Exploring Hidden Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus Admitted to Shinshu University Hospital

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Using the event-triggered recorder, SpiderFlash-t AFIB, which allows us to detect asymptomatic or symptomatic arrhythmia, we examined the prevalence of hidden atrial fibrillation (AF) in patients with type 2 diabetes admitted to our hospital. In total, we enrolled 69 patients with type 2 diabetes mellitus admitted to the hospital due to hyperglycemia. Averages of HbA1c, age, duration of the disease, and BMI were 8.9 %, 64.8 years old, 14.8 years, and 26.0 kg/m^2, respectively. Neuropathy, retinopathy, and nephropathy were found in 37 (53.6 %), 27 (39.1 %), and 27 (39.1 %), respectively. Macroangiopathy was found in 13 (18.9 %). In the first series of surveys where we attached the recorder for 7 days no sustained AF events were found, and only 2 transient events. We attached the recorder for 14 days with 39 subjects in the second series of the survey, and fail to find any AF rhythm. This study is the first attempt to reveal the frequency of hidden AF in diabetes. This finding suggests that screening of atrial fibrillation with SpiderFlash-t AFIB for patients with type 2 diabetic patients hospitalized for glycemic control may not be useful in assessing the prevalence of atrial fibrillation. *Shinshu Med J 69 : 75—81, 2021*

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I Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia in clinical practice. As the aging of society proceeds, the number of patients with AF is steadily increasing worldwide because aging is a strong risk factor for the development of AF[1]. In Japan, it is estimated that over 2 million subjects suffer from AF, and it could be a common disease. AF is a high risk factor for developing strokes and is largely preventable with anti-coagulation therapy. However, approximately 40 % of Japanese patients with AF remained asymptomatic[2]. Therefore, it is important to identify subclinical or paroxysmal AF in individuals without persistent AF to consider the application of anti-coagulation therapy. Type 2 diabetes mellitus (T2D), which relates to sedentary lifestyle and overeating, has spread rapidly worldwide, and it is established as a strong risk factor for atherosclerosis. Incidence of T2D among AF patients was reported to be higher than among non-AF individuals[3].

Several lines of evidence suggest that there is a strong correlation between the presence of T2D and the development of stroke[4]. In addition, T2D is generally considered one of the risk factors for AF although the pathophysiological relationship between diabetes mellitus and AF is unknown. Indeed, in the Framingham Heart Study, the presence of diabetes was shown to be associated with a significant increase in the development of AF with odds ratio being 1.1 for men and 1.5 for women[5]. Accordingly, it is possible that T2D without apparent AF has

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hidden paroxysmal AF with no symptoms such as palpitation. However, the precise prevalence of paroxysmal AF in patients with T2D has not been established due to a lack of accurate and feasible equipment for its evaluation.

In this study we examined the prevalence of paroxysmal AF in T2D patients who were admitted to our hospital in order to control hyperglycemia, using an event-triggered recorder, SpiderFlash-t AFIB. Given that this recorder allows us to detect asymptomatic or symptomatic arrhythmia including transient AF over periods of weeks, we will be able to uncover the clinical importance of searching for hidden AF in T2D.

Ⅱ Materials and Methods

A External loop recorder

For the detection of asymptomatic and symptomatic arrhythmic events, we used an extended external loop recorder (SpiderFlash-t AFIB ; Sorin, France, Medical device approval number : 222AHBZI00013000). The recording consisted of continuous electrocardiography (ECG) recording for the initial 24h, auto-trigger episodes, and patient-activated episodes for 7days or 14 days. The SpiderFlash-t AFIB can record an ECG for up to 7.5 min before and 15 min after detection of arrhythmias or patient activation.

B Subjects

We attached SpiderFlash-t AFIB for 7 days to 39 T2D patients admitted to Shinshu University Hospital from April 1, 2014 to September 30, 2014 (Period 1). From April 1, 2015 to September 30, 2015, the second series of the study was performed with 30 T2D admitted to Shinshu University Hospital (Period 2). In the second population, we attached SpiderFlash-t AFIB for 14 days to enhance the possibility of detection of the events. Gladstone et al. reported that the detection rate with SpiderFlash-t AFIB of atrial fibrillation increased 7.4 % in 7days and 11.6 % in 14 days in patients with transient stroke and cerebral infarction[6]. Based on this finding we decided to review again by extending the wearing of the monitor. The characteristic features of the patients are summarized in Table 1. We included T2D with normal ECG on admission and no history of AF. We analyzed various clinical parameters of the patients. When we identified AF or transient AF rhythms in the patients, we performed brain MRI/MRA and consulted cardiologists as to whether they needed to receive anticoagulant therapy. The patients were advised to press the button on the recorder if they felt chest symptoms such as palpitation, chest pain, and dizziness. We defined paroxysmal AF as irregular R-R interval and a lack of P-wave of more than 60 seconds, and supraventricular tachycardia (SVT) as 120 beats per minute or lasting 8 minutes or more, and bradycardia as 45 beats per minute or less for more than 20 seconds.

