrophages and lymphocytes in the regions with FDG uptake.

Conclusions: Higher atrial FDG uptake was associated with AF. PET/CT could be a useful tool for detecting local inflammation in the atria with AF.

1. Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that may result in life-threatening complications, such as stroke and heart failure [1]. The worldwide incidence, prevalence, and mortality from AF are increasing; thus, AF presents a rapidly growing public health and economic burden [2]. Inflammation is involved in AF pathophysiology [3]. Increased C-reactive protein (CRP) levels predicted the development of new-onset AF in several large, prospective cohorts [4,5]. Inflammation might result in atrial structural and electric remodeling, the main pathophysiological mechanisms contributing to the initiation and maintenance of AF. However, direct evidence of local inflammatory activity in the atria of patients with AF is scarce.

Noninvasive imaging techniques, such as ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), can facilitate detection of regional atrial inflammation. However, to date, only a few case reports have been published. This study aimed to assess the capability of PET/CT to diagnose AF by visually or quantitatively determining FDG activity in the atrial wall. Additionally, we

Abbreviations: AF, atrial fibrillation; AUC, area under the curve; CRP, C-reactive protein; CT, computed tomography; CTR, cardiothoracic ratio; FDG, fluorodeoxyglucose; Hb, hemoglobin; LA, left atrium; LV, left ventricle; MIP, maximum intensity projection; PET/CT, positron-emission tomography/computed tomography; RA, right atrium; ROC, receiver operator characteristic; ROI, region of interest; SUVmax, maximum standard uptake value; TBR, target-to-background ratio.

☆ All above authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Radiology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 7910295, Japan.
E-mail address: emirim.0911@gmail.com (E. Watanabe).

https://doi.org/10.1016/j.ijcard.2018.10.106
0167-5273/

explored the factors influencing enhanced accumulation of FDG in the atrium.

2. Methods

2.1. Study population

Between April 2011 and June 2016, 8233 patients underwent whole-body FDG-PET/CT examination as a pretreatment work-up or follow-up for malignancies at Ehime University Hospital. Among them were 180 consecutive patients with AF (2.2%). All patients completed an interview questionnaire about the duration of fasting, medical history, and cardiac risk factors. Based on an interview, we included 137 patients with AF (76.1%) who had fasted for at least 12 h before FDG injection for inclusion in the experimental group (88 men and 49 women; 72.7 ± 8.9 years). We excluded patients with active inflammatory diseases, cardiac tumor or tumor metastatic to the heart, pericardial diseases, or pericardial effusion. As controls, we included were 62 age- and sex-matched patients without a history of AF who had also fasted for at least 12 h before FDG injection. Patients with diabetes were excluded from the control group.

From the charts, we collected information on current illnesses; medical history, including AF treatments, such as ablation and cardioversion; various blood tests results; blood pressure; and echocardiography and other clinical examination results. >1 year (up to 2.5 ± 1.1 years) after the PET/CT examination, we observed the condition and outcome of patients and classified their AF as either paroxysmal or persistent: paroxysmal AF was defined as AF that terminates spontaneously or with intervention within 7 days of onset, while persistent AF that is sustained >7 days. Therapeutic and follow-up methods for each patient were decided by the attending physician.

The study protocol was approved by the Institutional Research Ethics Committee (No. 1803001) of Ehime University Graduate School of Medicine. All patients provided written informed consent before enrollment in the study.

2.2. FDG-PET/CT imaging and analyses

PET/CT images were obtained using a multi-slice scanner (Discovery 600 PET/CT; GE Healthcare, Milwaukee, WI) 90 min after intravenous administration of FDG at 3.7 MBq/kg body weight. The fasting plasma glucose (FPG) level was measured just before FDG injection. Head-to-thigh images from 6 to 7 bed positions were acquired for 3 min/bed position. Unenhanced CT scan data were collected for attenuation correction and diagnosis. PET/CT fusion images (3.27-mm thick) and maximum intensity projection (MIP) images were reconstructed and reviewed on an Advantage Workstation Version 7.4 (GE Healthcare).

For visual analysis, the PET/CT fusion images were independently reviewed by 2 experienced nuclear medicine physicians blinded to patient clinical data, using a 4-point grading system: grade 0, atrial FDG uptake was lower than the adjacent blood pool (background); grade 1, uptake was similar; grade 2, atrial FDG uptake was slightly higher than the background; and grade 3, cardiac FDG uptake was evidently higher than the background. Grade 2–3 atrial FDG uptake was defined as positive. The uptake site in the atria was recorded. In cases of discordant findings, the final decision was made by consensus.

