

## ORIGINAL ARTICLE

# Influence of substrate modification in catheter ablation of atrial fibrillation on the incidence of acute complications: Analysis of 10 795 procedures in J-CARAF Study 2011-2016

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## Abstract

**Background and purpose:** In expectation of better outcome of catheter ablation of atrial fibrillation (AF), several strategies of extra-PV (pulmonary vein) substrate modification have been utilized. We assessed whether substrate modification or ablation of extra-PV source is a predictor of complications.

**Methods:** Japanese Heart Rhythm Society requested electrophysiology centers to register the data of patients who underwent AF ablation.

**Results:** The data of 10 795 AF ablation cases (age;  $63.8 \pm 10.6$  years) treated during 2011-2016 were registered. Pericardial effusion ( $n = 105$ ), massive bleeding ( $n = 108$ ), stroke ( $n = 6$ ), atrial-esophageal fistula ( $n = 2$ ), and other 114 complications occurred in 323 patients (3.0%). Univariate analysis revealed that age  $\geq 65$  years, female gender, heart failure, CHA2DS2-VASc  $\geq 3$ , hemodialysis, deep sedation, and complex fractionated atrial electrogram (CFAE)-guided ablation ([+] vs [-] = 4.3% vs 2.8%,  $P = .005$ ) were related with the higher incidence of complications. Redo session, 3-D imaging system ([+] vs [-]: 4.4% vs 2.9%,  $P = .017$ ), and periprocedural dabigatran

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were related with the lower incidence of complications. None of the linear ablation of the left atrium, ganglionated plexi ablation, and superior vena cava ablation affected the incidence of complications. Multiple logistic regression analysis showed that in addition to 3-D imaging system, age  $\geq 65$  years, redo session, and deep sedation, CFAE ablation was an independent predictor of the risk of complications (OR 1.78,  $P = .001$ ). Specifically, implantation of a permanent pacemaker due to emerging sinus node dysfunction was frequent after CFAE ablation (CFAE [+] vs [-] = 4/1047 vs 2/9748,  $P < .001$ ).

**Conclusions:** Among extra-PV ablation strategies, CFAE-guided ablation is a predictor of ablation-related complications.

#### KEYWORDS

atrial fibrillation, catheter ablation, complex fractionated atrial electrogram, complication

## 1 | INTRODUCTION

In expectation of better outcome of catheter ablation for the cure of atrial fibrillation (AF), adjunctive ablation strategies such as complex fractionated atrial electrogram (CFAE) ablation and nonpulmonary vein (PV) trigger ablation have been introduced into clinical practice.<sup>1-4</sup> Although the recent studies suggested that these adjunctive ablation strategies do not drastically reduce AF recurrence rate in either of paroxysmal AF (PAF) or persistent AF,<sup>5-7</sup> some physicians still believe in the extra-PV ablations as potential means to improve the outcome in selected clinical settings.<sup>2</sup> On the other hand, it is conceivable that adjunctive extra-PV ablations inadvertently increase the incidence of complications because of complicated manipulations and prolonged procedure time. In this report, we assessed whether substrate ablation, trigger ablation, or ablation of extra-PV source is a predictor of acute complications of catheter ablation for AF.

## 2 | METHODS

The data from the Japanese Catheter Ablation Registry of Atrial Fibrillation (J-CARAF) were used in this study. This annual nationwide registry of catheter ablation for AF started in 2011.<sup>8-11</sup> The method of the survey has been previously reported.<sup>9,10</sup> In short, the relevant data of AF ablation procedures performed in the designated months were registered by members of the Japanese Heart Rhythm Society (JHRS).

The data on patients' backgrounds, methods of PV isolation and related techniques, complications, as well as the periprocedural pharmacological treatments were collected for AF ablation sessions performed in each September from 2011 to 2016 and in May 2012. Patient data included age, gender, previous AF ablation, AF type (PAF, persistent, or long-standing persistent), thromboembolic risk factors, and echocardiographic parameters. With the intention of clarifying clinically significant predictive factors for complications, only serious adverse events that needed invasive treatment or watchful monitoring were included in the analysis. Electrophysiology (EP) centers with  $\geq 10$  procedures per month were defined as high-volume centers.