C Statistical analysis

Values from Periods 1 and 2 were compared with non-paired Students` T test, and a p value less than 0.05 was considered statistically significant.

The protocol of this study was approved by the ethics committee of Shinshu University School of Medicine (Approved number 2702). All patients provided written informed consent.

Ⅲ Results

A Characteristics of the subjects

As shown in **Table 1**, the characteristic features of the subjects in Period 1 and Period 2 were essentially similar. As a whole, they had 14.8±11.8 year duration of type 2 diabetes, and exhibited microvascular complications in neuropathy 53.6 %, retinopathy 39.1 %, nephropathy more than state 2 39.1 % and macrovascular complications 18.9 %. Glycemic control was poor (HbA1c 8.9±1.8 %) because most of the patients were admitted to the hospital to control hyperglycemia. Thus our patients were considered to be a relatively advanced stage population rather than newly diagnosed.

B Results of SpiderFlash-t FIB

In **Table 2**, we summarize the incidence of arrhythmias in this study. In Period 1, none of the subjects were detected to have AF with SpiderFlash-t FIB, and only 2 out of 39 subjects were found to experience transitory AF rhythm lasting less than 10 beats. Both of the events were asymptomatic. Then

Table 1　Clinical Characteristics of the patients

	Period 1 n＝39	Period 2 n＝30	Total n＝69
Gender			
Male, n (%)	26 (67)	18 (60)	43 (62.3)
Female, n (%)	13 (33)	12 (40)	26 (37.7)
Age, median, years	62.1 (13.7)	67.6 (11.7)	64.8 (12.6)
HbA1c (%)	8.9 (1.6)	9.1 (2.0)	8.9 (1.8)
Body mass index (kg/m^2)	27.1 (6.3)	25.3 (4.9)	26 (5.7)
Time since diagnosis of type 2 diabetes	12.7 (11.9)	16.3 (11.6)	14.8 (11.8)
Neuropathy	12 (35.2)	15 (50.0)	37 (53.6)
Retinopathy	14 (41.1)	13 (40.0)	27 (39.1)
Nephropathy*			
stage1	30 (76.9)	12 (40.0)	42 (60.9)
stage2	3 (7.7)	9 (30.0)	12 (14.5)
stage3	6 (15.4)	3 (10.0)	9 (13.0)
stage4	0	6 (20.0)	6 (8.7)
stage5	0	0	0
History of athererosclerotic vascular disease			
Coronary	7 (17.9)	6 (20.0)	13 (18.9)
Cereberovascular disease	11 (36.6)	14 (46.6)	25 (36.2)
Pulmonary embolism	2 (5.1)	3 (10.0)	5 (7.1)
Hypertension	28 (71.7)	21 (70.0)	49 (71.0)
Hyperlipidemia	18 (46.1)	13 (43.3)	31 (44.9)
Hyperuricemia	2 (5.8)	6 (20.0)	8 (11.6)

Baseline characteristics of the subjects. Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate.
*Stage of nephropathy, stage 1 is normal albuminuria＝UACR＜30 mg/g and eGFR＞30, stage 2 is microalbuminuria ＝UACR≧30to≦300mg/g and eGFR＞30, stage 3 is macroalbuminuria＝UACR＞300mg/g and eGFR＞30, Stage 4 is eGFR＜30.

