Impact of Preprocedural Serum Eicosapentaenoic Acid to Arachidonic Acid Ratio on Post-Ablation Recurrence of Atrial Fibrillation

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Summary
The aim of this study was to examine the impact of the serum eicosapentaenoic acid (EPA) to arachidonic acid (AA) ratio on recurrence after catheter ablation (CA) for atrial fibrillation (AF).

A total of 192 patients who underwent first-time radio frequency CA for AF were enrolled in this study. They were divided into two groups based on the median serum EPA/AA ratio before CA: a LOW group (< 0.30; n = 96) and a HIGH group (≥ 0.30; n = 96). Patients in the LOW group were younger and had smaller left atrial diameter (LAD) than those in the HIGH group. Although pulmonary vein triggers initiating AF were more frequently observed in the LOW group than the HIGH group (63% versus 46%, respectively; P = 0.021), no significant between-group difference was observed regarding the incidence of AF recurrence since the last procedure (17% versus 17%, respectively; P = 0.78; median follow-up, 37 months). Multivariate Cox regression analysis after adjustment for age and LAD revealed that EPA/AA of < 0.30 was not a significant predictor of AF recurrence (hazard ratio, 1.12; 95% confidence interval 0.53-2.37; P = 0.76). However, in the non-paroxysmal AF subgroup (n = 65), the incidence of AF recurrence was significantly higher in the LOW group than in the HIGH group (25.7% versus 6.7%, respectively; P = 0.031).

In conclusion, a lower preprocedural EPA/AA ratio, which was associated with younger age and small left atrium, was not a predictor for the risk of AF recurrence after CA for AF. The potential impact of the ratio on recurrence in non-paroxysmal AF subgroups should be examined with larger samples.

(Key words: Atrial tachyarrhythmia, Catheter ablation, Omega-3 polyunsaturated fatty acids)

Inflammation has been implicated in the pathogenesis of atrial fibrillation (AF).1-3 Inflammatory markers, such as C-reactive protein (CRP), interleukin-6, and tumor necrosis factor (TNF-α), reflect the extent of myocardial fibrosis and correlate with recurrence of AF after radiofrequency catheter ablation (CA).4-21

Omega-3 polyunsaturated fatty acids (n-3 PUFA), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), attenuate the inflammatory response by generating precursors to resolvins, protectins, and other inflammation-resolving mediators, which help ameliorate systemic inflammation.22-23 EPA and DHA also exhibit local anti-inflammatory effects that might be difficult to assess with circulating biomarkers.23 Incorporation of n-3 PUFA into cellular membranes and the subsequent alteration of protein function and signaling may contribute to potential anti-inflammatory and anti-arrhythmic effects.24-27

A low serum EPA to arachidonic acid (AA) (EPA/AA) ratio predicts worse clinical conditions and outcomes,28 especially in patients with atherosclerotic diseases, such as coronary artery disease29 and ventricular arrhythmia post myocardial infarction.30 However, there is no consensus with regard to atrial arrhythmia, owing to inconsistent results.22-30 Recent meta-analyses did not support the use of n-3 PUFAs for the prevention of AF in the setting of post-operative AF after cardiac surgery and post-cardioversion recurrent AF.14,15 However, in the setting of CA for AF, the anti-arrhythmic effect of n-3 PUFAs on AF recurrence is not well characterized. We examined the association between preprocedural EPA/AA ratio and AF recurrence in patients who underwent radiofrequency CA for AF.

Methods
Study population: This was a retrospective observational cohort study. A total of 258 consecutive patients [paroxysmal AF (PAF), n = 171; non-PAF, n = 87] underwent first-time radiofrequency CA for AF at our institution between July 2011 and October 2014. Among these patients,
Figure 1. Schematic illustration of the study design and patient-selection criteria. AA indicates arachidonic acid; AF, atrial fibrillation; CA, catheter ablation; DHA, docosahexaenoic acid; and EPA, eicosapentaenoic acid.
trigger (Figure 2). In cases where trigger ectopy was suspected to have originated from an extra-PV area uncovered by the catheters, we determined that the case had extra-PV trigger.

