Journal of Cardiology 78 (2021) 362–367

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

Pathophysiological background and prognosis of common atrial flutter in non-elderly patients: Comparison to Atrial Fibrillation

Haruhiro Takahira (MD)[a], Takatsugu Kajiyama (MD, PhD)[b,*], Yusuke Kondo (MD, PhD, FJCC)[a], Masahiro Nakano (MD, PhD)[b], Miyo Nakano (MD, PhD)[a], Ryo Ito (MD)[a], Mari Kitagawa (MD)[a], Masafumi Sugawara (MD)[a], Toshinori Chiba (MD)[a], Yoshio Kobayashi (MD, PhD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan
[b] Department of Advanced Cardiorhythm Therapeutics, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

ARTICLE INFO

Article history:
Received 20 January 2021
Revised 25 April 2021
Accepted 7 May 2021
Available online 14 June 2021

Keywords:
Atrial fibrillation
Common atrial flutter
Non-elderly
Pacemaker
Prognosis

ABSTRACT

Background: It is unclear whether there is any difference in the background and prognosis between non-elderly patients who undergo catheter ablation of atrial fibrillation (AF) and common atrial flutter (CAFL).

Purpose: To investigate the difference between the patient background of both CAFL and AF in the non-elderly.

Methods: In 526 consecutive patients who underwent catheter ablation of clinical paroxysmal/persistent CAFL or AF in our hospital, we enrolled only patients under 60 years old. Cases harboring both AFL and AF were excluded. We analyzed the patient characteristics, echocardiographic findings, electrocardiographic (ECG) abnormalities during sinus rhythm, and clinical course after ablation.

Results: In total, 196 patients (Cohort 1: 142 males, 156 AF cases) were analyzed. AFL patients were younger than AF patients (47.4 ± 10.6 vs. 50.2 ± 6.4years, $p = 0.031$) and organic heart disease (OHD) was significantly more common in AFL patients than AF patients (42.5% vs. 11.5%, $p<0.001$). In 161 patients excluding OHD (Cohort 2), ECG abnormalities were more frequent in AFL than in AF patients (78.3% vs. 39.1%, $p = 0.001$). There were no significant differences in all-cause death, onset of heart failure, and cerebral strokes. On the other hand, the number of cases that required a pacemaker was significantly higher in the CAFL group than AF group (0.0% vs. 26.1%, p-value <0.001). These results suggested that CAFL may reflect occurrence of any atrial myocardial damage, even if it does not lead to heart failure.

Conclusions: Our present study suggested that CAFL may be associated with a broader atrial myocardial disorder in non-elderly patients.

Introduction

Common atrial flutter (CAFL) is an atrial arrhythmia which is often encountered in clinical practice. CAFL is a macro-reentrant tachycardia reciprocating in the right atrium around the tricuspid valve [1]. Atrial fibrillation (AF) is also a common arrhythmia at the bedside. AF potentially originates from both atria, while pulmonary veins are dominant pathogenic structures [2]. According to some large-scale epidemiological cohorts, those two arrhythmias have not been always clearly distinguished [3-7]. However, in recent years, the differences in the clinical background and prognosis between those two arrhythmias have been reported in some studies [8, 9]. Common implications of those studies were that the CAFL-group had an inferior prognosis to the AF-group. On the other hand, both atrial arrhythmias are more prevalent in the elderly, who are likely to have more comorbidities affecting their cardiac function [9]. Therefore, comparative studies in non-elderly subjects may emphasize the fundamental difference between those two arrhythmias. In the present report, we investigated the patient background and clinical course after catheter ablation of AF and CAFL, exclusively in non-elderly people.