For quantitative analysis, regions of interest (ROIs) encompassing the cardiac atria were manually drawn on the serial transaxial and coronal fusion images (Supplemental Fig. 1). We carefully adjusted the ROI positions to include areas adjacent to the epicardial adipose tissue (EAT), but not the paracardial adipose tissue. We obtained the highest standard uptake value (SUV) for the sum of ROIs of all serial slices and determined the maximum SUV (SUVmax) in the volume of the left (LA) and right atrial (RA) and left ventricular (LV) myocardium. We also obtained the mean SUV in a spherical volumetric ROI (approximately 2.5 cm^3) for the blood pool in the ascending aorta, immediately distal to the aortic valve, as background [6]. Then, we calculated the target-to-background ratio (TBR) of maximum target myocardial activity to blood pool activity.

2.3. Echocardiographic analysis

Echocardiography was performed with a Vivid E9 or iE33 ultrasound system (GE Medical, Horten, Norway; Philips Medical Systems, Andover, MA). Conventional echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography [7]. LA and RA areas were measured by tracing the maximum area during systole in the apical 4-chamber view. LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction were measured using the biplane modified Simpson's method. All measurements were averaged from 2 cardiac cycles.

2.4. Histological examination

Immunohistochemical analyses were performed on autopsy heart samples from 4 patients with AF. Tissue samples were taken and fixed in 4% formaldehyde at autopsy. Paraffin-embedded specimens were serially sectioned and stained with hematoxylin–eosin, followed by immunostaining with antibodies against CD68, CD3, and CD20. Then, the microscopic findings were compared with FDG accumulation on PET/CT imaging.

2.5. Statistical analysis

Categorical variables are described as numbers and percentages, whereas continuous variables are expressed as medians and interquartile ranges or means and 95% confidence intervals (CIs) where appropriate. Differences between AF and control groups were calculated with Student's *t*-test, chi-square test, or Fisher's exact test, as appropriate. Visual and quantitative analysis data were compared using one-way analysis of variance and a post-hoc Tukey–Kramer test. A *P*-value < 0.05 was considered significant. Diagnostic performance was assessed by univariate and multivariate analyses. Accuracy of each parameter in the detection of AF was assessed in terms of the area under receiver operating characteristic (ROC) curves, which were compared using the DeLong method. The optimal cut-off points were selected using ROC curves.

The accuracy of the different methods was compared using a paired McNemar's test. To evaluate independent predictors of AF, forward-stepwise logistic regression analysis was used with variables of clinical importance or a *P*-value < 0.05. SPSS Statistics (version 25; IBM, Armonk, NY) and R version 3.4.2 were used for analysis. Intra- and inter-operator reproducibility evaluation of the TBR and SUVmax are summarized in Supplemental results.

3. Results

3.1. Clinical characteristics of the study patients

The fasting duration was 16.5 (14.6–18.2) h at the time of FDG injection in 137 patients with AF, and 16.9 (15.4–19.6) h in 62 controls ($P = 0.103$). FPG levels were significantly higher in the AF group (100 [91–110] mg/dl) than in controls (94 [85–102] mg/dl, $P = 0.038$).

The characteristics of all study patients are summarized in Table 1. Systolic blood pressure (SBP), frequency of mitral valve diseases, serum cholesterol, hemoglobin (Hb) A1c, brain natriuretic peptide (BNP), cardiothoracic ratio (CTR), echocardiographic RA and LA areas, and atrial maximum SUVs and TBRs differed significantly. The proportion of heart failure patients was 36.5% in the AF group and 11.3% in controls ($P = 0.0003$). The LA area was weakly correlated with BNP ($r = 0.308$).

Echocardiography was performed within 2.8 months before and after the PET/CT. The LA area was greater than the RA area in both patients with AF and controls ($P < 0.0001$). Atrial FDG accumulation did not correlate with either atrial area.

It has been reported that patients with recent upper gastrointestinal surgery have an increased risk of developing AF postoperatively. However, there was no significant difference between these two groups (15 patients with previous upper gastrointestinal surgery in the AF group and 5 such patients in the control group: $P = 0.531$).

3.2. FDG-PET/CT results

The diagnostic capability for detecting AF based on FDG uptake by the RA and/or LA is summarized in Table 2. Of the 137 patients with AF, 64 (46.7%) demonstrated accumulation in the RA, and 57 (41.6%) in the LA ($P = 0.394$), whereas 63 (46.0%) demonstrated no accumulation. The overall sensitivity, specificity, accuracy, positive-predictive value, and negative-predictive value for detecting AF by atrial FDG uptake visually was 54.0%, 95.2%, 66.8%, 96.1%, and 48.4%, respectively.

In 74 patients who were positive for atrial FDG accumulation, we classified the site of accumulation as follows: 52 (70.3%) in the RA appendage, 54 (73.0%) in the RA free wall, 45 (60.8%) in the interatrial septum, 43 (58.1%) in the LA appendage, 39 (52.7%) in the LA anterior wall, and 25 (33.8%) in the LA posterior wall.

