Characteristics of patients with atrial flutter and spontaneous 1:1 atrioventricular conduction with and without anti-arrhythmic drug treatment

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Abstract

Background: Atrial flutter (AFL) is a large re-entrant circuit located in the right atrium. Anti-arrhythmic drugs (AADs) can provoke AFL with 1:1 atrioventricular conduction (AVC) to cause hemodynamic collapse. We elucidated the characteristics of patients with AFL exhibiting spontaneous 1:1 AVC. Methods: Fifteen patients (1:1 AFL group; 11 males, 52.4±13.7 years old) who documented AFL with 1:1 AVC were enrolled and compared to 77 patients without 1:1 AVC (Control group; 71 males, 68.1±10.9 years old). Results: The use of AADs was greater in the 1:1 AFL group than in the control group (60.0 vs. 14.3%, $p < 0.001$). AFL cycle length during maximum AVC was significantly longer in the 1:1 AFL group than in the control group (274.7 ± 37.0 vs. 220.4 ± 26.2 msec, $p < 0.001$). Among 1:1 AVC group, 9 patients had AADs and AFL cycle length was significantly longer during 1:1 AVC as compared with 2:1 AVC documented the other day (284.4 ± 41.3 vs. 233.3 ± 26.0 msec, $p < 0.001$), suggesting enhancement effect of the AADs during 1:1 AVC. Remaining 6 patients who did not take AADs, 2 patients showed enlargement of the tricuspid annulus and 3 patients developed 1:1 AVC during exercise. Conclusions: In addition to the enhancement of AAD effect, prolonged AFL cycle length associated with enlargement of the tricuspid annulus and shortened refractory period of the AV node might increase the risk of 1:1 AVC during AFL. Keywords: atrial flutter, atrial flutter cycle length, tricuspid annulus. Atrioventricular node, atrioventricular conduction, anti-arrhythmic drug

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Introduction

Common type of atrial flutter (AFL) is one of the most common arrhythmias. Anti-arrhythmic drugs (AADs), including class Ia or Ic for the treatment of atrial fibrillation (AF) can cause AFL[1]. These AADs have pro-arrhythmic effects by prolonging the flutter cycle length, resulting in 1:1 atrioventricular conduction (AVC) in patients with AFL [1-5]. AFL with 1:1 AVC is rare but can cause hemodynamic collapse and require emergent treatment [6,7]. Nevertheless, there are few studies of the risk factors predisposing patients to 1:1 AVC in AFL especially in the absence of AADs. Therefore, the purpose of this study was to determine the clinical and echocardiographic characteristics of patients with AFL with 1:1 AVC with and without AAD treatment.

Methods

Study population

Medical records were retrospectively reviewed, including patients with common type of AFL with documented 1:1 AVC on electrocardiogram (ECG) from 1998 to 2018 at the Nippon Medical School Hospital. Fifteen patients with clinically documented AFL with 1:1 AVC were included in the 1:1 AFL group. Seventy-seven consecutive common type AFL patients without 1:1 AVC were chosen as the control group (2011 to 2015; control group). the 12-lead ECGs during AFL showed the typical saw tooth pattern in inferior leads in all patients. Flutter waves were confirmed when the AVC ratio was less than 2:1. Patients with atypical AFL and atrial tachycardia were excluded. This study was approved by the Nippon Medical School Institutional Review Board (IRB B-2020-340).

Electrocardiographic and transthoracic echocardiographic analysis

ECG parameters including PR interval, P wave duration, QRS duration, and heart rate were determined during sinus rhythm. Flutter cycle length and flutter wave amplitude in lead II were also measured. AFL cycle length were measured during 1:1 AVC in the 1:1 AFL group and during 2:1 AVC in control group. In addition, all patients in the 1:1 AFL group were documented AFL with AVC of 2:1 on the other day, AFL cycle length was also measured during 2:1 AVC.

Comprehensive transthoracic echocardiographic examinations, including M-mode and Doppler echocardiography were performed in all patients. Interventricular septal thickness, posterior left ventricular wall thickness, left atrial dimension, left ventricular end-diastolic dimension, and left ventricular end-systolic dimension were measured in the parasternal long-axis view. The left ventricular ejection fraction was also estimated using the long-axis view with the Teichholz method. Continuous wave Doppler ultrasound of the tricuspid annulus was obtained in the apical 4-chamber view.

Statistical analysis

Statistical analyses were performed using independent sample tests. Continuous data are presented as mean ± standard deviation, and categorical data are expressed as numbers and percentages. Differences between two groups were tested using the Student's t-test for continuous variables and the Fisher's exact test for categorical variables. The mean differences between groups that had been split in two within subjects were tested using two-way repeated measures ANOVA. P-values less than 0.05 were considered statistically significant. All analyses were performed using GraphPad Prism version 7.0 software (GraphPad Software, Inc., San Diego, California).