* Corresponding author.
E-mail address: tak4poincar@gmail.com (T. Kajiyama).

https://doi.org/10.1016/j.jjcc.2021.05.008
0914-5087/

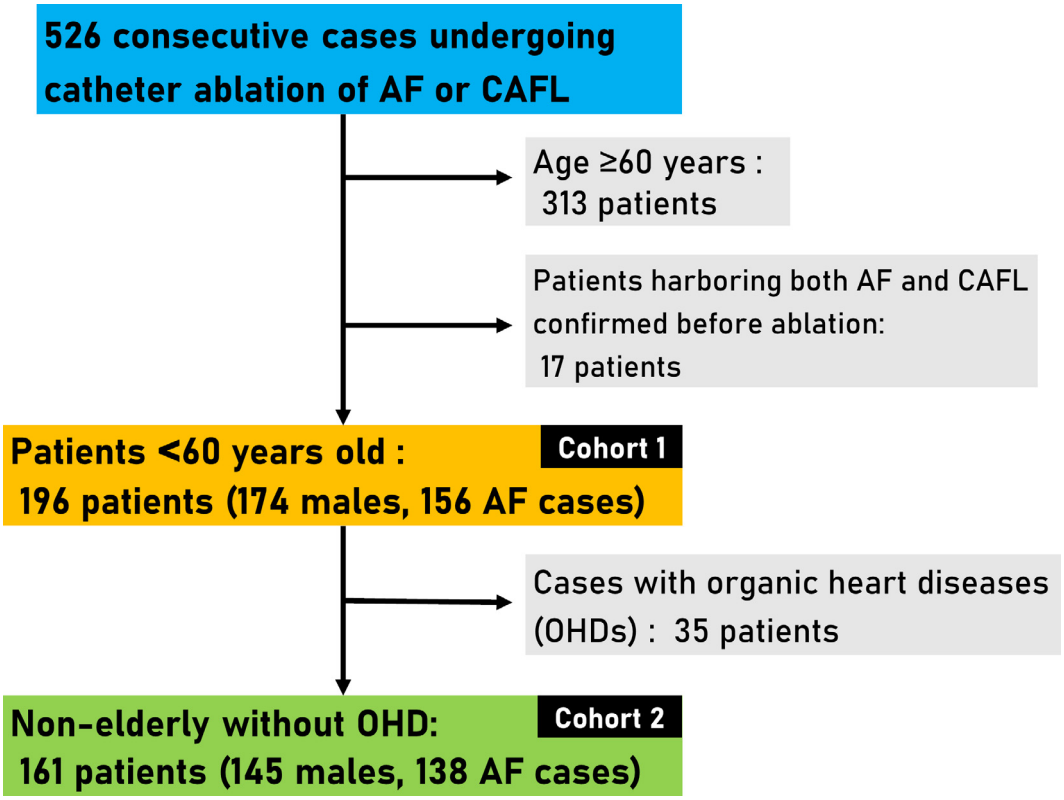

Fig. 1.. Patient enrolment flowchart.
AF, atrial fibrillation; CAFL, common atrial flutter.

Methods

Patient enrolment

A patient enrolment flowchart is shown in Fig. 1. We enrolled patients under 60 years of age who underwent a first-time catheter ablation for AF or CAFL in our single center between October 2003 and September 2018. Patients were excluded if they were diagnosed with both CAFL and AF before the index procedure. All patients were to receive all treatments including catheter ablation and anticoagulation based on contemporary guidelines. The patient demographics and background were retrospectively collected, including the electrocardiography (ECG) during sinus rhythm after catheter ablation, transthoracic echocardiography, and the clinical course after the catheter ablation. The present study was carried out analyzing two cohorts. First, all patients were compared between the AF and CAFL groups (Cohort 1). Cohort 1 was analyzed to mainly assess the background of the subjects. Second, among the primary cohort, only the patients who had no known organic heart disease (OHD) were compared for the clinical prognosis (Cohort 2). The analysis of Cohort 2 aimed to reveal the difference in the underlying electrical/anatomical abnormalities between AF and CAFL as well as the prognosis after the procedure. The study complied with the Declaration of Helsinki.