The principle strategy was extensive encircling pulmonary vein isolation (PVI) which was performed using an open-irrigated ablation catheter (Navistar Thermocool, Biosense-Webster, Diamond Bar, CA, USA). We used the double-lasso technique under the guidance of a 3D mapping system (CARTO XP or CARTO3, Biosense-Webster, Diamond Bar, CA, USA). The activated clotting time was maintained over 300 seconds throughout the procedure. The endpoint of the PVI was achievement of bidirectional conduction block between the left atrium and the PVs. Twenty minutes after the completion of PVI and restoration of sinus rhythm, high-dose isoproterenol (4-20 μg/minute) was routinely administered to evaluate acute reconnection and the presence of extra-PV triggers, which were defined as ectopies initiating AF originating from extra-PV origins. In case of induction of recurrent atrial fibrillation (AF) during the procedure, PVs were addressed until acute reconnection was achieved by the use of isoproterenol. The occurrence of extra-PV triggers was noted and categorized according to their origin.

Figure 2. Assessment of AF trigger using isoproterenol. Example of intracardiac electrocardiogram (A) and fluoroscopic images (B) when AF initiation (denoted by red arrows) was identified within RSPV after two normal sinus beats. The earliest spike was recorded using Lasso 17 and 18 electrodes that were placed in the RSPV ostium. Accordingly, this focus was determined to be a trigger ectopy within PV, and the patients were determined to have PV trigger. Prevalence and distribution of AF trigger counted by each anatomical structure were described in C. PVs were the main AF trigger site. Although not statistically significant, prevalence of PV trigger within LIPV and RIPV was numerically higher in the LOW group than in the HIGH group. Prevalence of extra-PV trigger was heterogeneous between the groups. *P = 0.093, †P = 0.12. AF indicates atrial fibrillation; CS, coronary sinus; CT, crista terminalis; LAO, left atrial oblique; LA PW, left atrial posterior wall; LIPV, left inferior pulmonary vein; LLRA, low lateral right atrium; LSPV, left superior pulmonary vein; PV, pulmonary vein; RA, right atrium; RAO, right anterior oblique; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; and SVC, superior vena cava.
Table 1. Characteristics of the Study Population

