Does Epicardial Adipose Tissue Influence Postoperative Atrial Fibrillation?

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Purpose: Epicardial adipose tissue (EAT) is associated with atrial fibrillation. We investigated the effect of EAT on postoperative atrial fibrillation (POAF) after cardiac surgery.

Methods: In all, 77 patients underwent scheduled cardiac surgery. Before the operation, we measured total epicardial adipose tissue (Total EAT) and left atrial (LA) EAT by three-dimensional computed tomography (CT). During surgery, we obtained samples of the right atrial appendage, aortic fat, and epicardial fat. The primary endpoint was occurrence of POAF within 1 week after surgery.

Results: POAF occurred in 21 patients (27%). Assessment of preoperative characteristics revealed significant differences of age and the use of aldosterone blockers and loop diuretics between the patients with and without POAF. In univariate analysis, the LA EAT/Total EAT ratio, age, use of aldosterone blockers and loop diuretics, P wave duration, cardioplegia volume, and central venous pressure (CVP) were all higher in POAF group. However, logistic regression analysis with propensity score matching found no significant differences of these factors although the LA EAT/Total EAT ratio was higher in POAF group.

Conclusion: The use of loop diuretics showed the strongest association with POAF. Logistic regression analysis suggested that a high LA EAT/Total EAT ratio had the second strongest association with POAF.

Keywords: epicardial adipose tissue, postoperative atrial fibrillation, left atrial adipose tissue

Introduction

Postoperative atrial fibrillation (POAF) is one of the most common complications of cardiac surgery. The incidence of POAF has variously been reported to range from 10% to 40%. POAF complicates postoperative management and prolongs the hospital stay, as well as increasing the risk of cerebral infarction, leading to elevation of both short-term and long-term mortality. In particular, embolism associated with POAF has a high mortality. The causes of POAF are reported to include cardiac failure, valvular disease, aging, and atrial fibrosis, but the detailed mechanisms remain unclear.

The combination of electrical and structural remodeling leads to lone atrial fibrillation (AF), and inflammation and metabolic syndrome are independent risk factors for lone AF. It has been suggested that epicardial adipose tissue (EAT) is one of the factors related to AF, with Nagashima et al. reporting that patients with lone AF have a higher EAT volume than persons in sinus rhythm. There have been reports that obesity and metabolic syndrome are related to POAF, but the relationship between POAF and EAT is currently unknown.
Materials and Methods

Study protocol
This study enrolled 77 patients who underwent scheduled cardiac surgery from May 2013 to July 2014 at our hospital. Patients with active malignancy, inflammatory disease, connective tissue disease, hematological disease, and thyroid disease were excluded. This study was registered with the University Hospital Medical Information Network (UMIN) (study ID: UMIN000013673) and was approved by the Ethics Committee of Nihon University School of Medicine Itabashi Hospital. We explained the details of the study to the candidate subjects and obtained written informed consent.

In 77 patients, surgery was performed via median sternotomy with cardiopulmonary bypass and crystalloid cardioplegia. All patients received infusion of landiolol hydrochloride, an ultrashort-acting β₁-selective β-blocker (Ono Pharmaceutical Co., Ltd., Osaka, Japan), at 2 µg/kg/min for 2 days after weaning from cardiopulmonary bypass to prevent POAF. After surgery, all patients received potassium chloride to maintain the potassium concentration above 4.5 mEq. After extubation, all patients received bisoprolol or carvedilol with furosemide and eplerenone as basal therapy. To detect POAF, we monitored the electrocardiogram for 1 week after surgery. When the heart rate was under 80/min, an external pacemaker was used to maintain it above this rate. POAF was defined as persistence of AF for >5 minutes or AF associated with hemodynamic changes such as a decrease in blood pressure or urine output.

In this study, the presence or absence of POAF and the following measurements were examined.

P wave duration
P wave duration was determined on the signal averaged electrocardiogram. Patients underwent 24-hour Holter electrocardiography and data obtained at 2:00 am were used to minimize the influence of the sympathetic nervous system. Electrocardiograms were obtained using the Spider View (ELA Medical, Inc., Arvada, CO, USA).

