18F-FDG uptake in the heart of patients with atrial fibrillation

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Abstract

Background: There are several ideas on the pathophysiology of atrial fibrillation (AF). One of the most common hypotheses is that inflammation may exist in the atrial walls of patients suffering from AF. Due to this hypothesized theory, we aimed to investigate the cardiac 18F-FDG uptake in patients with AF compared to patients without cardiac diseases.

Methods: 82 adult patients were retrospectively enrolled. The cases (N=47) had a history of AF prior to the PET/CT scan. The controls (N=35) had no history of AF or other cardiac diseases. Both cases and controls used oral anticoagulants. Standardized uptake values (SUV_{max}) of the liver, heart, spleen and the psoas muscle were determined. The target to background ratios (TBR) of the liver, heart and spleen were obtained by dividing the targets by the background uptake (SUV_{max} of the psoas major muscle).

Results: There was no significant difference in 18F-FDG uptake in the heart between the AF and control group (4.64 IQR: 3.06-6.59 against 3.71 IQR: 2.99-5.65, respectively; p=0,494). There was also no significant difference in 18F-FDG uptake in the liver between the two groups (3.23 IQR: 2.72-3.91 against 3.40 IQR: 2.75-3.89; p=0.497). In contrast to the liver and heart, we found a significant difference in 18F-FDG uptake in the spleen with a P value of 0.014.

Conclusion: This case-control study showed no significant differences in the cardiac- and hepatic 18F-FDG uptake between patients with AF and patients without cardiac diseases. A statistically significant difference in the splenic 18F-FDG uptake has been observed.

Key words: 18F-FDG, atrial fibrillation, PET/CT imaging

Introduction

Atrial fibrillation (AF) is a frequent persistent cardiac arrhythmia. It is responsible for approximately one-third of hospitalized patients with cardiac arrythmia. The estimated prevalence is approximately 2% in developed countries. This equates to approximately 33 million people. In 40% of the cases, patients suffer from silent AF. 25% of patients with unexplained ischemic strokes are diagnosed with AF [4]. In the Netherlands, it is estimated that the incidence of AF in 2020 was around 2.0%. It is expected that this figure will increase to 3.2% in 2050. Also, it is expected that with increasing AF subjects, stroke rate will rise. This is mainly due to higher age of subjects and an increase in patients with more morbidities [1]. AF causes increase in health-care related costs and reduces quality of life. Furthermore, it can contribute to depressing moods and mild cognitive impairment in patients [1,2]. In a study, it was shown that AF caused 1 or more hospitalizations per year and that 10% of the patients had 2 or more hospitalization [3]. This indicates the need for further research and an earlier diagnosis.

The diagnosis of this arrythmia is still a challenge. Patients with this arrhythmia have an increased risk of developing a stroke and peripheral thromboembolic events. This risk

can be reduced by treating these patients with antithrombotic therapy. Hence, it is important to diagnose AF before the first complications occur [5].

There are many hypotheses regarding the pathophysiology of AF. One of the most prominent ideas is the hypothesis that inflammation is potentially present in the atrial walls of patients with AF. There is also a structural remodelling in the atria of patients with this disease. This remodelling is caused by the arrythmia itself. The longer the atrial fibrillation persists, the more remodelling occurs. This reduces the chance of restoring the sinus rhythm [5].

The use of molecular imaging could provide crucial information that could ensure a timely and smooth treatment procedure. This can be achieved by using 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). It is known that this technique could be used for diagnoses with a high level of sensitivity. This technique is already used to diagnose cardiac sarcoidosis. Given the successes of this diagnosis method, this novel method could be a breakthrough for the diagnosis of atrial fibrillation. In this work, we explored the use of molecular imaging in detecting 18F-FDG uptake in the heart of patients with AF as compared to subjects without this disease [5]. We tested the hypothesis that the cardiac 18F-FDG-uptake will be higher in patients with AF compared to subject without cardiac diseases.