Results

Baseline characteristics

The clinical characteristics of the present study population are shown in Table 1. There were 11 men (73.3%) in the 1:1 AFL group and 71 men (92.2%) in the control group. The 1:1 AFL group was significantly younger than the control group (52.4 ± 13.7 vs. 68.1 ± 10.9 years, p <0.001). There were no differences in the prevalence of underlying heart disease (ischemic heart disease, valvular disease, cardiomyopathy or congenital heart disease) between the groups. There were no differences between the groups in terms of the presence of diabetes mellitus, stroke/TIA, or prior history of AF; however, hypertension was more frequent in the control group (13.3% vs. 57.1%, p = 0.004). AADs were prescribed more frequently for the 1:1 AFL group. The use of class Ia or Ic AADs was greater in the 1:1 AFL group (60% vs. 14.3%, p < 0.001). Of the 6 patients who did not take AADs in the 1:1 AFL group, two had arrhythmogenic right ventricular cardiomyopathy and atrial septal defects, and both showed right atrial dilatation with tricuspid valve annulus enlargement. The 1:1 AFL occurred during vigorous exertion in the other 3 patients. In the remaining patient, the specific reasons were not identified for AFL with 1:1 AVC.

Transthoracic echocardiographic parameters

Table 2 shows the results of the transthoracic echocardiography parameters. Right atrial area was significantly larger in the 1:1 AFL group than in the control group (20.5 ± 7.6 vs. 17.2 ± 4.4 cm^2, p = 0.038). There were no differences in terms of left atrial dimension, left atrial area, interventricular septal thickness, posterior wall thickness, left ventricular end-diastolic dimension, or tricuspid regurgitation pressure gradient between the groups. Left ventricular end-systolic dimension was larger in the 1:1 AFL group (35.1 ± 8.6 vs. 29.8 ± 7.9 mm, p = 0.022); however, there were no differences in terms of left ventricular ejection fraction between the groups (54.4 ± 15.2 vs. 62.5 ± 14.8%, p = 0.058).

Electrocardiographic parameters

Table 3 shows the electrocardiographic parameters of this study. There were no differences in terms of PR interval, P-wave duration, or QRS duration during sinus rhythm between the groups. Heart rate during sinus rhythm was significantly faster in the control group (60.4 ± 11.4 vs. 69.9 ± 11.9 bpm, p = 0.007). There were no differences in flutter amplitude in lead II between the groups. AFL cycle length in the 1:1 AFL group was significantly longer than that in the control group (274.7 ± 37.0 vs. 220.4 ± 26.2 msec, p < 0.001). In the control group, 11 patients (14.3%) took Ia or Ic AADs. AFL cycle length was significantly longer in the 11 patients who took AADs than in the remaining 66 patients who did not (236.7 ± 33.2 vs. 218.1 ± 24.6 msec, p = 0.046). However, in the 1:1 AFL group, there was no differences in 1:1 AFL cycle length between the 9 patients who took AADs and the 6 patients who did not (284.4 ± 41.3 vs. 260.0 ± 26.1 msec, p = 0.222) (Table 3).

All patients in the 1:1 AFL group also had documented ECG of AFL with maximum AVC of 2:1 on other days. We compared the difference of AFL cycle length between 1:1 and 2:1 AVC in the 1:1 AFL group. In the 9 patients who took AADs, AFL cycle length was significantly longer during 1:1 AVC than that during 2:1 AVC (284.4 ± 41.3 vs. 233.3 ± 26.0 msec, p < 0.001). On the other hand, there were no significant differences in the AFL cycle length between 1:1 AVC and 2:1 AVC in the remaining 6 patients not taking AADs (260.0 ± 26.1 vs. 251.7 ± 22.3 msec, p = 0.554) (Figure 1A). In the 1:1 AFL group, FF interval ratio between 1:1 AVC and 2:1 AVC was significantly larger in the patients with AADs (Ia/Ic) than those without AADs (1.23 ± 0.14 vs. 1.04 ± 0.03, p = 0.008). Figure 1B showed a representative ECG of AFL with 1:1 AVC and 2:1 AVC in the 1:1 AFL group who took AADs and who did not.