The continuous variables with a normal distribution were expressed as the means  $\pm$  SD. Categorical variables were compared using Tukey's test. A multiple logistic regression analysis was performed for variables with univariate  $P$  value  $< .1$ , to detect the independent determinants for the occurrence of complications. A  $P < .05$  was considered statistically significant. All analyses were performed using Statistical Analysis ver. 2.0 (ESUMI Co., Ltd., Tokyo, Japan).

## 3 | RESULTS

### 3.1 | General observations

The data of 10 795 AF ablation sessions were collected ( $1542 \pm 586$  procedures from  $165 \pm 36$  centers for each month of 7 separated survey periods;  $63.8 \pm 10.6$  years old; 73.0% male). Among these sessions, there was 21.7% redo AF ablation. PAF shared 64.1% ( $n = 6915$ ) of targeted AF. The proportions of persistent AF and long-standing persistent AF were 23.1% ( $n = 2496$ ) and 12.8% ( $n = 1384$ ), respectively.

### 3.2 | Complications

A total of 335 major complications occurred in 323 patients (3.0%). The numbers of each event are shown in Table 1. Cardiac tamponade occurred in 105 subjects. Hematoma at the puncture site shared the second largest number of complications. Gastroparesis, pseudoaneurysm, and protracted phrenic nerve paralysis were seen in 0.2% of patients, respectively. Implantation of a permanent pacemaker was required in 3 patients with advanced AV block and in 6 with sinus node dysfunction.

#### 3.2.1 | Results of univariate analysis: clinical condition and profile

Relevance of each clinical condition and profile to the occurrence of complications is shown in Table 2.

Complications occurred at the similar rate in the first half (3.1%; 2011-2013) and the second half of the survey (2.9%, 2014-2016).

**TABLE 1** Summary of complications

| No. of procedures                   | 10 795 | %   |
|-------------------------------------|--------|-----|
| Cardiac tamponade                   | 105    | 1.0 |
| Hematoma at puncture site           | 103    | 1.0 |
| Gastroparesis                       | 24     | 0.2 |
| Pseudoaneurysm                      | 22     | 0.2 |
| Phrenic nerve paralysis             | 19     | 0.2 |
| Air embolism                        | 16     | 0.1 |
| Arteriovenous fistula               | 11     | 0.1 |
| Pericarditis                        | 6      | 0.1 |
| Cerebral infarction                 | 6      | 0.1 |
| TIA                                 | 3      | 0.0 |
| Sinus node dysfunction <sup>a</sup> | 6      | 0.1 |
| Advanced AV block <sup>a</sup>      | 3      | 0.0 |
| Atrioesophageal fistula             | 2 (1)  | 0.0 |
| Others                              | 9 (1)  | 0.1 |
| No. of events                       | 335    | -   |
| No. of patients                     | 323    | 3.0 |

AV, atrioventricular; TIA, transient ischemic attack.

Numbers in parenthesis indicate fatal complications.

<sup>a</sup>Patients who needed permanent pacemaker implantation.

**TABLE 2** Incidence of complications and clinical profiles

|                             | Yes             | No                | P value |
|-----------------------------|-----------------|-------------------|---------|
| Last 3 years (2014-2016)    | 185/6358 (2.9%) | 138/4437 (3.1%)   | .548    |
| High volume center          | 208/7386 (2.8%) | 115/3409 (3.4%)   | .114    |
| Age $\geq$ 65 years         | 212/5829 (3.6%) | 111/4966 (2.2%)   | <.001   |
| Age $\geq$ 75 years         | 48/1500 (3.2%)  | 275/9295 (3.0%)   | .611    |
| Male                        | 217/7822 (2.8%) | 106/2193 (3.6%)   | .017    |
| Redo session                | 45/2342 (1.9%)  | 278/8453 (3.3%)   | .001    |
| PAF                         | 206/6915 (3.0%) | 117/3880 (3.0%)   | .915    |
| CHADS2 score $\geq$ 2       | 101/2999 (3.3%) | 222/7796 (2.8%)   | .155    |
| CHA2DS2-VASc score $\geq$ 3 | 135/3517 (3.8%) | 188/7278 (2.6%)   | <.001   |
| LVEF < 0.6                  | 98/2984 (3.3%)  | 225/7811 (2.9%)   | .271    |
| LAD $\geq$ 42 mm            | 135/4441 (3.0%) | 188/6354 (3.0%)   | .808    |
| CHF                         | 60/1472 (4.1%)  | 263/9323 (2.8%)   | .009    |
| Hypertension                | 172/5444 (3.2%) | 151/5351 (2.8%)   | .303    |
| Diabetes mellitus           | 51/1435 (3.6%)  | 272/9360 (2.9%)   | .180    |
| Stroke/TIA                  | 25/809 (3.1%)   | 298/9986 (3.0%)   | .865    |
| Vascular disease            | 24/663 (3.6%)   | 299/10 132 (3.0%) | .327    |
| Hemodialysis                | 8/128 (6.3%)    | 313/10 667 (2.9%) | .028    |

CHF: congestive heart failure; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation.