In quantitative analysis, the SUVmax values of the 2 atria were both significantly higher in patients with AF than in controls (RA SUVmax: 2.50 [2.10–3.00] vs. 2.00 [1.80–2.20], $P < 0.0001$; LA SUVmax: 2.50 [2.20–3.05] vs. 2.10 [1.88–2.30], $P < 0.0001$) (Table 1). There was no significant difference between the background FDG uptake in patients with AF and controls (1.50 [1.30–1.60] vs. 1.40 [1.30–1.55], $P = 0.669$). The TBRs of both atria were also significantly higher in the AF group than in controls (RA TBR: 1.62 [1.42–2.11] vs. 1.39 [1.33–1.54], $P < 0.0001$; LA TBR: 1.65 [1.50–2.00] vs. 1.48 [1.37–1.64], $P < 0.0001$). In the AF group, there were no significant differences in SUVmax ($P = 0.573$) or TBR ($P = 0.638$) between the RA and LA.

ROC analyses were performed to identify cut-off values for the above 4 indices. The area under the curve (AUC) for detection of AF was 0.795 (95%CI: 0.733–0.856) for RA SUVmax, 0.749 (0.681–0.818) for LA SUVmax, 0.738 (0.669–0.807) for RA TBR, and 0.689 (0.614–0.765) for

Table 1
Characteristics of study patients.

		Atrial fibrillation	Control	*P* value
Number of patients		137	62	
Female		49 (36)	30(48)	0.092
Age (years)		73(68–80)	73(68–76)	0.681
Body mass index (kg/m^2)		22.8(20.6–25.4)	22.2(20.5–24.4)	0.559
Systolic blood pressure (mm Hg)		118(108–130)	128(118–137)	0.02
Diastolic blood pressure (mm Hg)		66(60–73)	68(62–77)	0.18
Hypertension		72(54)	26(42)	0.125
Hyperlipidemia		44(32)	25(40)	0.275
Smoking		75(60)	26(50)	0.244
Drinking		35(29)	14(34)	0.51
Mitral valve disease		28(21)	2(4)	0.009
Implantable device		15(11)	3(5)	0.174
Blood test	Total cholesterol (mg/dL)	175(146–195)	194(166–221)	0.0003
	HDL cholesterol (mg/dL)	43(36–55)	54(44–67)	<0.0001
	LDL cholesterol (mg/dL)	99(79–116)	114(82–137)	0.028
	Triglyceride (mg/dL)	102(76–139)	108(78–133)	0.907
	Creatinine (mg/dL)	0.90(0.77–1.13)	0.80(0.67–1.00)	0.208
	HbA1c (%)	5.9(5.6–6.5)	5.7(5.4–6.0)	<0.0001
	CRP (mg/dL)	0.20(0.06–0.89)	0.11(0.05–0.34)	0.134
	Hemoglobin (g/dL)	12.7(11.1–14.0)	13.0(12.0–13.9)	0.127
	BNP (pg/mL)	149.0(56.7–316.0)	22.6(9.0–46.4)	<0.0001
Echocardiography	Ejection fraction (%)	63(54–68)	62(52–69)	0.929
	RA area (cm^2)	21.8(14.6–34.8)	9.0(6.6–9.6)	<0.0001
	LA area (cm^2)	30.7(20.6–65.0)	12.9(11.4–14.0)	<0.0001
FDG PET/CT	CTR (%)	51(47–58)	48(44–52)	0.001
	RA SUVmax	2.50(2.10–3.00)	2.00(1.80–2.20)	<0.0001
	LA SUVmax	2.50(2.20–3.05)	2.10(1.88–2.30)	<0.0001
	LV SUVmax	4.70(2.70–8.10)	3.05(2.28–6.03)	0.09
	RA TBR	1.62(1.42–2.11)	1.39(1.33–1.54)	<0.0001
	LA TBR	1.65(1.50–2.00)	1.48(1.37–1.64)	<0.0001
	LV TBR	2.94 (1.80–5.49)	2.17(1.59–4.76)	0.304

Continuous variables are expressed as median (interquartile ranges), or number (%).
HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; CRP, C-reactive protein; BNP, brain natriuretic peptide; RA, right atrium; LA, left atrium; LV, left ventricle; CTR, cardiothoracic ratio; SUVmax, maximum standardized uptake value; TBR, target-to-background ratio.

LA TBR. RA SUVmax had the largest AUC, which was significantly greater than that of RA TBR ($P = 0.049$).

Multivariable logistic regression analysis of 11 clinical and imaging variables (BMI, SBP, frequency of mitral valve diseases, total cholesterol, CRP, Hb, RA and LA area, CTR, and RA and LA SUVmax) showed statistically significant associations with RA SUVmax (odds ratio [OR]: 14.353, 95% CI: 1.383–148.911, $P = 0.026$), and LA area (OR: 1.371, 95% CI: 1.160–1.622, $P = 0.0001$).