Ablation procedure

All antiarrhythmic drugs were basically discontinued for at least five half-lives prior to the procedure. The surface electrocardiogram and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (RMS-4000/RMS-5000, NIHON KODEN, Tokyo, Japan). The bipolar electrograms were filtered from 30 to 500 Hz. A 5Fr 10-pole mapping catheter was inserted through the right femoral vein for pacing and recording within the coronary sinus. As for the treatment of AF, the procedure was performed under conscious sedation obtained with dexmedetomidine. A 100 IU/kg body weight of heparin was administered immediately following the venous access, and heparinized saline was additionally infused to maintain the activated clotting times at 300–400 s. A single transseptal puncture was performed with an 8-Fr long sheath (SL0, AF Division, SJM, Minneapolis, MN, USA). An additional long sheath was inserted into the left atrium through the same puncture. A circular mapping catheter was used for mapping all pulmonary veins before and after the ablation to confirm the electrical isolation. Radiofrequency energy was applied to achieve an enlarged encircling pulmonary vein isolation. Additional ablation including a left atrial roof line, left atrial bottom line, and mitral isthmus line was performed if needed, whereas the isolation of the superior vena cava and ablation targeting ganglionated plexi was rarely performed. All procedures were performed using a three-dimensional mapping system. As for the treatment of CAFL, minimum sedation with pentazocin was used to perform the ablation procedure. Another 10-pole catheter was positioned on the tricuspid annulus. Radiofrequency current was delivered to the cavo-tricuspid isthmus to establish bidirectional electrical block. Basically, no additional ablation was performed.

Follow-up

All patients were followed-up at our institution or nearby clinic. If adequate data for the present analysis were lacking, it was complemented by individual interviews over the telephone. The primary endpoint was defined as the composite of all death, onset of heart failure, and cerebral strokes. The secondary endpoint was defined as additional catheter ablation or a pacemaker implantation.

Table 1.
Patient characteristics.

Cohort 1 (including OHD)	AF ($N = 156$)	CAFL ($N = 40$)	p-value
Age, years	50.2 ± 6.4)	47.4 ± 10.6	0.031*
Men, n (%)	142 (91.0)	32 (80.0)	0.087
HT, n (%)	49 (31.4)	11 (27.5)	0.704
DM, n (%)	13 (8.3)	5 (12.5)	0.375
OHD, n (%)	18 (11.5)	17 (42.5)	<0.001*
Persistent, n (%)	56 (35.9)	17 (42.5)	0.467
Rate control drug, n (%)	78 (50.0)	27 (67.5)	0.052
Rhythm control drug, n (%)	102 (65.4)	5 (12.5)	<0.001*
Cohort 2 (excluding OHD)	AF ($N = 138$)	CAFL ($N = 23$)	p-value
Age, years	50.0 ± 6.5	45.61±12.2	0.011*
Men, n (%)	125 (90.6)	20 (87.0)	0.704
HT, n (%)	43 (31.2)	4 (17.4)	0.221
DM, n (%)	12 (8.7)	0 (0.0)	0.218
OHD, n (%)	0 (0)	0 (0)	1.000
Persistent, n (%)	48 (34.8)	7 (30.4)	0.814
Rate control drug, n (%)	65 (47.1)	12 (52.2)	0.660
Rhythm control drug, n (%)	92 (66.7)	2 (8.7)	<0.001*

* $p<0.05$AF atrial fibrillation, CAFL: common atrial flutter, DM: diabetes mellitus, HT hypertension, OHD: organic heart disease.

Statistical analysis

All statistical analyses were performed using R version 3.6.1 software (R Project for Statistical Computing, Vienna, Austria) [10]. Continuous variables were reported as the mean ± SD and were compared using the Student t-test. Differences between proportions were compared using Fisher's exact tests. A Kaplan-Meier curve was used to express the percentage of patients free from events after the index procedure and any differences were analyzed with a log-rank test. All p-values were 2-sided, and statistical significance was established at a $p < 0.05$.

Results

Patient characteristics (Cohort 1)

We finally enrolled 196 patients consisting of 156 cases with AF and 40 with CAFL. All ablation procedures were successful, while no fatal complications were observed related to the procedures. The background of the patients is shown in Table 1. As compared to the AF group, the age was significantly younger in the CAFL group (50.2 ± 6.4 years vs. 47.4 ± 10.6 years, $p = 0.03$), and OHD (e.g. any cardiomyopathy and history of surgical operation) was significantly more frequent in the CAFL group (11.5% vs 42.5%, $p<0.001$). There was no significant difference in the number of persistent cases, of which the atrial arrhythmias continued for ≥7 days. There were significantly more patients taking antiarrhythmic drugs in the AF group than CAFL group (65.4% vs. 12.5%, $p<0.001$).