Material and methods

Study population

This study was conducted at the Amsterdam University Medical Centre location AMC in the Netherlands and retrospectively enrolled 82 adult patients aged 24 up to 91 years old. Before starting this study, it was approved by the Medical Ethics Assessment Committee of the Amsterdam University Medical Centre. Cases with the following criteria were included: 18 years or older, history of AF (persistent or paroxysmal) and the use of direct oral anticoagulants (DOACs) or vitamin k antagonists (coumarins). The controls were included if they were 18 years old or older, had no history of AF or other cardiac diseases and used DOACs or coumarins. All subjects were treated with FDG and underwent PET/CT during the period September 2011 till July 2022. The cases (N=47) had a history of AF prior to the PET/CT scan. The cases used one of the following medicines: apixaban, dabigatran, edoxaban, rivaroxaban, acenocoumarol or fenprocoumon. Some of the cases received a dose of heparin prior to the PET/CT scan. The controls (N=35) had no history of AF and no history of other cardiac diseases. They used one of the following oral anticoagulants for a variety of clinician indications: apixaban, dabigatran, edoxaban, rivaroxaban or acenocoumarol. Heparin was administered to some of them before they were scanned. The cases were compared with the controls. The matching was done by sex and body mass index (BMI). We chose to match based on BMI because adipose tissue may have higher 18F-FDG uptake [7]. A significant difference between the groups could introduce bias. Analyses were done on the PET/CT scans of these patients who had been referred to the Department of Nuclear Medicine for a variety of clinical reasons.

Image analysis

The Hybrid Viewer program (version 5.1.0, Hermes Medical Solutions, Sweden) was used to evaluate the 18F-FDG PET/CT images. The maximum standardized uptake value (SUV_{max}) was computed using the spherical volume of interest (VOI) tool. The VOI was drawn in the heart, liver, spleen, and left psoas major muscle. A fixed VOI of 10 cm^3 was used for the VOI of the heart. For the liver, a fixed VOI of 4 cm^3 was used. For the centre of the left psoas major muscle and the spleen, we used a fixed VOI of 2 cm^3. To account for background uptake, the SUV_{max} of the major psoas muscle is utilized. The target to background ratios

(TBR) were obtained by dividing the targets by the background uptake. The following 18F-FDG PET/CT parameters were obtained: SUV_{max} heart to-background ratio (SUV_{max} hbr) = (SUV_{max} heart / SUV_{max} psoas major muscle), SUV_{max} liver-to-background ratio (SUV_{max} lbr) = (SUV_{max} liver / SUV_{max} psoas major muscle) and the SUV_{max} spleen-to-background ratio (SUV_{max} sbr) = (SUV_{max} spleen / SUV_{max} psoas major muscle).

Patient preparation and PET/CT imaging

Before the scan occurred, patients were informed to drink 2 liters of water and to avoid the intake of carbohydrates 24 hours before 18F-FDG administration. They were permitted to drink one liter of water on the day of the examination. As a result, the physiological myocardial glucose uptake would be reduced. Blood glucose levels of the study patients were measured before the scan started. These levels were in a range from 1.5 to 12.7 mmol/L (cases: 5.55 ± 1.76 mmol/L; controls: 5.68 ± 2.05 mmol/L). 60 minutes before they were scanned, patients received an activity of 18F-FDG. This activity is weight dependent. They were administered about 2.25 MBq/kg body weight. Heparin was also administered to some of the patients. They were administered an intravenous dose (i.v.) of 50 IE/kg heparin 15 minutes before the PET scan. The purpose of heparin administration was to suppress myocardial glucose metabolism. Patients underwent a whole-body PET scan combined with a diagnostic CT scan (3 mm of 5 mm coupes, 1- or 3-mm reconstruction). Patients were administered water orally and prior to the CT scan i.v. Xenetix 350 (Guerbet, France), oral contrast Telebrix 5% (Guerbet, France) and Ultravist 300 (Bayer, Germany) i.v or i.v. Lomeron 300 (Bracco Imaging Deutschland GmbH, Germany) and oral Telebrix 5%.

The Gemini Time-of-Flight PET/CT scanner (Philips, the Netherlands) was utilized up to October 2017. During the injection of 100 ml intravenous contrast agent, diagnostic CT was conducted in portal phase from the skull base to the thigh (120 kV, 150 mAs, 16 × 1.5 collimation, 0.8013 pitch). The PET acquisition was then carried out, with a scan period of 2.5 minutes per bed. Since October 2017, a Biograph mCT Flow PET/CT scanner (Siemens, Germany) with increased axial field of vision (TrueV) scanner was utilized. Diagnostic CT was done in portal phase with automated regulation of current and voltage. The reference values were 120 kV and 160 mA, 128 x 0.6 collimation, and 0.9 pitch. The CT was conducted following the injection of 90 mL of intravenous iodinated contrast medium (Xenetix 350). PET was done with a constant bed motion of 1.5 mm/s. CT data was utilized for PET attenuation correction and PET data reconstruction in both scanners. Iodinated contrast agent was only used in the absence of contraindications.