The optimal cut-off values for RA and LA TBR were 1.57 and 1.71, respectively. When these cutoff values were adopted, the overall sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for detecting AF based on atrial FDG uptake were 65.7%, 75.8%, 68.8%, 85.7%, and 50.0%, respectively (Table 2). When comparing the TBR values with each visual grade, there were significant differences between grades 1 and 2, and between grades 2 and 3 ($P < 0.0001$, Supplemental Fig. 2). There was a significant difference between the TBR values of positive and negative visual findings (RA TBR: 2.15 [1.79–2.63] vs. 1.41 [1.33–1.54], $P < 0.0001$; LA TBR: 2.16 [1.80–2.64] vs. 1.50 [1.38–1.63], $P < 0.0001$). Finally, there was no significant difference in the diagnostic accuracy between visual and quantitative analyses based on the TBR ($P = 0.182$).

3.3. Characteristics of patients with paroxysmal or persistent AF

The characteristics of the patients with paroxysmal or persistent AF are summarized in Supplemental Table 1. Classification of the type of AF for each patient was made by the attending physician according to the 2014 AHA/ACC/HRS Guidelines [8]. Patients with long-standing, persistent AF that had lasted longer than 12 months were also included in the persistent AF group. There were significant differences in age, SBP, CTR, RA and LA areas, and RA SUVmax and RA TBR. The CRP of persistent AF was not significantly different from that of paroxysmal AF, but it was significantly greater than that of controls ($P = 0.038$).

Multivariable logistic regression analysis for persistent AF among 11 clinical and imaging variables (age, BMI, SBP, HbA1c, CRP, Hb, RA and LA area, CTR, and RA and LA SUVmax) showed statistically significant associations with RA SUVmax (OR: 2.095, 95% CI: 1.039–4.224, $P = 0.039$), CTR (OR: 1.087, 95% CI: 1.013–1.166, $P = 0.020$), and RA area (OR:

Table 2
Diagnostic capability for detecting atrial fibrillation based on atrial FDG-uptake.

		Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
Visual analysis	RA grading	46.7(64/137)	98.4(61/62)	62.8(125/199)	98.5(64/65)	45.5(61/134)
	LA grading	41.6(57/137)	95.2(59/62)	58.3(116/199)	95.0(57/60)	42.4(59/139)
	Overall grading	54.0(74/137)	95.2(59/62)	66.8(133/199)	96.1(74/77)	48.4(59/122)
Quantitative analysis	RA TBR	58.4(80/137)	80.6(50/62)	65.3(130/199)	87.0(80/92)	46.7(50/107)
	LA TBR	46.7(64/137)	83.9(52/62)	58.3(116/199)	86.5(64/74)	41.6(52/125)
	Overall TBR	65.7(90/137)	75.8(47/62)	68.8(137/199)	85.7(90/105)	50.0(47/94)

Values are expressed as a percentage, followed by the number of patients listed in parentheses.
RA, right atrium; LA, left atrium; TBR, target-to-background ratio.

1.047, 95% CI: 1.010–1.085, $P = 0.012$). RA SUVmax and TBR were significantly greater in patients with persistent AF than in patients with paroxysmal AF (both $P < 0.0001$). In quantitative analysis, the overall sensitivity for detecting paroxysmal AF was 54.3% (38/70), and that for detecting persistent AF was 79.1% (53/67).

3.4. Outcomes after AF treatment and FDG PET/CT findings

Among the 137 patients with AF, 21 patienversion as a treatment for AF before FDG-PET/CT imaging. Supplemental Table 2 summarizes the age, sex, type of AF, interval between the treatment and PET imaging, presence or absence of recurrence after treatment, and FDG-PET/CT results. The FDG uptake in the atria was considered as positive in cases with TBR exceeding the cut-off value of >1.56 for the RA or >1.71 for the LA. In 15 patients with recurrent AF after treatment, 10 (66.7%) had positive FDG uptake, while none of 6 patients without recurrence were positive for FDG uptake ($P = 0.006$, Fig. 1).

3.5. Histological findings of postmortem cardiac specimens

During the observation period, 34 patients died. Pathological investigations were conducted on 4 autopsy hearts within 3 months after PET/CT imaging. Two hearts had demonstrated FDG accumulation in both atria, while other 2 had not shown significant accumulation. In the atrial myocardium specimens from the former 2 hearts, numerous extravascular CD68-positive macrophages and CD3- or CD20-positive lymphocytes had infiltrated in the regions demonstrating FDG uptake (Fig. 2). In the latter patients' hearts, however, immune cells were scarce despite a significant increase in atrial fibrosis.

4. Discussion

4.1. Major findings of FDG PET/CT for AF

To the best of our knowledge, no previous study has comprehensively demonstrated the diagnostic value of FDG-PET/CT for detection and identification of inflammatory activity in the atria of patients with AF. The high positive-predictive value and specificity (both >95% by visual analysis) indicate that it may be possible to identify patients with AF when they undergo an oncological PET/CT examination. Moreover, multivariable analysis for AF showed significant associations with RA SUVmax and LA area. The intensity of FDG uptake on PET/CT can be measured by SUVmax, i.e., the voxel having the highest FDG intensity. To correct for background blood-pool activity, we determined the TBR in each patient and found it was closely correlated with visual grading. The diagnostic accuracy of visual and quantitative analyses based on TBR are highly similar and may be equally available for clinical use.