| Baseline characteristics | All patients $n = 192$ | High EPA/AA $n = 96$ | Low EPA/AA $n = 96$ | $P$ value |
|---------------------------|------------------------|----------------------|---------------------|-----------|
| Age, years                | 60.4 ± 9.9             | 65.5 ± 9.0           | 57.3 ± 10.6         | < 0.001   |
| Male, n (%)               | 140 (73)               | 70 (73)              | 70 (73)             | 1.00      |
| Body mass index, kg/m²    | 23.9 ± 4.2             | 24.4 ± 4.0           | 23.4 ± 4.4          | 0.10      |
| CHADS2 score, n (%)       |                       |                      |                     |           |
| 0-1                       | 145 (76)               | 68 (71)              | 77 (80)             |           |
| ≥ 2                       | 47 (24)                | 28 (29)              | 19 (20)             |           |
| AF type*, n (%)           |                       |                      |                     |           |
| Paroxysmal                | 127 (66)               | 66 (69)              | 61 (63)             |           |
| Persistent                | 37 (19)                | 20 (21)              | 17 (18)             |           |
| Long-standing persistent  | 28 (15)                | 10 (10)              | 18 (19)             |           |
| Comorbidities, n (%)      |                       |                      |                     |           |
| Congestive heart failure  | 22 (12)                | 11 (12)              | 11 (12)             | 1.00      |
| Coronary artery disease   | 17 (9)                 | 10 (10)              | 7 (7)               | 0.45      |
| Valvular heart disease    | 9 (5)                  | 7 (7)                | 2 (2)               | 0.088     |
| Hypertension              | 79 (41)                | 43 (45)              | 36 (38)             | 0.31      |
| Diabetes mellitus         | 20 (10)                | 10 (10)              | 10 (10)             | 1.00      |
| Stroke                    | 12 (6)                 | 8 (8)                | 4 (4)               | 0.19      |
| Laboratory data           |                       |                      |                     |           |
| Hemoglobin, g/dL          | 14.4 ± 1.4             | 14.3 ± 1.4           | 14.4 ± 1.4          | 0.57      |
| Blood urea nitrogen, mg/dL| 14.8 ± 3.8             | 15.0 ± 4.0           | 14.5 ± 3.5          | 0.40      |
| Serum creatinine, mg/dL   | 0.91 ± 1.27            | 1.00 ± 1.78          | 0.82 ± 0.17         | 0.33      |
| High-sensitivity CRP, mg/dL| 0.10 ± 0.17            | 0.18 ± 0.49          | 0.10 ± 0.20         | 0.17      |
| HbA1c, %                  | 5.7 ± 0.5              | 5.7 ± 0.5            | 5.7 ± 0.5           | 0.29      |
| Fatty acid                |                       |                      |                     |           |
| n-6 fatty acid            |                       |                      |                     |           |
| Serum DHLA, µg/mL         | 36.8 ± 11.7            | 33.1 ± 11.9          | 40.5 ± 10.2         | < 0.001   |
| Serum AA, µg/mL           | 195 ± 47               | 184 ± 41             | 206 ± 50            | < 0.001   |
| n-3 fatty acid            |                       |                      |                     |           |
| Serum EPA, µg/mL          | 75 ± 50                | 107 ± 51             | 43 ± 16             | < 0.001   |
| Serum DHA, µg/mL          | 151 ± 53               | 178 ± 54             | 123 ± 35            | < 0.001   |
| Serum EPA/AA              | 0.41 ± 0.29            | 0.60 ± 0.31          | 0.21 ± 0.06         | < 0.001   |
| Serum DHA/AA              | 0.80 ± 0.29            | 0.99 ± 0.27          | 0.62 ± 0.18         | < 0.001   |
| Cardiac imaging           |                       |                      |                     |           |
| Transthoracic echo        |                       |                      |                     |           |
| Left atrial diameter, mm  | 42.6 ± 6.9             | 44.0 ± 6.6           | 41.2 ± 7.0          | 0.004     |
| Left ventricular diastolic diameter, mm | 49.7 ± 4.6 | 49.7 ± 4.8 | 49.6 ± 4.3 | 0.99      |
| Left ventricular systolic diameter, mm | 31.0 ± 4.7 | 30.9 ± 5.0 | 31.1 ± 4.4 | 0.88      |
| Left ventricular ejection fraction, % | 67.2 ± 8.5 | 67.3 ± 9.4 | 67.0 ± 7.4 | 0.78      |
| Tranesophageal echo       |                       |                      |                     |           |
| Left atrial appendage flow velocity, cm/second | 52.7 ± 20.5 | 50.5 ± 19.0 | 54.9 ± 21.7 | 0.15      |
| Computed tomography       |                       |                      |                     |           |
| Maximum left atrial volume, mL | 105 ± 34       | 109 ± 34             | 101 ± 33            | 0.14      |
| Medication, n (%)         |                       |                      |                     |           |
| Baseline drugs            |                       |                      |                     |           |
| Calcium channel blocker   | 46 (24)                | 28 (29)              | 18 (19)             | 0.092     |
| ACE-inhibitor/ARB         | 69 (36)                | 36 (38)              | 33 (34)             | 0.65      |
| Diuretics                 | 13 (7)                 | 5 (5)                | 8 (8)               | 0.39      |
| Statin                    | 49 (26)                | 27 (28)              | 22 (23)             | 0.41      |
| Antiplatelet              | 26 (12)                | 17 (15)              | 9 (8)               | 0.10      |
| Vitamin K antagonist      | 71 (37)                | 36 (38)              | 35 (37)             | 0.88      |
| DOAC                      | 70 (37)                | 37 (39)              | 33 (34)             | 0.55      |
| Antiarrhythmic drugs at discharge |               |                      |                     |           |
| Class I (Na channel blocker) | 52 (27)            | 30 (31)              | 22 (23)             | 0.20      |
| Class II (β blocker)      | 72 (38)                | 31 (32)              | 41 (43)             | 0.14      |
| Class III (amiodarone)    | 10 (5)                 | 6 (6)                | 4 (4)               | 0.52      |
| Class IV (bepridil)       | 40 (21)                | 19 (20)              | 21 (22)             | 0.72      |
| Class IV (verapamil)      | 7 (4)                  | 4 (4)                | 3 (3)               | 0.70      |