Age of 65 years or more was related with the increase in complications ( $\geq$ 65 vs <65: 3.6% vs 2.2%,  $P < .001$ ), while age of 75 years or more did not significantly affect the appearance of complications. Complications more frequently occurred in female patients and in

patients with CHA2DS2-VASc score 3 or more. Congestive heart failure (CHF) and chronic hemodialysis were related with the higher rate of complication.

### 3.2.2 | Results of univariate analysis: procedural features of AF ablation

The incidences of complications were also compared between patient groups divided by factors related with AF ablation procedures (Table 3). None of the superior vena cava (SVC) ablation, cavotricuspid isthmus ablation, left atrial (LA) linear ablation, or ganglionated plexi ablation apparently affected the frequency of complications. In contrast, complications more frequently occurred when CFAE ablation was performed ([+] 4.4% vs [-] 2.8%,  $P = .005$ ).

Deep sedation ([+] 3.4% vs [-] 2.5%,  $P = .006$ ) was related with the higher rate of complications. Periprocedural administration of dabigatran ([+] 2.1% vs [-] 3.2%,  $P = .018$ ) and use of 3D imaging system ([+] 2.9% vs [-] 4.4%,  $P = .017$ ) were associated with lower incidence of complications.

### 3.3 | Results of multivariate logistic regression analysis on the relationship between the incidence of complications and clinical or procedural variables

As shown in Table 4, age  $\geq$  65 years, CFAE ablation, and deep sedation were independent predictors of higher complication rate (odds ratio: 1.56, 1.78, and 1.33). Conversely, redo ablation and use of 3-D imaging system were the factors related with the lower complication rate (odds ratio: 0.56 and 0.64). Thus, among several means of adjunctive extra-PV ablation analyzed in the present study, only CFAE ablation was relevant to the frequency of complications.

When the incidence of each complication was compared between procedures with CFAE ablation and those without it, the emergence of clinically critical sinus node dysfunction was apparently affected by this maneuver (Table 5). CFAE ablation was performed in the left atrium of 998 patients (9.2%) and in the right atrium of 396 patients (3.7%). Among them, 347 subjects were treated by biatrial CFAE ablation (3.2%). In 6 patients whose sinus node dysfunction needed a permanent pacemaker 3 and 1 subjects underwent single left and biatrial CFAE ablation, respectively. Critical sinus node dysfunction appeared in the absence of CFAE ablation in the remaining 2 patients. CFAE ablation was employed in 33.6% of EP centers in 2011, while only 21.8% of them utilized this method in 2017.

## 4 | DISCUSSION

### 4.1 | Major findings

The major findings of the present study are as follows: (i) SVC ablation, cavotricuspid isthmus ablation, LA linear ablation, or ganglionated plexi ablation did not affect the frequency of AF ablation-related complications and (ii) CFAE ablation independently enhanced the rate of complications.