Table 2　Arrthymic patterns detected by the SpiderFlash-t AFIB and the number in 69 cases

	AF*	PAC	PVC	Pause	Brady	VT	second degree AV block
event	2	56	37	12	4	2	2
%	2.9	81.2	53.6	17.4	53.6	2.9	2.9

AF : atrial fibrillation, PAC : premature atrial contraction, PVC : premature ventricular contraction,
VT : ventricular tachycardia ;
*AF rhythm lasted too short to define as AF.

we performed 24-hour Holter electrocardiography in both patients, and did not find any evidence of transitory AF rhythm. In Period 2, where cardiac rhythms were monitored for 14 days (actual recorded periods were 12.03±4.02 days) with SpiderFlash-t AFIB, there was no AF rhythm recorded, and no transitory AF in all 30 subjects. In total, we only found 2 out of 69 subjects exhibiting transitory AF rhythm. Atrial extrasystoles and supraventricular premature contractions were observed in all cases. There were 2 cases who exhibited 5 sequential ventricular premature contractions, so beta-blocker was started just in case of serious ventricular arrhythmias. More than triplet supraventricular premature contractions were found in 38 cases (55 %).

The 2 patients with AF rhythm underwent MRI/MRA and were referred to cardiologists. We describe the clinical features of the 2 cases in brief.

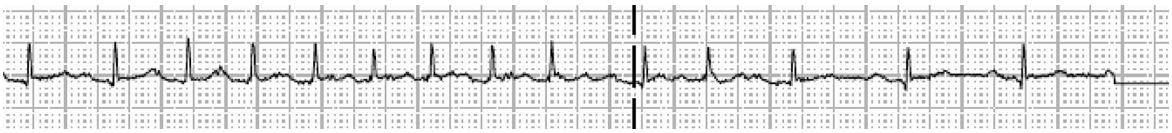

Fig. 1　Subclinical AF of about 10 heart beats recognized by SpiderFlash-t AFIB (Case 1).

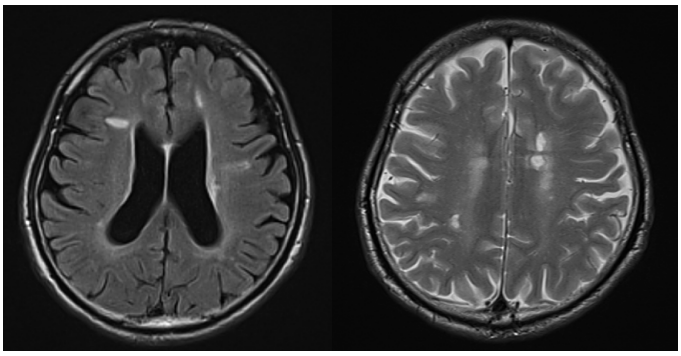

Fig. 2　MRI revealed that the vicinity of the right ventricle is high (flair image : left).
Right picture is T1WI. Old multiple lacunar infarction was observed.

C　Case 1

A 68-year-old male was admitted to our hospital to control hyperglycemia. His recent HbA1c was 8.5 %. He had a history of type 2 diabetic mellitus over 10 years. He had no diabetic neuropathy, diabetic retinopathy or diabetic nephropathy. He smoked 20 cigarets per day for 30 years. Electrocardiogram at hospitalization was normal. We used the event-triggered recorder SpiderFlash-t AFIB for 7 days. **Fig. 1** shows AF rhythms for about 10 heart beats. Brain MRI/MRA revealed old multiple lacunar infarctions, and an acute phase of cerebral infarction was observed in the vicinity of the right ventricle full angle **(Fig. 2)**. We referred the patient to a cardiologist and a neurologist. After that, Holter ECG for 24 hours was done, but no AF rhythms were detected. It was judged that anticoagulation therapy was not indicated in this patient. If there were to be repeatability of AF rhythms in the future, it was over policy to start anticoagulation therapy. An antiplatelet drug was started for acute stage cerebral infarction.

D　Case 2

A 71-year-old male was admitted to our hospital to control hyperglycemia. He had a history of T2D over 40 years. Immediately before addmittion, his HbA1c was 10.0 % . His mother has diabetes, and cerebral vascular disease. He had been smoking 30 cigaretes a day for 50 years. Past history was cataract operation. There was no diabetic neuropathy and diabetic retinopathy, but there was microalbuminuria compatible with early stage of diabetic nephropathy. BMI was 27.8 kg/m^2, and blood pressure was 118/69 mmHg. The electrocardiogram at hospitalization was normal. We tried using the event-triggered recorder SpiderFlash-t AFIB for 7 days. **Fig. 3** shows subclinical AF of about 7 ventricular beats. We referred him to a cardiologist. Holter ECG was done, but AF was not identified. Anticoagulation therapy was not indicated.