*AF was categorized into 3 types: paroxysmal (AF terminated spontaneously or under AADs within 7 days of onset), persistent (AF lasting for more than 7 days up to 1 year or AF requiring termination by cardioversion), and long-standing persistent (AF lasting for ≥ 1 year). Both persistent AF and long-standing persistent AF were defined as non-paroxysmal AF. AA indicates arachidonic acid; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CRP, C-reactive protein; DHA, docosahexaenoic acid; DHLA, dihydrlipoic acid; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; and Na, sodium.
tachycardia, we attempted to identify the circuit and make block lines such as cavotricuspid isthmus line, left atrial roof line, left atrial bottom line, and mitral isthmus line with bidirectional conduction block used as the endpoint. In cases of induction of recurrent AF, cardioversion of sustained AF was undertaken to identify any extra-PV trigger site. We tried to eliminate any extra-PV trigger that occurred spontaneously during the above loading test. If recurrent AF was observed even after the above procedures, we finally approached ablation for complex fractionated atrial electrograms (CFAEs), which was defined as electrograms displaying > 2 deflections that are fractionated or have a short cycle length < 120 ms in their maximal form giving continuous electrical activity. During the repeat procedure, the methods of electrophysiological studies were similar to those in the first procedure. We searched for the reconnection of PV potentials, consolidated the precious lesion set, identified AF triggers, and attempted to perform ablation on them.

Post-ablation care and endpoints: Post CA, all patients underwent ambulatory monitoring during the first 3 post-procedural days until the day of discharge. Patients were scheduled to receive periodical follow-up at the outpatient clinic every 2 months for at least 1 year post CA. Subsequent follow-up protocols were left to the discretion of the attending physician. A 12-lead electrocardiogram was conducted at each follow-up visit. All patients were advised to report any symptoms of arrhythmia experienced between scheduled visits. They were additionally seen by the referring cardiologist for 24-hour Holter monitoring at the end of 3, 6, and 12 months post procedure. In principle, AADs were stopped 3 months after the ablation procedure except for patients with highly symptomatic AF recurrence. Recurrences during this blanking period were treated with AADs and/or cardioversion, if needed.

The endpoint of the study was the incidence of AF recurrence after the last procedure. AF recurrence was defined as documented symptomatic or asymptomatic recurrent atrial tachyarrhythmia lasting for ≥ 30 seconds after the blanking period of 90 days post CA. In principle, second ablation procedures were recommended for all patients with AF recurrence over the blanking period of the initial procedure. Three or more ablation procedures for refractory AF were recommended only when the patient preferred the repeat procedure to medical therapy.