Measurement of EAT
Before cardiac surgery, all patients underwent computed tomography (CT) with a three dimensional (3D) spiral scanner (Aquilion One 320-row detector dynamic volume CT scanner; Toshiba Medical Systems, Tokyo, Japan). The heart rate was maintained below 80/min using β-blockers to minimize motion artifacts. Total EAT, left atrial EAT (LA EAT) volume, and LA volume were measured using images reconstructed on a workstation (ZIO M900 QUADRA, Amin Co., Ltd., Tokyo, Japan). Total EAT was measured from the diaphragm to the bifurcation of the pulmonary artery and LA EAT was extracted from Total EAT.

Laboratory parameters
Blood samples were obtained before surgery to measure the following parameters: brain natriuretic peptide (BNP), human atrial natriuretic peptide (HANP), adiponectin, leptin, serotonin, fatty acids, malondialdehyde modified low-density lipoprotein cholesterol (MDA-LDL), high sensitivity C-reactive protein (CRP), monocyte chemotactic protein-1 (MCP-1), pyridoline cross-linked carboxyterminal telopeptide of type I collagen (I-CTP), sialylated carbohydrate antigen (KL-6), aldosterone, renin, angiotensin II, creatinine, and cystatin C.

Hemodynamic monitoring
The heart rate, rhythm, blood pressure, urine output, and central venous pressure (CVP) were monitored while patients were in the intensive care unit after surgery. A daily fluid balance was calculated. Monitoring by electrocardiography was continued for 1 week.

Histological examination
A tissue sample (5 × 5 mm) was harvested from the right atrial appendage at the initiation of cardiopulmonary bypass. Samples were fixed in formalin, embedded in paraffin, and subjected to Masson trichrome staining. A slice was excised randomly from each patient’s right atrial appendage sample and was used to measure the percent area of adipose tissue and fibrous tissue with Image-Pro Premier software (Nippon Roper Co., Ltd., Tokyo, Japan). To calculate the percent area, the whole slice was imported and semi-automatically colored as follows: blue for adipose tissue, green for fibrous tissue, and red for muscle tissue.

Statistical analysis
Continuous variables were expressed as the median and interquartile range. The Mann–Whitney U test and Fisher’s exact test were used to analyze differences between the patients with and without POAF, and p < 0.05 was considered to indicate statistical significance. All analyses were conducted with SPSS software (version 21; SPSS, Chicago, IL, USA).
The Relationship between EAT and POAF

Results

POAF occurred in 21/77 patients (27%). There were no postoperative deaths and no major adverse events. The incidence of POAF varied depending on the underlying disease, being 19% in patients having coronary artery bypass grafting (CABG), 26% in patients undergoing valve surgery, and 50% in patients receiving aortic surgery (Table 1).

Although there was no significant difference of cardiopulmonary bypass time or operating time between the POAF group and the non-POAF group, the crystalloid cardioplegia volume was significantly larger in the POAF group (Table 1).

The POAF group was significantly older than the non-POAF group (p = 0.030). Preoperative use of aldosterone blockers and loop diuretics was higher in the POAF group than in the non-POAF group.

Preoperative findings and postoperative hemodynamics

Preoperative physiological findings and laboratory test results, as well as histological parameters of the right atrial appendage, are shown in Table 1. The P wave duration was prolonged in the POAF group compared with the non-POAF group. The LA EAT/Total EAT ratio calculated from 3D-CT data was higher in the POAF group.

Daily fluid balance showed no significant differences between the POAF group and non-POAF group (Fig. 1, left panel). On the first and second postoperative days (PODs), CVP at midnight was higher in the POAF group than the non-POAF group (Fig. 1, right panel).

Univariate analysis identified the following potential risk factors for POAF: age, aldosterone blocker use, loop diuretic use, prolonged P wave, LA EAT/Total EAT ratio, and CVP (POD 1 and 2). Multivariate logistic regression analysis was performed by incorporating these factors and the surgical procedure, with CABG being set as the standard and the odds ratios being calculated for valve surgery and aortic surgery. The odds ratio thus determined are shown in Table 2A. It was found that use of loop diuretics was the strongest risk factor for POAF.