4.2. Comparison with previous studies

There have been a few case reports of PET/CT detection of atrial FDG uptake in patients with AF. They reported FDG uptake in the LA appendage [9], the lateral wall of the RA [10], and the crista terminalis, a crescent-shaped muscle band located in vicinity to the RA appendage [11]. The sinoatrial node lies above it and its localization is important for cardiac electrophysiology studies. We verified the uptake of FDG at the abovementioned and other regions and found that 81% (60/74) of patients had positive uptake in >1 region. Lange et al. performed PET/CT imaging in 37 patients with AF, and reported that there was a slightly higher FDG uptake in the atrial wall of patients with AF; however, the difference in atrial TBR values between AF patients and controls was not statistically significant [12]. They suspected that detection of inflammatory activity in the atria may be hampered by the physiological FDG uptake in the heart when performed under routine oncological PET. In order to reduce physiologic myocardial FDG uptake [13], we only included patients with AF who had fasted for at least 12 h, (fasting duration: 16.5 [14.6–18.2] h) before FDG injection. Prolonged fasting before FDG injection is likely to contribute to the substantially high specificity by visual analysis.

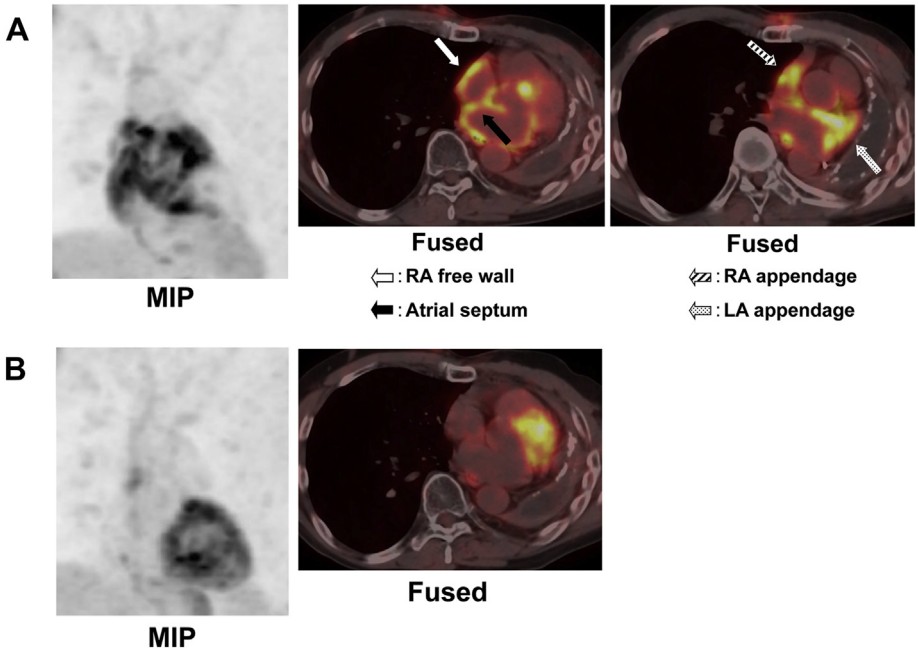

Fig. 1. A male patient in his 50s had undergone a lung cancer surgery 14 years previously, and was followed up by several PET/CT examinations. He had severe atrial tachyarrhythmia when PET/CT imaging was performed, prior to ablation therapy. (A) Avid accumulation of FDG was found in the right atrium (RA) appendage and free wall, atrial septum, left atrium (LA) appendage, and LA anterior and posterior walls (RA target-to-background ratio [TBR]: 5.00; LA TBR: 5.85). (B) Ten months later, he received additional treatment with cardioversion for relapsed atrial fibrillation, which was effective. Normal sinus rhythm was restored. At the 1-year PET/CT follow-up study, no FDG uptake was observed in either atrium (RA TBR: 1.29; LA TBR: 1.71). MIP indicates maximum intensity projection.