**TABLE 3** Incidence of complications and procedural features of AF ablation

|   | Yes               | No                | P value |
|---|-------------------|-------------------|---------|
| Extra-PV ablation                           |                   |                   |         |
| SVC ablation and substrate modification     | 54/1898 (2.8%)    | 269/8897 (3.0%)   | .679    |
| Cavotricuspid isthmus                       | 169/5593 (3.0%)   | 154/5202 (2.9%)   | .852    |
| LA linear ablation                          | 76/2437 (3.1%)    | 247/8358 (3.0%)   | .677    |
| Ganglionated plexi                          | 7/319 (2.2%)      | 316/10 476 (3.0%) | .396    |
| CFAE  | 46/1047 (4.4%)    | 277/9748 (2.8%)   | .005    |
| Periprocedural OAC                          |                   |                   |         |
| Warfarin                                    | 111/3231 (3.4%)   | 212/7564 (2.8%)   | .077    |
| Dabigatran                                  | 33/1598 (2.1%)    | 290/9197 (3.2%)   | .018    |
| Rivaroxaban                                 | 52/1712 (3.0%)    | 271/9083 (3.0%)   | .905    |
| Apixaban                                    | 66/2025 (3.3%)    | 257/8780 (2.9%)   | .433    |
| Edoxaban                                    | 12/482 (2.5%)     | 311/10 313 (3.0%) | .508    |
| Anesthesia, cryoballoon, and imaging system |                   |                   |         |
| Deep sedation                               | 182/5299 (3.4%)   | 141/5496 (2.6%)   | .008    |
| General anesthesia                          | 11/317 (3.5%)     | 312/10 478 (3.0%) | .612    |
| Cryoballoon catheter                        | 32/874 (3.5%)     | 291/9921 (2.9%)   | .226    |
| 3-D imaging system                          | 290/10 049 (2.9%) | 33/746 (4.4%)     | .017    |

CFAE, complex fractionated atrial electrogram; LA, left atrium; OAC, oral anticoagulant; PV, pulmonary vein; SVC, superior vena cava.

**TABLE 4** Results of multiple logistic regression analysis

| No. of procedures           | Complications (+)<br>323 | Complications (–)<br>10 474 | Odds ratio (95% CI) | P value |
|-----------------------------|--------------------------|-----------------------------|---------------------|---------|
| Age $\geq$ 65 years         | 212 (65.6%)              | 5617 (53.6%)                | 1.56 (1.20-2.04)    | .001    |
| Male                        | 217 (67.2%)              | 7665 (73.2%)                | 0.83 (0.64-1.07)    | .141    |
| Redo session                | 45 (13.9%)               | 2297 (21.9%)                | 0.56 (0.41-0.78)    | <.001   |
| CHA2DS2-VASc score $\geq$ 3 | 135 (41.8%)              | 3382 (32.3%)                | 1.05 (0.79-1.39)    | .744    |
| CHF                         | 60 (18.6%)               | 1412 (13.5%)                | 1.36 (1.01-1.85)    | .045    |
| Hemodialysis                | 8 (2.5%)                 | 120 (1.1%)                  | 1.99 (0.95-4.18)    | .069    |
| CFAE                        | 46 (14.2%)               | 1001 (9.6%)                 | 1.78 (1.29-2.46)    | .001    |
| Warfarin                    | 111 (34.4%)              | 3120 (29.8%)                | 1.11 (0.87-1.42)    | .406    |
| Dabigatran                  | 33 (10.2%)               | 1565 (14.9%)                | 0.74 (0.51-1.08)    | .115    |
| Deep sedation               | 182 (56.3%)              | 5117 (48.9%)                | 1.31 (1.04-1.64)    | .019    |
| 3-D imaging system          | 290 (89.8%)              | 9759 (93.2%)                | 0.64 (0.44-0.93)    | .018    |

Abbreviations are explained in Tables 1-3.

## 4.2 | Earlier studies

Deshmukh et al<sup>12</sup> reported the status of acute complications associated with AF ablation in the United States. Complications occurred in 6.29% of 93 801 procedures performed between 2000 and 2010 with cardiac complications being the most frequent (2.54%). They found the association between hospital volume and adverse outcomes. Also, age and female gender were predictors of higher total complication rate. In the worldwide survey by Michowitz et al<sup>13</sup>, cardiac tamponade occurred in 0.9% of 34 943 procedures. They also reported that a number of procedures in each hospital and female gender were related with this complication.

In terms of adjunctive extra-PV ablation, SVC isolation has been suggested to increase the phrenic nerve injury.<sup>14</sup> Meta-analysis of 1415 procedures found no increase in procedural-related adverse events as well as no improvement in midterm clinical outcome.<sup>15</sup>

In STAR AF-II trial, no reduction in the rate of recurrent AF was observed when either linear ablation across the left atrial roof and mitral valve isthmus or CFAE ablation was performed in addition to PV isolation in persistent AF.<sup>7</sup> It was also found that either of the 2 adjunctive extra-PV strategies did not increase the rate of major procedure-related adverse events. Until now, no undisputable evidence is available to know whether extra-PV adjunctive ablation is 1 of the predictors of higher rate of AF-related adverse events or not.<sup>6</sup>