Statistical analysis: Data are expressed as the mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. Normally distributed continuous variables were compared using Student’s t-test; the Mann-Whitney U test was used in cases of non-normal distribution. Categorical variables were compared using the chi-squared test or Fisher’s exact test when the expected cell size was ≤ 5. The study population was stratified according to the median serum EPA/AA ratio in the study cohort: LOW group (< 0.30) and HIGH group (≥ 0.30). Between-group differences with respect to patient characteristics including laboratory data such as fatty acid fractions, EPA/AA ratio, and DHA/AA ratio were assessed. The time to AF recurrence after the last procedure was analyzed using the Kaplan-Meier method and between-group differences assessed using the log-rank test. Hazard ratios (HR) with the corresponding 95% confidence intervals (CI) are reported. Subgroup analysis was also performed by stratification according to age, sex, body mass index (BMI), CHADS2 scores (≥ 2), AF type, left atrial diameter (LAD) (≥ 45 mm), and CRP level (≥ 0.1 mg/dL). Cox regression analysis was performed to assess the impact of low EPA/AA ratio or low DHA/AA ratio at baseline on AF recurrence. Statistical analysis was performed using the MedCalc (version 18.5. for Windows) software. P values < 0.05 were considered statistically significant.

Results

Study population: The baseline characteristics of patients stratified by median serum EPA/AA ratio are summarized in Table I. Patients in the LOW group were younger and had smaller LAD than those in the HIGH group. No significant between-group differences were observed with respect to the type of AF, baseline disease, CHADS2 score, laboratory data, echocardiographic parameters, computed tomography findings, or medication use.

Outcomes after CA: Extensive encircling PVI was completed in all patients with the endpoint of electrical bidirectional block (entrance and exit block). Over a median follow-up period of 41 months (IQR, 28-50), 58 patients (30%) developed AF recurrence; among these, 40 patients (69%) underwent a second session, and one patient (2%) underwent a third session. None of the enrolled patients underwent a fourth or more ablation.

Intraprocedural electrophysiological findings are described in Table II and Figure 2C. In both the first and most recent repeat sessions, PV triggers were identified more frequently in patients in the LOW group than those in the HIGH group. Patients in the LOW group were more prone to receive CFAE ablation. There was no significant between-group difference with respect to the other findings and ablation procedures. Almost all patients who received a repeat session exhibited PV reconnection, and repeat PV isolation was performed in these patients. A total of 5 patients developed complications in this cohort. Two patients developed groin hematoma, one patient experienced cardiac tamponade that required drainage, one patient experienced right coronary air embolization that required intervention with aspiration system, and one patient developed sick sinus syndrome that required pacemaker implantation.

After the last procedure, 32 patients (17%) experienced AF recurrence over a median follow-up period of 37 months (IQR, 21-49). The incidence of AF recurrence was not significantly different between the LOW and HIGH groups (16.7% versus 16.7%, respectively; HR, 1.10; 95% CI, 0.55-2.21; log-rank, P = 0.78) (Figure 3A). Multivariate Cox regression analysis after adjustment for age and LAD revealed that EPA/AA ratio < 0.30 was not a significant predictor of AF recurrence (HR, 1.12; 95% CI, 0.53-2.37; P = 0.76) (Table III).

The DHA/AA ratio correlated with the level of EPA/AA ratio (r = 0.61, P < 0.001). The incidence of AF recurrence did not differ between the low DHA/AA group (< 0.75 [median]; n = 96) and the high DHA/AA group.
AF triggers* were identified as ectopy initiating AF spontaneously or induced by administration of isoproterenol (0.5-20 μg/minute) during ablation procedure. PV and extra-PV triggers mean AF trigger originating from PVs and extra-PVs, respectively. Per-patient data are described in this Table. When at least one PV trigger was identified out of four PVs, we assigned the case to "presence of PV trigger," whereas, when PV trigger was not identified within all four PVs, we assigned the case to "absence of PV trigger" and did not count the number. CFAE indicates complex fractionated atrial electrogram; CTI, cavitricuspid isthmus; EPA/AA, ratio of eicosapentaenoic acid to arachidonic acid; GP, ganglionated plexi; MVI, mitral valve isthmus; PV, pulmonary vein; and SVC, superior vena cava.
Table III. Results of Cox Regression Analysis Showing the Predictors of AF Recurrence