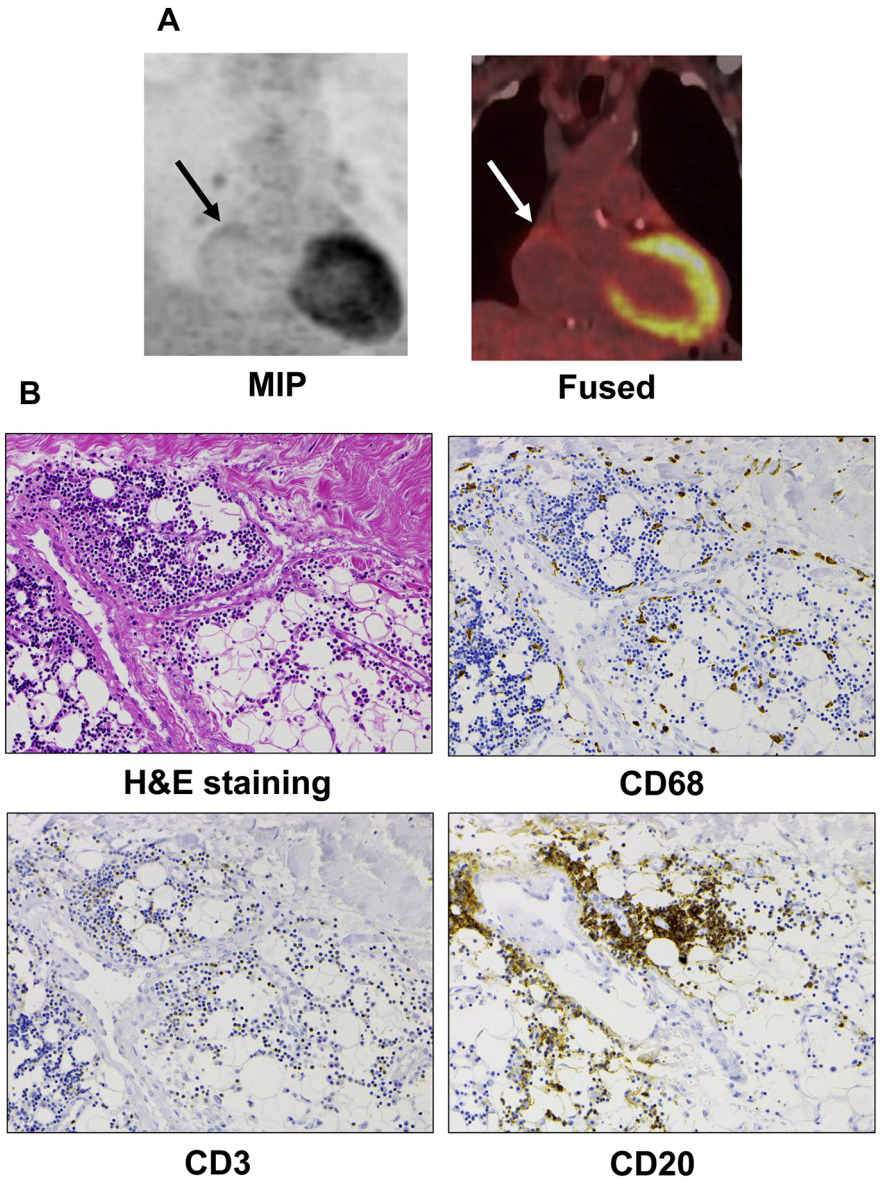

Fig. 2. A male patient in his 80s who had experienced persistent lone atrial fibrillation (AF) for >7 years underwent PET/CT imaging as a pretreatment examination for duodenal cancer. (A) He had grade 2 FDG accumulation in the right atrium (RA) (arrow). Pathological investigation of the heart was conducted at his autopsy performed 3 months after the PET/CT. (B) Histopathology of the pericardium of the RA appendage. Hematoxylin–eosin (H&E) staining shows lymphocyte infiltration around blood vessels in adipose tissue (×200). Numerous CD68-positive macrophages had infiltrated the whole pericardial tissue. Lymphocytes are partly positive for CD3 and CD20 (×200). MIP indicates maximum intensity projection.

4.3. FDG uptake in the epicardial adipose tissue and the atrium

Mazurek et al. performed PET/CT imaging in 21 patients with suspected neoplastic disease and reported that higher SUVs were found on the EAT in the roof of the left atrium, in the atrioventricular groove and in the left main artery of patients with AF, as compared to the control group [14]. This ectopic fat depot, distinct from paracardial fat, surrounds the myocardium and coronary arteries. The EAT is considered to be a metabolically active tissue that produces proinflammatory adipokines [15]. They reported an association of pro-inflammatory activity of the EAT, rather than of the atria, with the occurrence of AF.

The mean atrial wall thickness has been reported as ranging being 1–4 mm, with a range between 0.5 and 12 mm in post-mortem studies [16]. In CT measurements, Nakamura et al. found that the anterior LA wall thickness was significantly greater in patients with paroxysmal AF (2.4 ± 0.2 mm) than in those without AF (1.9 ± 0.2 mm) [17]. In CT imaging, the Hounsfield unit (HU) intensity is used to discriminate between the tissue types. In some portions, the atrial wall will have similar HU intensity to neighboring structures, which could make accurate identification of the epicardial surface challenging [16]. Moreover, according to a histological study [15], the EAT sometimes infiltrates into the myocardium, due to the lack of fascia between the EAT and the atrial myocardium. Since PET imaging has limited spatial resolution, FDG uptake into the EAT or into the atrium is virtually indistinguishable, especially with various cardiac motions. Thus, in the present study, we decided to adopt a simplistic approach for setting the atrial ROIs, which included the adjacent EAT. Accordingly, we could assess FDG uptake in the atrium, including the EAT, with inter-observer and intra-observer reproducibility with a >95% correlation coefficient.