Statistical analysis

For categorical variables, the results were presented as frequencies with percentages and for continuous variables, as mean ± standard deviation (SD) or median with interquartile range (IQR). The following tests were used: Student T-test, Chi-squared test and the Mann-Whitney U test. All tests were two-tailed, and statistical significance was defined as a P value less than 0.05.

The data was analysed using descriptive statistics using SPSS statistics software version 28 (IBM Corp, USA) and Excel 2016 software (Microsoft Corp, Redmond, WA).

Results

Study population

In this study, two groups were compared (Table 1). The first group consisted of 47 patients with AF (68.1 % male). The second group, the control, consisted of 35 subjects without AF (57.1% male) with a significant lower age

compared to the first group (56.9 ± 17.8 and 71.9 ± 11.7 years respectively; p = < 0.001). There was no significant difference for the BMI between the groups (26,81 ± 6.23 against 24,83 ± 6.40, p=0.173). Also, there was no significant difference for the 18F-FDG uptake that was observed between subjects with AF and without AF (2.29 ± 0.62 against 2.23 ± 0.53 MgB/kg body weight).

Looking at the history of subjects of both groups, a significant part of the patients with AF had a history with heart failure, while no heart failures were reported for subjects without AF (31 against 0; p = <0.001). Moreover, more cases of cerebrovascular accidents were reported for patients with AF compared to subjects without AF (16 against 4; p = 0.018). Also, cases of coronary heart diseases and endocarditis were reported for patients with AF, while no cases were reported for subjects without AF (14 and 7 against 0 and 0 respectively; p < 0.001 and p = 0.0017). There was no significant difference for the occurrence of diabetes and malignancy between the patients in the group with- and without AF (p=0.130, p=0.557). Also, hypertension was reported in the case and the control group and was not statistically different (48.9% against 28.6% respectively; p=0.063).

Comparing the medication use of both groups, no significant differences of the use of corticosteroids were observed between subjects with- and without AF (8 against 11; p = 0.520). A significant difference of the use of anticoagulants was observed (p < 0.001). Here, we observe that 17 subjects with AF used DOACs compared to 26 subjects without AF. Moreover, 30 cases of coumarin use were reported for the group with AF as opposed to 9 of the group without AF. No significant difference was found for the use of heparin comparing the subjects with- and without AF (27 against 13 reported cases; p = 0.069).

18F-FDG uptake

As presented in table 2, there was no significant difference of 18F-FDG uptake in the heart between the group of patients with- and without AF (4.64 IQR: 3.06-6.59 against 3.71 IQR: 2.99-5.65, respectively; p=0.494). There was also no significant difference between the two groups in uptake of 18F-FDG in the liver (3.23 IQR: 2.72-3.91 against 3.40 IQR: 2.75-3.89, respectively; p=0.497). In contrast to the results for the liver and heart, we found a significant difference in uptake of 18F-FDG in the spleen with a P value of 0.014. The median uptake in the group of patients with AF was 2.47 with an IQR of 2.07-2.86, it was compared with the median for the group of patients without AF (2.90 with an IQR of 2.16-3.76). Hence, there was no significant difference between the group of patients with- and without AF for uptake of 18F-FDG in the liver and heart. In contrast, for the spleen, we found a significant difference between the groups.

Table 2. SUV_{max} values of patients with- and without AF.

Characteristic	Patients with AF	Patients without AF	P value
SUV_{max} hbr*	4.64 (3.06 – 6.59)	3.71 (2.99 – 5.65)	0.494
SUV_{max} lbr*	3.23 (2.72 – 3.91)	3.40 (2.75 – 3.89)	0.497
SUV_{max} sbr*	2.47 (2.07 – 2.86)	2.90 (2.16 – 3.76)	0.014

* median (IQR)

Mbr, heart-to-background ratio; lbr, liver-to-background ratio; sbr, spleen-to-background ratio; SUV_{max}, maximum standardized uptake value