Ⅳ　Discussion

Despite an intensive search for hidden AF in Japanese patients with T2D, we failed to detect any AF events in the patients who were admitted to our hospital for the purpose of glycemic control and education. Two events of 10 or less beats of irregular R-R, which did not reach the criteria of AF, were found in two patients. This result was totally unexpected.

Recently, by using noninvasive ambulatory ECG monitoring, Gladstone et al, found paroxysmal AF in 7.4 % and 11.6 % of the patients with cryptogenic stroke with 1 week and 2 weeks monitoring, respectively[5]. Affordability of extended external auto-triggered loop recorder monitoring, which is exactly the same

Fig. 3 Subclinical AF of about 7 heart beats of recognized in SpideFlash-t AFIB (Case 2).

Table 3 AF risk factors raised by Framingham study and Hisayama study, in our survey

risk factor	All patients
age	64.8 (12.6)
smoking	57.9
diabetes mellitus	100
left ventricular hypertrophy	31.9
hypertention	71
ischemic heart disease	14.5
congestive heart falure	10.1
antiarrhythmic drug	7.2

Data are n (%) or mean (SD).

equipment used in our study, had been reported in AF patients after catheter ablation[7]. Several studies have shown that the patients with T2D have an increased risk of AF[8]. For example, T2D is reported as an independent risk factor for AF in the Chinese population. Diabetes mellitus is an independent risk factor for atrial fibrillation in a general population[9]. Recent meta-analyses of 100 thousand people revealed that the risk of AF is increased by 40 % in diabetic subjects compared to non-diabetic subjects[10].

We expected the presence of intermittent and asymptomatic AF evading detection under usual clinical evaluation such as careful physical examination and a single recording of electrocardiography (ECG) in our T2D patients. The T2D patients in this study included various stages of the disease. Many of them were advanced and high-risk patients as shown.

The prevalence of paroxysmal AF in the general population was reported to be approximately 3 %[11]. Aging and having heart disease were strong risk factors for the development of AF[4]. **Table 3** shows the risk factors for atrial fibrillation, as identified in the Framingham study and Hisayama stydy[12] and our study patients. As a result, in this study, the rate of smoking, left ventricular hypertrophy, and blood pressure were high and obviously all of the subjects had T2D. The percentage of each factor was high, but the detection rate of atrial fibrillation was low. In Japan, research on AF prevalence studies includes nationwide surveillance of cardiovascular disease[13][14], epidemiology survey of Japanese cardiovascular disease[15], and a survey of Kurashiki city[16]. Comparing the average age in this study, there was no particular difference. Although there has been no survey targeting diabetic patients, this study suggested that the frequency of latent AF in Japanese diabetic patients does not change with the prevalence rate in the general population in the ages we studied.

Therefore, the lack of episodes of AF even under prolonged monitoring in this study is not likely due to patient profile. Rather, our findings suggest that the prevalence of intermittent and paroxysmal AF in Japanese T2D patients who apparently have no history and no AF on ECG is low.

To the best of our knowledge, the incidence of

paroxysmal, or preclinical, AF in T2D is not previously reported. To elucidate subclinical AF in a patient without a prior history of AF, it is important to use proper monitoring techniques. In this sense, we consider that our approach with SpiderFlash-t AFIB monitoring for an average of 9.2±3.6 days is reasonable enough to detect subclinical AF.

The limitation of our study is obviously the small number of study individuals. We could not propose the actual number of the incidence of subclinical AF, rather we could suggest the rare incidence of subclinical AF in Japanese T2DM who were admitted to our hospital for controlling their hyperglycemia. Although an implantable loop recorder allows us to monitor for a longer period of time, it is slightly invasive and not suitable for screening of subclinical AF. Nevertheless, we need both elongation of monitoring periods and accumulation of study subjects to propose an accurate incidence of subclinical AF in Japanese T2D. Another limitation of the study is that the recordings were performed during admission. This may be one of the reasons for the decrease in the occurrence of paroxysmal AF.

In conclusion, we failed to detect any single event of paroxysmal AF compatible with our definition in 69 Japanese T2D patients without a prior episode of AF. This finding suggests that the screening of atrial fibrillation with SpiderFlash-t AFIB for patients with type 2 diabetic patients hospitalized for glycemic control may not be useful in assessing the prevalence of atrial fibrillation.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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