Echocardiographic findings (Cohort 1)

In the CAFL group of Cohort 1, a larger left ventricular end-diastolic diameter index (LVDdi) (26.7 ± 3.7 mm vs. 29.4 ± 5.0 mm, $p = 0.002$) and lower left ventricular ejection fraction (LVEF) (61.0 ± 8.1% vs. 53.6 ± 14.8%, $p<0.001$) was observed. Aortic valve regurgitation, pulmonary valve regurgitation, and tricuspid valve regurgitation of an American Society of Echocardiography (ASE) grade ≥2 was more frequent in the CAFL group (13.4% vs. 33.3%, $p = 0.008$, 2.1% vs. 5.6%, $p = 0.02$, 16.7% vs. 37.5%, $p = 0.008$) (Table 2).

Table 2.
Echocardiographic findings.

Cohort 1	AF ($N = 156$)	CAFL ($N = 40$)	p-value
LAD, mm	39.2 ± 5.9	39.6 ± 7.7	0.77
LAD index, mm	21.6 ± 4.0	23.2 ± 4.2	0.055
LVDd, mm	49.1 ± 5.3	50.1 ± 7.3	0.38
LVDd index, mm	26.7 ± 3.7	29.4 ± 5.0	0.002*
LVEF,%	61.0 ± 8.1	53.6 ± 14.8	<0.001*
LVH, n (%)	5 (3.5)	4 (11.1)	0.08
AS of grade≥2, n (%)	0 (0.0)	0 (0.0)	NA
AR of grade≥2, n (%)	19 (13.4)	12 (33.3)	0.008*
MR of grade≥2, n (%)	38 (26.7)	16 (44.4)	0.08
PR of grade≥2, n (%)	3 (2.1)	2 (5.6)	0.02*
TR of grade≥2, n (%)	26 (16.7)	15 (37.5)	0.008*
Cohort 2	AF ($N = 138$)	CAFL ($N = 23$)	p-value
LAD, mm	38.9 ± 5.8	36.1 ± 5.2	0.06
LAD index, mm	21.3 (3.8)	21.3 (1.9)	0.970
LVDd, mm	48.9 ± 5.0	47.2 ± 4.7	0.18
LVDd index, mm	26.4 (3.7)	27.84 (3.9)	0.185
LVEF,%	62.2 (6.8)	56.9 (8.8)	0.004*
LVH, n (%)	4 (3.2%)	5 (15.8%)	0.05
AS of grade≥2, n (%)	0 (0.0)	0 (0.0)	NA
AR of grade≥2, n (%)	4 (3.2)	1 (5.3)	0.24
MR of grade≥2, n (%)	32 (25.8)	5 (26.3)	0.88
PR of grade≥2, n (%)	3 (2.4)	0 (0.0)	0.06
TR of grade≥2, n (%)	23 (16.7)	5 (21.7)	0.557

* $p<0.05$AF atrial fibrillation, AR: atrial regurgitation, AS: atrial stenosis, CAFL: common atrial flutter, LAD: left atrial diameter, LVEF: left ventricular ejection fraction, LVDd: diastolic left ventricular diameter, LVH left ventricular hypertrophy, MR mitral regurgitation, PR: pulmonary regurgitation, TR: tricuspid regurgitation.

Electrocardiographic findings (Cohort 1)

The ECG abnormalities were classified into three components including the atria, conduction system, and ventricles. Overall, ECG abnormalities were more frequently observed in the CAFL group than AF group (40.4% vs. 70.0%, $p = 0.001$). The classified comparisons are described in Table 3.

Patient characteristics (Cohort 2)

As a result of the exclusion of patients with OHD, Cohort 2 included 161 patients consisting of 138 cases with AF and 23 with CAFL. Even in those subjects, the age was still significantly younger in the CAFL group (50.0 ± 6.5 years vs. 45.6 ± 12.2 years, $p = 0.01$). The use of antiarrhythmic drugs was more frequent in the AF group (66.7% vs. 8.7%, $p<0.001$) (Table 1).