| Subgroup | Incidence of AF recurrence after last procedure | Hazard ratio (95% CI) | P value for interaction |
|----------|-----------------------------------------------|-----------------------|------------------------|
|          | High Group                                    | Low Group             |                        |
| All patients | 17% (16/96)                                   | 17% (16/96)           | 0.78 (0.55-2.21)       | 0.20 |
| Age ≥ 65 years | 19% (10/52)                                   | 9% (2/22)             | 0.41 (0.09-1.88)       | 0.67 |
| Age < 65 years | 14% (6/44)                                    | 19% (14/74)           | 1.58 (0.61-4.13)       | 0.35 |
| Male      | 19% (13/70)                                   | 17% (12/70)           | 0.77 (0.37-1.61)       | 0.25 |
| Female    | 12% (3/26)                                    | 15% (4/26)            | 1.00 (0.29-3.46)       | 0.25 |
| BMI ≥ 24 kg/m² | 22% (10/46)                                  | 15% (6/40)            | 0.82 (0.30-2.26)       | 0.16 |
| BMI < 24 kg/m² | 12% (6/50)                                   | 18% (10/56)           | 1.51 (0.55-4.15)       | 0.012|
| CHADS2 ≥ 2 | 29% (8/28)                                    | 16% (3/19)            | 0.51 (0.14-1.93)       | 0.012|
| CHADS2 < 2 | 12% (8/68)                                    | 17% (13/77)           | 1.63 (0.68-3.94)       | 0.37 |
| Paroxysmal AF | 21% (14/66)                                  | 12% (7/61)            | 0.54 (0.22-1.36)       | 0.53 |
| Non-paroxysmal AF | 7% (2/30)                                   | 26% (9/35)            | 4.64 (1.01-21.5)       | 0.012|
| LAD ≥ 45 mm | 12% (5/41)                                    | 18% (6/33)            | 1.58 (0.48-5.19)       | 0.25 |
| LAD < 45 mm | 20% (11/55)                                   | 16% (10/63)           | 0.91 (0.38-2.17)       | 0.25 |
| High-sensitive CRP ≥ 0.1 mg/dL | 19% (5/27)                                   | 25% (5/20)            | 1.35 (0.39-4.66)       | 0.37 |
| High-sensitive CRP < 0.1 mg/dL | 16% (11/69)                                  | 15% (11/76)           | 1.02 (0.44-2.36)       | 0.53 |

Discussion

Main findings: We examined the impact of preprocedural serum EPA/AA ratio on AF recurrence in patients undergoing radiofrequency CA for AF. By disaggregating the study population into two groups using the median serum EPA/AA ratio, we found that patients in the LOW group were younger and had smaller LAD than those in the HIGH group. Although PV triggers initiating AF were more frequently observed in the LOW group than in the HIGH group, no significant between-group differences were observed with respect to the incidence of AF recurrence. Multivariate Cox regression analysis after adjustment for age and LAD revealed that EPA/AA of < 0.30 was not a significant predictor of AF recurrence.

Patient characteristics: In the present study, patients in the LOW group were younger and had smaller LAD than those in the HIGH group. Generally, young patients with a small left atrium represent a low-risk population of developing cardiovascular events such as coronary artery disease, atrial fibrillation, stroke, and heart failure. The retrospective study design that only included patients with already diagnosed AF may explain the result; indeed, patients in the LOW group might develop AF regardless of low cardiovascular risk (i.e. younger age and smaller left
eicosapentaenoic acid; LAD, left atrial diameter; and L

Their result is similar to that observed in the non-
tation with n-3 PUFAs was associated with a lower inci-

The impact of serum n-3 fatty acid level on AF recurrence

When CA for AF was not established as a first-line ther-

Reference period of the previous study was 2004-2007

Second, the reference period of the previous study was 2004-2007

Baseline values directly reflect patients’ lifestyle and the
difference between classifications would contribute to the result.