4.4. Comparison of atrial FDG uptake between paroxysmal and persistent AF

We found that the RA FDG uptake was higher in patients with persistent AF than in those with paroxysmal AF. Thus, the sensitivity for detection based on atrial TBR increased from 54.3% for paroxysmal AF to

79.1% for persistent, possibly due to an increase in the number of inflammatory cells in the atria of patients with persistent AF. Multivariable analysis for persistent AF showed significant associations with RA SUVmax, CTR, and RA area. In a large cohort of patients with AF, LA enlargement was an independent predictor of stroke and systemic embolism [18]. In the present study, the size of LA was greater than that of the RA in both AF and controls. The RA and LA size increases in the order: patients with sinus rhythm, paroxysmal AF, and persistent AF. The relationship between the enlargement of RA and AF has been investigated in both experimental animals and humans [19,20]. These studies revealed that electrical remodeling and RA enlargement promote AF inducibility and perpetuation. Our results revealed a close relationship between RA FDG uptake and AF, which may suggest that inflammation is involved not only in the LA, but also in the RA.

Platonov et al. collected atrial specimens of 30 autopsy hearts in 3 equal-sized age-matched groups: patients without AF, with paroxysmal AF, or with persistent AF [21]. Patients with persistent AF had more extensive fibrotic replacement of atrial myocardium and more CD3- and CD45-positive leukocytes than patients with paroxysmal AF. Atrial structural changes in the post-mortem material were significantly correlated with the presence and severity of AF. We also examined specimens of autopsy hearts obtained after the patients' PET/CT examination and found that various inflammatory cells, such as macrophages or lymphocytes, had infiltrated in areas that agreed well with the atrial regions of FDG uptake.

4.5. Follow-up studies

It has been reported that the maintenance of sinus rhythm after cardioversion or catheter ablation of persistent AF leads to a gradual decrease in CRP levels; these levels remain unchanged in patients with recurrent AF [22,23]. In the present study, two-thirds of patients with recurrence after various AF treatments demonstrated FDG uptake, while none of the patients without recurrence had significant FDG uptake. Regression of inflammation in the atria was presumed to be the cause of the disappearance of FDG uptake in the latter patients. Thus, FDG-PET/CT could be a useful tool for detecting local inflammation in the atria of patients with AF, especially during follow-up after antiarrhythmic therapy. However, the retrospective nature of the study hampered extension of the diagnostic parameters to various clinical situations. A prospective study should be considered, which would lead to more clinically relevant results.

Recently, Ohyama et al. demonstrated that the coronary perivascular TBR of adipose tissue was significantly increased in patients with vasospastic angina, as compared to controls (1.04 ± 0.03 vs. 0.85 ± 0.04, $P < 0.01$), and it was markedly decreased after long-term treatment with calcium-channel blockers [24]. These findings indicate that FDG PET/CT could be useful for assessing disease activity even in low-grade inflammatory diseases. Finally, detecting inflammation in AF patients may facilitate development of tailored anti-inflammatory strategies for the treatment and prevention of AF.

4.6. Study limitations

This study had some limitations. The 4-point grading system, derived visually by the 2 nuclear medicine physicians, might be inherently subjective. Therefore, using not only such a visual analysis, but also a quantitative analysis based on the TBR would be a better option in a clinical context. We included patients who had fasted for at least 12 h before FDG injection in order to eliminate physiological uptake in the myocardium. However, fasting for at least 18 h before FDG injection, and using a low carbohydrate and/or high-fat diet together with a heparin injection may have resulted in additional reduction of the physiological uptake [13]. PET imaging has limited spatial resolution, and both cardiac and respiratory motions increase image noise and reduce PET signal. In addition, partial volume effects can influence quantitative PET analysis of small or thin structures. We may have attained a better sensitivity with the use of ECG-gated or respiratory-gated PET/CT. Finally, due to limited insurance coverage, most patients who had AF underwent imaging due to suspected malignant neoplastic disease, which might have been a confounding factor.

5. Conclusions

PET/CT findings demonstrated an association between higher atrial uptake of FDG and AF. Persistent AF had higher atrial FDG uptake than paroxysmal. A high positive-predictive value and specificity indicated that it could be possible to identify patients with AF when they undergo PET/CT for oncological reasons. FDG-PET/CT could be a useful tool for detecting local inflammation and for assessing disease activity in the atria of patients with AF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.106.

Conflicts of interest

None declared.

Sources of funding

This work was partly supported by Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Scientific Research (category C) (grant number 25461830).