Echocardiographic findings (Cohort 2)

In Cohort 2, only the LVEF was significantly lower in the CAFL group (62.2 ± 6.8% vs. 56.9 ± 8.8%, $p = 0.004$). The LVDdi and the degree of regurgitations did not significantly differ (Table 2).

Electrocardiographic findings (Cohort 2)

In Cohort 2, cases exhibiting negative T waves were significantly more frequent in the CAFL group, but there was no significant difference in the cases that OHD was excluded (18.8% vs. 34.8%, $p = 0.099$). On the other hand, ECG abnormalities of the atrial system and conduction system were still significantly higher in the CAFL group (Table 3).

Clinical prognosis (Cohort 2)

The average follow-up period from the catheter ablation in the cases without OHD was significantly longer in the CAFL group, but

Table 3.
Electrocardiographic findings.

Cohort 1	AF ($N = 156$)	CAFL ($N = 40$)	p-value
Total ECG abnormalities, n (%)	63 (40.4)	28 (70.0)	0.001*
Atrium			
Prolonged P wave, n (%)	15 (9.6)	16(40.0)	<0.001*
Ectopic atrial rhythm, n (%)	3 (1.9)	2 (5.0)	0.270
Left atrial overload, n (%)	1 (0.6)	1 (2.5)	0.367
Right atrial overload, n (%)	2 (1.3)	4 (10.0)	0.017*
Conduction system			
First degree AV block, n (%)	15 (9.6)	13 (32.5)	0.001*
Bundle branch block / fascicular block, n (%)	12 (7.7)	6 (15.0)	0.214
Nonspecific conduction delay, n (%)	12 (7.7)	8 (20.0)	0.036*
Ventricle			
Left ventricular high voltage, n (%)	13 (8.3)	6 (15.0)	0.231
Negative T wave, n (%)	31 (19.9)	17 (42.5)	0.006*
Cohort 2	**AF ($N = 138$)**	**CAFL ($N = 23$)**	**p-value**
Total ECG abnormalities, n (%)	54 (39.1)	18 (78.3)	0.001*
Atrium			
Prolonged P wave, n (%)	12 (8.7)	9 (39.1)	0.001*
Ectopic atrial rhythm, n (%)	3 (2.2)	1 (4.3)	0.464
Left atrial overload, n (%)	1 (0.7)	0 (0.0)	1.000
Right atrial overload, n (%)	2 (1.4)	3 (13.0)	0.021*
Conduction system			
1st degree AV block, n (%)	13 (9.4)	7 (30.4)	0.011*
Bundle branch block / fascicular block, n (%)	10 (7.2)	0 (0.0)	0.360
Nonspecific conduction delay, n (%)	8 (5.8)	6 (26.1)	0.006*
Ventricle			
Left ventricular high voltage, n (%)	10 (7.2)	4 (17.4)	0.119
Negative T wave, n (%)	26 (18.8)	8 (34.8)	0.099

* $p<0.05$AF atrial fibrillation, CAFL: common atrial flutter.

Table 4.
Prognosis after the procedure.

Cohort 2	AF ($N = 138$)	CAFL ($N = 23$)	p-value
Follow-up period (months)	53.7 ± 34.9	86.9 ± 52.3	<0.001
Primary endpoints	0 (0)	1 (4.3)	0.143
Death, n (%)	0 (0)	0 (0)	1.000
Onset of heart failure, n (%)	0 (0)	0 (0)	1.000
Onset of cerebral infarction (%)	0 (0)	1 (4.3)	0.143
Secondary endpoints	39 (28.3)	8 (34.8)	0.621
Additional ablation (%)	39 (28.3)	4 (17.4)	0.321
Pacemaker implantation (%)	0 (0.0)	6 (26.1)	<0.001

*$p<0.05$.
AF atrial fibrillation, CAFL: common atrial flutter.

both groups had an average follow-up period of more than four years (53.7 ± 34.9 months vs. 86.9 ± 52.3 months, $p<0.001$). There were no significant differences in the primary endpoints between the two groups. As for the secondary endpoints, those who required a pacemaker for bradycardia were significantly more prevalent in the CAFL group than AF group (26.1% vs. 0.0%, $p<0.001$) (Table 4). A Kaplan-Meier curve is shown in Fig. 2. The average period until the implantation of a pacemaker from the index ablation was 22.3 months, and the causative diseases were 4 with sick sinus syndrome and 2 with atrioventricular block.