Electrophysiological findings and perspective: An inter-
action between trigger and the underlying atrial substrate
usually governs the course of AF. A trigger usually initi-
ates the AF, and the substrate determines its persistence.16,24,25) Electrophysiological findings in the present
study revealed a significant between-group difference with
respect to the prevalence of PV trigger (more frequent in the
LOW group) (Table II and Figure 2C). In animal
models, n-3 PUFAs have been shown to suppress ectopic
firing in PVs through enhancement of diastolic hyperpol-
rization, reduction of the amplitude of delayed after de-

Comparison with previous studies: Currently, data about
the impact of serum n-3 fatty acid level on AF recurrence
after CA are limited. In a retrospective study of 258 pa-
tients undergoing AF ablation by Patel, et al, supplemen-
tation with n-3 PUFAs was associated with a lower incidence
of AF recurrence as compared to that in non-
users.25) Their result is similar to that observed in the non-
PAAF subgroup in our study, but not consistent with the
findings of the entire cohort; this may be attributable to
several factors. First, different baseline characteristics,
such as race, ethnicity, and lifestyle habits including fish
intake, are associated with the EPA/AA ratio and would be
acknowledged. Japanese have been reported to have higher plasma EPA levels than Caucasians.25) Second, the
reference period of the previous study was 2004-2007
when CA for AF was not established as a first-line ther-
apy and various methodologies of ablation for AF were in
use. Recent advances in ablation technology have helped
improve ablation outcomes; the recurrence rate in this
study (7.3% per year) was approximately 50% lower than
that in a previous study (15.3% per year).25) Third, we
evaluated preprocedural EPA/AA ratio which differs from
that after the supplementation of n-3 PUFA. Individual
baseline values directly reflect patients’ lifestyle and the
difference between classifications would contribute to the result.

| Laboratory data | All patients | High EPA/AA (n = 66) | Low EPA/AA (n = 61) | P value* | All patients | High EPA/AA (n = 30) | Low EPA/AA (n = 35) | P value* |
|----------------|-------------|---------------------|--------------------|----------|-------------|---------------------|--------------------|----------|
| Serum creatinine, mg/dL | 0.94 ± 1.55 | 1.08 ± 2.15 | 0.79 ± 0.16 | 0.28 | 0.87 ± 0.17 | 0.84 ± 0.15 | 0.89 ± 0.18 | 0.20 |
| High-sensitive CRP, mg/dL | 0.10 ± 0.19 | 0.10 ± 0.16 | 0.10 ± 0.22 | 0.91 | 0.10 ± 0.13 | 0.11 ± 0.10 | 0.10 ± 0.15 | 0.79 |
| Transesophageal echo | | | | | | | | |
| LAD, mm | 40.7 ± 6.2 | 42.1 ± 5.9 | 39.1 ± 6.2 | 0.006 | 46.5 ± 6.6 | 48.3 ± 6.0 | 44.9 ± 6.8 | 0.036 |
| LVEF, % | 68.9 ± 8.1 | 69.4 ± 8.5 | 68.4 ± 7.7 | 0.47 | 63.7 ± 8.1 | 62.7 ± 9.8 | 64.5 ± 6.2 | 0.38 |
| Electrophysiological findings | | | | | | | | |
| Identification of AF triggers, n (%) | 83 (65) | 39 (59) | 44 (72) | 0.12 | 40 (62) | 17 (57) | 23 (66) | 0.46 |
| Presence of PV trigger | 72 (57) | 30 (46) | 42 (69) | 0.008 | 33 (51) | 15 (50) | 18 (51) | 0.91 |
| Presence of extra-PV trigger | 16 (13) | 11 (17) | 5 (8) | 0.15 | 12 (19) | 4 (13) | 8 (23) | 0.33 |