Then, the patients were divided into a loop diuretic group and a non-loop diuretic group. Multivariate logistic regression analysis was performed using the age, P wave duration, and LA EAT/Total EAT ratio, with the results being as follows: age 1.064 (p = 0.060), P wave duration 0.998 (p = 0.695), and LA EAT/Total EAT ratio 106.775 (p = 0.047) (Table 2B). This analysis revealed that a high LA EAT/Total EAT ratio was the second strongest risk factor for POAF.

Accordingly, we performed a detailed analysis of LA EAT using propensity score matching. The patients were separated into two groups at the median LA EAT/Total EAT ratio calculated by univariate analysis and log odds were calculated: \( \log(p/(1-p)) = 2.005 + (-0.338) \times \text{Age} + 0.0022 \times \text{P wave duration} + 0.492 \times \text{Aldosterone blocker use} + 1.177 \times \text{Loop diuretic use} + 0.0002 \times \text{Cardioplegia} + 0.141 \times \text{CVP (POD 1)} + (-0.129) \times \text{CVP (POD 2)} + 0.386 \times \text{Valve surgery} + 0.754 \times \text{Aortic surgery}. \) When drug intake and surgery was adapted, insert 1 instead. In this formula, “p” is the odds ratio and its value is 1.857 (p = 0.281). Although there was no significant relation, a higher LA EAT/Total EAT ratio tended to show an association with POAF.

Discussion

Risk factors for POAF

In this study, multivariate analysis indicated that loop diuretic use was the strongest risk factor for POAF and a high CVP (POD 2) also influenced POAF. This suggests that atrial overload before and after cardiac surgery may cause POAF. It has been reported that mechanical overload of the left atrium causes POAF, and our results support that finding. Preoperative use of loop diuretics suggests the presence of chronic heart failure. Univariate analysis comparing the patients with and without preoperative diuretics revealed that BNP, LA dimension, and LA volume were higher in the patients using diuretics before surgery (Table 3). These findings suggest that preoperative chronic heart failure can lead to POAF.

LA EAT

We expected that the amount of EAT might depend on the heart size and that the localization of EAT would show individual differences. However, univariate analysis revealed no significant differences of Total EAT or LA EAT between the AF group and the non-AF group. Then, we analyzed EAT in relation to body surface area (BSA) or the LA volume (Table 4). There were no significant differences between the AF and non-AF groups with respect to the Total EAT/BSA ratio, LA EAT/BSA ratio, and LA EAT/LA volume ratio. On the other hand, there was a significant correlation between Total EAT and BSA (Pearson’s correlation coefficient: 0.429, p = 0.001, \( \alpha = 0.01 \)), between Total EAT and LA EAT (Pearson’s correlation coefficient: 0.830, p = 0.001, \( \alpha = 0.01 \)), and between
### Table 1  Comparison of baseline characteristics, examinations, and sorts of operations