Discussion

To the best of our knowledge, this is the first report to evaluate the clinical difference in non-elderly patients who underwent catheter ablation of AF and CAFL. Our results showed that OHD was significantly more frequent in the CAFL group among the whole cohort. However, even in cases in which OHD was excluded, ECG abnormalities and the need for a pacemaker were still more common in the CAFL group than AF group.

CAFL has often been combined with AF in major epidemiological studies [3-7]. The sub-analysis of the Framingham study investigating the risk of developing AF did not distinguish CAFL from AF [7]. However, they should be classified as needing to be discussed because the underlying mechanisms are different. In recent years, studies clearly distinguishing CAFL from AF have been published, suggesting that the prognosis of CAFL is worse than that of AF [8, 9]. According to a sub-analysis of the Framingham study that investigated ECGs and the natural prognosis by separating CAFL cases from AF cases in all generations, the all-cause mortality in the CAFL group was higher than that in the control group [9]. The ECG findings in the study showed that the PR interval in the CAFL cases was significantly longer than in the AF cases. In a study comparing the prognosis of 2004 CAFL cases and 3803 AF cases after catheter ablation registered in the Danish National Health Registry, all-cause death, heart failure, and implantation of a pacemaker were more common in the CAFL group [8]. These two studies did not stratify the patients, and included the elderly and patients with a history of OHD, which potentially affected the prognosis. It is known that the prevalence of CAFL as well as AF increases with age [9]. The degeneration of the atrial myocardium with the aging process predisposes the patients to a new onset of atrial arrhythmias, while comorbities affecting the cardiovascular function may also increase the chance of myocardial damage. In contrast, patients under 60 years are expected to have less degeneration of the heart tissue and to reflect a more fundamental difference between those two arrhythmias.

In Cohort 1 in the present study, CAFL was significantly related to OHD as in the previous reports. In Cohort 2, there was no significant difference in the primary endpoint including all-cause death, onset of heart failure, and strokes, presumably because those endpoints were less likely in young patients without OHD. However, a significant difference was observed for the ECG abnormalities and incidence of a pacemaker implantation. Those findings may be explained by the observation that macroreentrant CAFL requires the presence of an adequate excitable gap to be maintained, while partial slowing of the conduction velocity in the human right atrium has already been reported [1]. The decrease in the conduction ve-