Table 1. Characteristics of the subjects

Patient characteristics	AF patients (N = 47)	Controls (N = 35)	P value
Sex			0.309
Male (%)	32 (68.1)	20 (57.1)	
Female (%)	15 (31.9)	15 (42.9)	
Age (years) *	71.9 (11.8)	56.9 (17.8)	<0.001
BMI (kg/m2) *	26.81 (6.23)	24.83 (6.40)	0.173
Glucose (mmol/L) *	5.55 (1.76)	5.68 (2.05)	0.765
History			
Diabetes (%)	15 (31.9)	6 (17.1)	0.130
Hypertension (%)	23 (48.9)	10 (28.6)	0.063
Malignancy (%)	12 (25.5)	7 (20)	0.557
Heart failure (%)	31 (66.0)	0 (0)	<0.001
Stroke (%)	16 (34.0)	4 (11.4)	0.018
Coronary artery disease (%)	14 (29.8)	0 (0)	<0.001
Endocarditis (%)	7 (14.9)	0 (0)	0.017
Medication			
Corticosteroids (%)	18 (38.3)	11 (31.4)	0.520
Anticoagulants			<0.001
DOAC			
Apixaban (%)	5 (10.6)	3 (8.6)	
Dabigatran (%)	3 (6.4)	2 (5.7)	
Edoxaban (%)	7 (14.9)	4 (11.4)	
Rivaroxaban (%)	2 (4.3)	17 (48.6)	
Coumarins			
Acenocoumarol (%)	25 (53.2)	9 (25.7)	
Fenprocoumon (%)	5 (10.6)	0 (0)	
PET/CT scan			
FDG activity (Mbq/kg) *	2.29 (0.62)	2.23 (0.53)	0.625
Heparin (%)	27 (57.4)	13 (37.1)	0.069

* mean (SD); BMI, body mass index; DOAC, direct oral anticoagulant

Discussion

In this study, we investigated the 18F-FDG uptake of the heart, liver and the spleen through PET/CT image analysis. This study demonstrated no significant difference of 18F-FDG uptake in the heart of patients with AF compared to subjects without AF. Furthermore, there was no significant difference of 18F-FDG uptake in the liver of patients with AF as compared to patients without AF. However, this study showed a significant difference of 18F-FDG uptake in the spleen of patients with AF compared to patients without AF. The median uptake of 18F-FDG within subjects without AF was greater compared to the group with AF. However, we expected not to find a significant difference in the 18F-FDG uptake in the spleen. In a study where the 18-FDG uptake was also investigated in patients with- and without AF, no higher 18-FDG uptake was found in the spleen. As a result, the discussed article is in accordance with our expectation, but fails to give further explanation about the increased uptake we found in the spleen [6]. The PET/CT image analysis approach of the 18-FDG uptake in the spleen has been studied less extensively than the heart, as evidenced by the studies found in the literature.

From the literature, we learn that some studies make a clear distinction between the right- and left atria. In addition, these studies demonstrate a higher 18-FDG uptake in the right atrium in patients with AF compared to patients without AF. Although, this was not found in the same subjects in the left atrium [6]. However, in this study, we chose to take the VOI of the whole heart due to a lack of time. For further research, it is recommended to differentiate between the left and right atria and to choose a VOI that best fits the atria used for the study.

This study had several limitations. First, the sample size was relatively small. Second, there was a statistical difference in age found between the group of patients with- and without AF. It was difficult to meet the criteria of having different groups with equal characteristics. It was also difficult to find controls that used oral anticoagulants and that were not cardiac loaded with the same age and anticoagulant use as the AF patients in the case group.

The use of the software Hermes had also some limitations. The first limitation associated with the use of Hermes, was drawing the VOI in the image. The VOI was drawn in the heart, the liver, spleen and the left psoas major muscle. Most care was taken to ensure that the right VOI was selected, including selecting only parts of interest and not of the other organs. However, even the slightest shift of the VOI in the image can give different SUV values. Furthermore, the quality of the scans was not uniform. This made it more complex to generate VOIs of equal quality. Moreover, two different PET/CT scanner devices were used. This could potentially have had an impact on the images, introducing various types of bias.

Conclusions

This case-control study showed no significant differences in the cardiac- and hepatic 18F-FDG uptake between patients with AF and patients without cardiac diseases. A statistically significant difference in the splenic 18F-FDG uptake was observed. Further research is needed in order to evaluate the cardiac uptake of 18F-FDG in patients with AF.

Disclosure

The authors have declared no conflicts of interest.

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