|                              | POAF group | Non-POAF group | p value |
|------------------------------|------------|----------------|---------|
| Number                       | 21         | 56             |         |
| Days until POAF              | 3 (2, 5)   | -              |         |
| Age (years)                  | 73.0 (70.5, 79.0) | 69.5 (65.0, 74.7) | 0.03*   |
| Sex (female)                 | 8 (38%)    | 22 (39%)       | 0.924   |
| BMI (kg/m²)                  | 22.0 (18.8, 24.7) | 22.8 (21.0, 24.9) | 0.227   |
| BSA (m²)                     | 1.559 (1.431, 1.655) | 1.589 (1.435, 1.764) | 0.25    |
| Basal disease (%)            |            |                |         |
| Diabetes mellitus            | 33 (7/21)  | 41 (23/56)     | 0.607   |
| Hypertension                 | 71 (15/21) | 53 (30/56)     | 0.199   |
| Dyslipidemia                 | 33 (7/21)  | 35 (20/56)     | 1       |
| Hyperuricemia                | 14 (3/21)  | 7 (4/56)       | 0.383   |
| Hemodialysis                 | 23 (5/21)  | 12 (7/56)      | 0.291   |
| Preoperative oral medications (%) |            |                |         |
| β-blocker                    | 48 (10/21) | 43 (24/56)     | 0.799   |
| ARB                          | 42 (9/21)  | 37 (21/56)     | 0.794   |
| ACE-I                        | 14 (3/21)  | 8 (5/56)       | 0.676   |
| Ca channel blocker           | 14 (9/21)  | 48 (27/56)     | 0.799   |
| Statin                       | 33 (7/21)  | 37 (21/56)     | 0.796   |
| Aldosterone blocker          | 23 (5/21)  | 5 (3/56)       | 0.031*  |
| Loop diuretic                | 57 (12/21) | 21 (12/56)     | 0.005*  |
| Postoperative medications (%)|            |                |         |
| Carperitide                  | 100 (21/21)| 100 (56/56)    | -       |
| Tolvaptan                    | 0 (0/21)   | 0 (0/56)       | -       |
| β-blocker (oral)             | 90 (19/21) | 71 (40/56)     | 0.199   |
| ARB                          | 48 (10/21) | 29 (16/56)     | 0.227   |
| ACE-I                        | 0 (0/21)   | 0 (0/56)       | -       |
| Ca channel blocker (oral)    | 48 (10/21) | 5 (3/56)       | 0.618   |
| Statin                       | 48 (10/21) | 59 (33/56)     | 0.373   |
| Transthoracic echocardiogram |            |                |         |
| Ejection fraction (%)        | 61.6 (57.3, 74.2) | 67.0 (57.3, 72.9) | 0.681   |
| Left atrial dimension (mm)   | 40.3 (33.8, 45.6) | 37.6 (34.8, 43.0) | 0.619   |
| 3D-CT                        |            |                |         |
| Total EAT (cm³)              | 195.8 (107.9, 247.5) | 157.3 (100.0, 231.8) | 0.708   |
| LA EAT (cm³)                 | 57.5 (32.5, 78.8) | 37.6 (22.2, 65.4) | 0.121   |
| LA EAT/Total EAT ratio       | 0.30 (0.26, 0.36) | 0.23 (0.20, 0.30) | 0.017*  |
| LA volume (cm³)              | 134.6 (105.9, 171.5) | 118.2 (100.0, 152.7) | 0.18    |
| Holter electrocardiogram     |            |                |         |
| Maximum HR (bpm)             | 96.0 (86.2, 106.0) | 102.0 (95.5, 112.0) | 0.109   |
| Average HR (bpm)             | 68.0 (61.0, 75.5) | 67.0 (64.0, 74.5) | 0.762   |
| Minimum HR (bpm)             | 51.0 (49.0, 58.7) | 53.0 (48.0, 57.5) | 0.965   |
| P duration (ms)              | 141.0 (136.0, 157.0) | 136.0 (124.7, 142.2) | 0.009*  |
| Blood examination            |            |                |         |
| BNP (pg/mL)                  | 132.0 (41.9, 386.2) | 85.6 (30.4, 171.0) | 0.220   |
| HANP (pg/mL)                 | 53.3 (33.6, 154.5) | 42.5 (25.0, 80.3) | 0.136   |
| Adiponectin (ng/mL)          | 5.19 (2.42, 8.95) | 5.95 (2.90, 9.79) | 0.624   |
| Reptin (ng/mL)               | 5.80 (2.65, 8.75) | 5.55 (2.97, 9.12) | 0.628   |
| Serotonin (ng/mL)            | 96.0 (64.5, 131.0) | 85.0 (57.0, 135.5) | 0.401   |
| LDL/HDL ratio                | 1.75 (1.34, 3.13) | 2.15 (1.56, 2.81) | 0.309   |
| MDA-LDL (U/L)                | 87.0 (86.5, 141.0) | 108.5 (88.7, 132.2) | 0.071   |
| Triglyceride (mg/dL)         | 96.0 (61.5, 138.0) | 104.0 (74.2, 171.5) | 0.253   |
| Fatty acid fraction          |            |                |         |
| Dihomo-γ-linolenic acid (μg/mL) | 33.4 (27.0, 41.4) | 34.4 (28.8, 45.0) | 0.612   |
| Arachidonic acid (μg/mL)     | 175.6 (151.1, 231.4) | 188.7 (169.2, 227.4) | 0.136   |
| Eicosapentaenoic acid (μg/mL)| 54.3 (42.5, 73.5) | 58.9 (37.4, 86.2) | 0.883   |
The Relationship between EAT and POAF