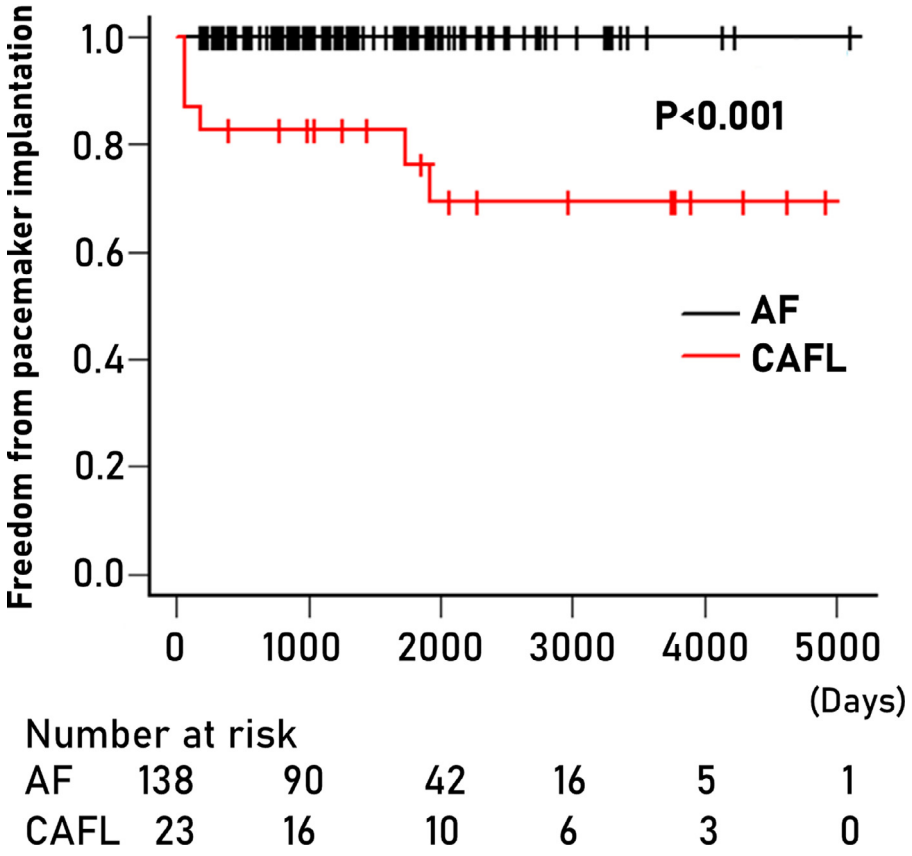

Fig. 2.. A Kaplan-Meier curve showing that the implantation of a pacemaker after the index ablation procedure was significantly more common in CAFL group than AF group. AF, atrial fibrillation; CAFL, common atrial flutter.

locity in CAFL cases may reflect latent atrial cardiomyopathy and potentially predict future development of cardiac diseases. In contrast, AF can be perpetuated only by high frequency electrical activity in a smaller portion of the atrial tissue such as the pulmonary veins, without significant decrease of the conduction velocity [2, 11]. Overall, in clinical practice, even young patients after catheter ablation of CAFL should be carefully followed-up. Moreover, as the analysis of the Danish nationwide health databases, mentioned above, reported that the highest risk factor for the onset of heart failure was the need for a pacemaker, physicians should be on the alert especially in patients with bradycardiac abnormalities [8].

Limitations

We assumed there were some limitations regarding the present study. First, this was a small-numbered, retrospective single-center study. Second, the selection of patients may have been biased because the present study was performed only in those who underwent catheter ablation. Third, the follow-up period was shorter than the prior studies from large registries. Further investigation with large-sized cohorts should be performed to validate the present results.

Conclusion

CAFL may be more closely associated with myocardial damage than AF even in non-elderly patients.

Disclosures

All authors declare no conflict of interest related to this study. The present study was approved by the institutional domestic ethical committee on 10th July 2020 (approval number: 3769).

Financial support

None

Declaration of Competing Interest

None

Acknowledgments

We thank Mr John Martin for his linguistic assistance in the preparation of this manuscript.

References

[1] Olshansky B, Okumura K, Hess PG, Waldo AL. Demonstration of an area of slow conduction in human atrial flutter. J Am Coll Cardiol 1990;16:1639–48.
[2] Cheniti G, Vlachos K, Pambrun T, Hooks D, Frontera A, Takigawa M, et al. Atrial fibrillation mechanisms and implications for catheter ablation. Front Physiol 2018;9:1458.
[3] Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J 2013;34:2746–51.
[4] Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011;123:1501–8.
[5] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

[6] Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668–78.
[7] Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–6.
[8] Skjoth F, Vadmann H, Hjortshoj SP, Riahi S, Lip GYH, Larsen TB. Disease progression after ablation for atrial flutter compared with atrial fibrillation: a nationwide cohort study. Int J Clin Pract 2018;72:e13258.
[9] Rahman F, Wang N, Yin X, Ellinor PT, Lubitz SA, LeLorier PA, et al. Atrial flutter: clinical risk factors and adverse outcomes in the Framingham Heart Study. Heart Rhythm 2016;13:233–40.
[10] Core Team R. R: a language and environment for statistical computing, Vienna, Austria: R Foundation for Statistical Computing; 2019. URL https://www.R-project.org/ .
[11] Viles-Gonzalez JF, Gomes JA, Miller MA, Dukkipati SR, Koruth JS, Eggert C, et al. Areas with complex fractionated atrial electrograms recorded after pulmonary vein isolation represent normal voltage and conduction velocity in sinus rhythm. Europace 2013;15:339–46.