Discussion

Prevalence and characteristics of 1:1 AVC in AFL

Despite the fact that there have been published short series of AFL with 1:1 AVC, the incidence of this arrhythmia remains unknown. The risk of AFL with 1:1 AVC during treatment with quinidine has been

reported since 1954 [2,8]. Later, the phenomenon was reported with use of class I AADs [1,3-5]. The incidence of atrial proarrhythmic effects caused by class I AADs is unknown. Nevertheless, the incidence of atrial proarrhythmic effects associated with class I AADs could be similar to the incidence of ventricular proarrhythmic effect of the same drugs, estimated between 5% and 10%[5,9]. In another study, risk factors were identified, including younger age, absence of heart disease, and treatment with class I AADs [10]. In addition to the usage of AAD, in our study, enlargement of tricuspid annulus and increased sympathetic activity were also identified as possible risk factors for 1:1 AVC during AFL.

Pro-arrhythmic effects of class Ia/Ic drugs

AFL with 1:1 AVC is a proarrhythmic complication of class I AADs[9,11]. Flecainide and some other AADs terminated AF by causing tachycardia-dependent increases in the atrial effective refractory period, which increases the wavelength at the rapid rates characteristic of AF to the point that the arrhythmia can no longer sustain itself [12,13]. AADs terminate AF by increasing the wavelength for reentry at rapid rates, eventually causing failure of reentrant excitation [10]. The mechanism of the 1:1 ventricular response in AFL under administration of AADs is the following: prolongation in the AFL cycle length is caused by drug-induced atrial conduction velocity slowing; if prolongation of AFL cycle length is longer than the effective refractory period of the AV node, this might lead to 1:1 AVC [10].

Kawabata et al. reported that longer AFL cycle length and enhanced AVC with increased sympathetic tone were predisposing factors for the development of AFL with 1:1 AVC [11]. In their report, all patients with documented AFL with 1:1 AVC had been treated with class Ia or Ic AADs. Average AFL cycle length in their study was 292 msec, which was consistent with the cycle length of the patients prescribed AADs in our study.

In the present study, the patients with taking Ia/Ic drugs in the 1:1 AFL group, the AFL cycle length was significantly prolonged at the time of 1:1 AVC than with 2:1 AVC that was recorded on other days. Therefore, day to day variation of AFL cycle length was observed in the patients prescribed Ia/Ic drugs. Development of 1:1 AVC during AFL in the patients with taking AADs might be associated with enhancement of AAD effect. Serum levels of class Ia/Ic drugs are influenced by several factors, including drug metabolism, drug interactions, dosing periods and dosing timing, all of which might affect the AFL cycle length prolongation, resulting in recovery from refractory of AV node. To avoid the risk of AFL with 1:1 AVC, it is important to confirm the patients' adherence of the AADs as well as the evaluation renal and liver function. Therapeutic drug monitoring might be help for the patient follow up in clinical practice.

Structural heart disease and 1:1 AFL

It the present study, right atrial area was significantly greater in the 1:1 AFL group than that in the control group, suggesting that structural factors also involved in the development of 1:1 AVC. Enlargement of tricuspid annulus associated with right atrial dilatation might contribute the AFL cycle length prolongation. Notably, there were 6 patients who showed 1:1 AVC even though they were not taking class Ia/Ic AADs. Among those patients, 1 had arrhythmogenic right ventricular cardiomyopathy and the other on had an atrial septal defect. Both patients had remarkably enlarged tricuspid annuli.

Effects of sympathetic hyperactivity on AV node conduction

Brembilla et al. reported that AFL with 1:1 AVC can occur in untreated patients [10]. Factors that favor this event are the presence of rapid AV nodal conduction [9]. The association of AFL with 1:1 AVC with sympathetic hyperactivity, such as exercise, has been documented [11,14]. In addition, electrophysiologic study revealed that the 1:1 AFL patients had a significantly more rapid AV nodal conduction time[11]. In the present study, three patients who were not taking AADs developed 1:1 AVC during vigorous exercise. AV node function accelerated by increased sympathetic tone might have a risk of 1:1 AVC in some patients.

Limitations

There are several limitations in this study. First, our study was based on retrospective analysis of a single

center experience. Multi-center studies are needed to validate our findings. Second, AV node function was not systemically evaluated by electrophysiological studies. The influence of intrinsic AV node function and response to catecholamine that might affect the development 1:1 AVC remains unclear. Third, AFL cycle length variation in the patients prescribed Ia/Ic drugs leading to 1:1 AVC might be associated with drug concentration. However, drug concentration was not evaluated in this study. Finally, although the study population of the 1:1 AFL group was small, and it was difficult to make matched control group, the present study revealed several important features of AFL with 1:1 AVC.

Conclusion

Electrophysiological modification of atrial conduction slowing by class Ia/Ic AADs were risk factors for the development of 1:1 AVC in patients with AFL. Moreover, tricuspid annulus enlargement or intensive exercise were also associated with the development of 1:1 AVC even in patients not taking AADs.

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Disclosures

All the authors declare that there are no conflicts of interest.

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