**TABLE 5** Summary of complications

| CFAE ablation               | +         | -         |
|-----------------------------|-----------|-----------|
| No. of procedures           | 1047      | 9748      |
| Patients with complications | 46        | 277       |
| No. of complications        | 46        | 289       |
| Cardiac tamponade           | 11 (1.1%) | 94 (1.0%) |
| Hematoma at puncture site   | 15 (1.4%) | 89 (0.9%) |
| Gastroparesis               | 4 (0.4%)  | 20 (0.2%) |
| Pseudoaneurysm              | 4 (0.4%)  | 18 (0.2%) |
| Phrenic nerve paralysis     | 4 (0.4%)  | 15 (0.2%) |
| Air embolism                | 1 (0.1%)  | 15 (0.2%) |
| Arteriovenous fistula       | 0         | 11 (0.1%) |
| Pericarditis                | 1 (0.0%)  | 5 (0.0%)  |
| Cerebral infarction         | 0         | 6 (0.1%)  |
| TIA                         | 1 (0.1%)  | 2 (0.0%)  |
| Sinus node dysfunction*     | 4 (0.4%)  | 2 (0.0%)  |
| Advanced AV block           | 0         | 3 (0.0%)  |
| Atrioesophageal fistula     | 0         | 2 (0.0%)  |
| Others                      | 1 (0.1%)  | 8 (0.1%)  |

\* $P < .001$ .

### 4.3 | Interpretation of the present results

In our registry, results of multiple logistic regression analysis revealed that only 2 factors, 3D imaging system and redo session, were associated with the lower incident rate. Although 3D imaging systems, CARTO system in most cases, may warrant precise identification of the foci or mechanisms of arrhythmic substrates, our observation suggests that they also enhance the safety of AF ablation. Manipulation of redo ablation session is presumably supplementary and limited to repairing of the incompleteness of the first ablation session. It is conceivable that less complicated maneuver and relatively short manipulation time of redo session may explain the lower rate of adverse events.

Contrary to observations in earlier studies,<sup>12</sup> we failed to detect substantial impact of center volume on frequency of complications. Although not significant in multiple logistic regression analysis, complication occurred more frequently in female patients in univariate analysis. Also, age  $\geq 65$  years was independently related with the higher incidence of complications. These observations are, to some extent, in good agreement with earlier reports, suggesting the importance of gender and age in the aspects of AF-related complications.<sup>12,13</sup>

This study has suggested that the ablation strategy for CFAE elimination was an independent risk for early complications. Because of the technical aspects of CFAE ablation, it is possible that this procedure causes endocardial injury and accelerates the formation of mural thrombi, increasing bleeding or thromboembolic complications<sup>1</sup> such as cerebral infarction and cardiac tamponade. However, the present observation did not confirm the validity of this view. This may be partly explained by that the frequency of a certain complication which is actually susceptible to some type of extra-PV ablation was too low to detect it. It is also possible that vascular or

endocardial injury by CFAE ablation is not remarkable enough to increase the rate of bleeding or thromboembolic complications.

Statistical analysis suggested a causal relationship between CFAE ablation and critical sinus node dysfunction after AF ablation. Because the close connection between the right atrial CFAE ablation and sinus node dysfunction was not confirmed, neither of direct injury to the sinus node or occlusion of sinus node artery seems to be a plausible explanation of this adverse event. Thus, we speculate that elimination of continuing AF or frequent paroxysmal AF uncovered symptoms of concealed sinus node dysfunction.

Complex fractionated atrial electrogram ablation has not shown a beneficial effect on ablation for paroxysmal AF.<sup>5</sup> Considering these facts, CFAE ablation should be performed utmost in selected persistent/long-standing persistent AF by experienced operators.<sup>2</sup> When CFAE ablation is performed, specific consideration is needed to the possibility of latent sinus node dysfunction.

### 4.4 | Limitations

The risk of early complications is subject to many factors, such as clinical features of patients and the techniques of AF ablation.<sup>9</sup> It is not deniable that the present study is not potent to point out the most crucial factor for complications. Because the registry was performed in Japan, the results could lack generalizability to other nations. The study was not a randomized comparison between different ablation strategies. Special care should be taken to interpret the present results that might have been biased by the limitations inherent to observational studies.

## 5 | CONCLUSIONS

CFAE ablation is 1 of the independent predictors to enhance the rate of AF ablation-related complications.

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### CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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