References

[1] S.S. Chugh, J.L. Blackshear, W.K. Shen, S.C. Hammill, B.J. Gersh, Epidemiology and natural history of atrial fibrillation: clinical implications, J. Am. Coll. Cardiol. 37 (2001) 371–378.
[2] L. Staerk, B. Wang, S.R. Preis, et al., Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study, BMJ 361 (2018) k1453.
[3] Y.F. Hu, Y.J. Chen, Y.J. Lin, S.A. Chen, Inflammation and the pathogenesis of atrial fibrillation, Nat. Rev. Cardiol. 12 (2015) 230–243.
[4] R.J. Aviles, D.O. Martin, C. Apperson-Hansen, et al., Inflammation as a risk factor for atrial fibrillation, Circulation 108 (2003) 3006–3010.
[5] S.C. Marott, B.G. Nordestgaard, J. Zacho, et al., Does elevated C-reactive protein increase atrial fibrillation risk? A Mendelian randomization of 47,000 individuals from the general population, J. Am. Coll. Cardiol. 56 (2010) 789–795.
[6] R. Langah, K. Spicer, M. Gebregziabher, L. Gordon, Effectiveness of prolonged fasting 18F-FDG PET-CT in the detection of cardiac sarcoidosis, J. Nucl. Cardiol. 16 (2009) 801–810.
[7] R.M. Lang, M. Bierig, R.B. Devereux, et al., Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology, J. Am. Soc. Echocardiogr. 18 (2005) 1440–1463.
[8] C.T. January, L.S. Wann, J.S. Alpert, et al., 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, Circulation 130 (2014) 2071–2104.
[9] B.D. Nguyen, PET demonstration of left atrial appendage in chronic atrial fibrillation, Clin. Nucl. Med. 30 (2005) 177–179.
[10] H. Fujii, M. Ide, S. Yasuda, Y. Takahashi, A. Shohtsu, A. Kubo, Increased FDG uptake in the wall of the right atrium in people who participated in a cancer screening program with whole-body PET, Ann. Nucl. Med. 13 (1999) 55–59.
[11] A.H. Maurer, M. Burshteyn, L.P. Adler, R.M. Steiner, How to differentiate benign versus malignant cardiac and paracardiac ^{18}F-FDG uptake at oncologic PET/CT, RadioGraphics 31 (2011) 1287–1305.
[12] P.S. Lange, N. Avramovic, G. Frommeyer, et al., Routine ^{18}F-FDG PET/CT does not detect inflammation in the left atrium in patients with atrial fibrillation, Int. J. Cardiovasc. Imaging 33 (2017) 1271–1276.
[13] M.T. Osborne, E.A. Hulten, V.L. Murthy, et al., Patient preparation for cardiac fluorine-18 fluorodeoxyglucose positron emission tomography imaging of inflammation, J. Nucl. Cardiol. 24 (2017) 86–99.
[14] T. Mazurek, M. Kiliszek, M. Kobylecka, et al., Relation of proinflammatory activity of epicardial adipose tissue to the occurrence of atrial fibrillation, Am. J. Cardiol. 113 (2014) 1505–1508.
[15] N. Venteclef, V. Guglielmi, E. Balse, et al., Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines, Eur. Heart J. 36 (2015) 795–805.

[16] J. Whitaker, R. Rajani, H. Chubb, et al., The role of myocardial wall thickness in atrial arrhythmogenesis, Europace 18 (2016) 1758–1772.
[17] K. Nakamura, N. Funabashi, M. Uehara, et al., Left atrial wall thickness in paroxysmal atrial fibrillation by multislice-CT is initial marker of structural remodeling and predictor of transition from paroxysmal to chronic form, Int. J. Cardiol. 148 (2011) 139–147.
[18] Y. Hamatani, H. Ogawa, K. Takabayashi, et al., Left atrial enlargement is an independent predictor of stroke and systemic embolism in patients with non-valvular atrial fibrillation, Sci. Rep. 6 (2016) 31042.
[19] J.A. Cabrera, D. Sanchez-Quintana, S.Y. Ho, et al., Angiographic anatomy of the inferior right atrial isthmus in patients with and without history of common atrial flutter, Circulation 99 (1999) 3017–3023.
[20] P.A. Boyden, B.F. Hoffman, The effects on atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs, Circ. Res. 49 (1981) 1319–1331.
[21] P.G. Platonov, L.B. Mitrofanova, V. Orshanskaya, S.Y. Ho, Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age, J. Am. Coll. Cardiol. 58 (2011) 2225–2232.
[22] G.M. Marcus, L.M. Smith, D.V. Glidden, et al., Markers of inflammation before and after curative ablation of atrial flutter, Heart Rhythm. 5 (2008) 215–221.
[23] E.M. Kallergis, E.G. Manios, E.M. Kanoupakis, et al., The role of the post-cardioversion time course of hs-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation, Heart 94 (2008) 200–204.
[24] K. Ohyama, Y. Matsumoto, K. Takanami, et al., Coronary adventitial and perivascular adipose tissue inflammation in patients with vasospastic angina, J. Am. Coll. Cardiol. 71 (2018) 414–425.