*High EPA/AA versus Low EPA/AA. AA indicates arachidonic acid; AF, atrial fibrillation; BMI, body mass index; CRP, C-reactive protein; EPA, eicosapentaenoic acid; LAD, left atrial diameter; and LVEF, left ventricular ejection fraction.
persist in the limited and small space.\textsuperscript{29} In both animal model and human situations, n-3 PUFA reduces the inducibility and duration of AF via prolongation of the atrial ERP and an increase in conduction velocity.\textsuperscript{29,30} The electrophysiological properties produced by n-3 PUFA may suppress electrical remodeling resulting in decreased sustainability of AF in the HIGH group. Moreover, a higher rate of CFAE ablation in the LOW group may reflect a greater proportion of patients with progressive atrial substrate. CFAE sites in patients without AF termination by PVI reportedly represented more damaged tissue responsible for persistent AF.\textsuperscript{30}

Finally, the present study posed a potential different impact of EPA/AA ratio by AF type. In principle, PAF is predominantly a phenomenon initiated by PV trigger and perpetuated by the substrate of the atrium around PVs.\textsuperscript{16,24,25,29} Conversely, non-PAF is a phenomenon associated with both PV and extra-PV triggers and substrates. By completion of extensive encircling PVI, trigger and substrate around PVs are expected to diminish, which may explain the equivalent recurrence rate observed in the HIGH and LOW groups of the PAF subgroup. On the contrary, PVI does not affect extra-PV triggers and substrate. The high contribution of the extra-PV trigger and substrate to the pathogenesis of non-PAF may explain the higher recurrence rate in the LOW group than that in the HIGH group. Although the prevalence of extra-PV triggers was equivalent between the non-PAF and PAF subgroups, patients in the non-PAF subgroup had larger LAD than those in the PAF subgroup. Thus, progressive extra-PV substrate, which is exhibited by left atrial structural remodeling, may be inherited in the non-PAF subgroup. Combined with electrical remodeling as mentioned earlier, patients in the LOW group had progressive substrates (i.e., both structural and electrical remodeling) in the non-PAF subgroup.

Limitations: This study has several limitations. First, this was a single-center retrospective observational study with a limited sample size. Potential selection bias toward healthier patients, who were suitable candidates for CA, was unavoidable in clinical practice. Second, cases of AF recurrence may have been missed, particularly if these were asymptomatic. Third, the EPA/AA ratio was evaluated only at baseline, whereas the ratio may change over time, leading to a potential false estimation of the association between fish intake and AF. Fourth, because of the heterogeneous nature of AF, we need to take possible confounding factors into consideration. Lifestyle habits such as high intake of salt, alcohol, smoking, low exercise level, and obesity were shown to be associated with the occurrence of AF.\textsuperscript{12,33} Racial and ethnic differences in the occurrence of AF were also acknowledged.\textsuperscript{30} These differences in individual lifestyle and Japanese ethnicity are likely to affect the EPA/AA ratio and the occurrence of AF recurrence, which may have influenced our results.

Conclusions

A lower preprocedural EPA/AA ratio, which was associated with younger age and small LAD, was not associated with the risk of AF recurrence after undergoing CA for AF. The potential contribution of the lower EPA/AA ratio to the increase in AF recurrence in patients with non-PAF should be properly examined in further studies involving larger sample sizes.

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Disclosure

Author contributions: We state that each author contributed not only to the design of study and the interpretation of data but also to critical reviewing for writing the manuscript. Dr. Masato Okada and Dr. Akio Hirata are the principal investigators who planned the protocol and performed the study with the help and valuable suggestions of other coauthors (Dr. Kazunori Kashiwase, Dr. Hiroyuki Nakanishi, Dr. Ryohei Amiya, Dr. Yoshiharu Higuchi, and Dr. Yasushi Sakata). Dr. Yasunori Ueda is the supervisor and contributed to important discussion of the present study.

Conflicts of interest: The authors declare that there is no conflict of interest.

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