| Pathological measurements of right atrial appendage | POAF group | Non-POAF group | p value |
|-----------------------------------------------------|------------|----------------|--------|
| Fat ratio                                           | 0.203 (0.144, 0.242) | 0.232 (0.146, 0.395) | 0.240  |
| Fibrosis ratio                                      | 0.290 (0.254, 0.472) | 0.319 (0.239, 0.414) | 0.588  |

| Sorts of operation (No.)                            | Total cases | Non-POAF group | p value |
|-----------------------------------------------------|-------------|----------------|--------|
| Total cases                                         | 21          | 56             | -      |
| Coronary artery bypass grafting                     | 5           | 21             | -      |
| Valve surgery                                       | 10          | 28             | -      |
| Congenital surgery                                  | 0           | 1              | -      |
| Aortic surgery                                      | 6           | 6              | -      |

| Operative data                                       |             |               |        |
|------------------------------------------------------|-------------|---------------|--------|
| Cardiopulmonary bypass time (min)                    | 171.0 (151.5, 268.5) | 162.0 (123.7, 208.5) | 0.181  |
| Aortic crossclamp time (min)                         | 121.0 (92.0, 198.0) | 111.5 (84.0, 147.7) | 0.248  |
| Operation time (min)                                 | 360.0 (276.5, 435.5) | 336.5 (267.0, 393.5) | 0.334  |
| Cardiopulmonary bypass fluid balance (mL)            | 2508.0 (1569.5, 3113.0) | 1893.0 (1202.0, 2946.0) | 0.416  |
| Cardioplegia (mL)                                    | 3000.0 (2500.0, 3500.0) | 2475.0 (2200.0, 3500.0) | 0.020* |

Values are the mean ± SD, median (25th, 75th interquartile range) or n (%). *p < 0.05. ARB: angiotensin II receptor blocker; ACE-I: angiotensin-converting enzyme inhibitor; BMI: body mass index; BNP: brain natriuretic peptide; BSA: body surface area; Ca: calcium; HANP: human atrial natriuretic peptide; HDL: high-density lipoprotein; LA: left atrial; LDL: low-density lipoprotein; MCP: monocyte chemotactic protein; MDA: malondialdehyde; POAF: postoperative atrial fibrillation; EAT: epicardial adipose tissue; 3D: three dimensional; hs-CRP: high sensitivity C-reactive protein; KL-6: sialylated carbohydrate antigen; EPA: eicosapentaenoic acid; AA: eicosapentaenoic acid; HR: heart rate; CT: computed tomography

![Fluid balance](image1)

![CVP](image2)

**Fig. 1** Postoperative data are shown. Fluid balance (left panel) calculated in each postoperative day, and there are no significant differences between POAF group and non-POAF group. CVP (right panel) is checked at 0 o’clock in each postoperative day. On first and second postoperative days, CVP is higher in POAF group than non-POAF group. CVP: central venous pressure; POAF: postoperative atrial fibrillation
### Table 2A Multivariate logistic regression analysis of risk factor for POAF

| Subjects                                | Odds ratio | 95% CI       | p value |
|-----------------------------------------|------------|--------------|---------|
| Age                                     | 1.083      | 0.990–1.185  | 0.083   |
| Aldosterone blocker intake              | 3.361      | 0.430–26.292 | 0.248   |
| Loop diuretics intake                   | 4.975      | 1.126–21.979 | 0.034*  |
| LA EAT/Total EAT ratio                  | 0.121      | 0.001–23.334 | 0.431   |
| P duration                              | 1.007      | 0.992–1.022  | 0.373   |
| Cardioplegia                            | 1          | 1.000–1.001  | 0.321   |
| CVP (POD1)                              | 0.869      | 0.681–1.110  | 0.262   |
| CVP (POD2)                              | 1.371      | 1.038–1.809  | 0.026*  |
| CABG                                    | 1          | -            | 0.125   |
| Valve surgery                           | 0.525      | 0.097–2.826  | 0.453   |
| Aortic surgery                          | 4.079      | 0.515–32.320 | 0.183   |

*p < 0.05. CABG: coronary artery bypass grafting; CVP: central venous pressure; LA: left atrial; POAF: postoperative atrial fibrillation; EAT: epicardial adipose tissue; CI: confidence interval; POD: postoperative day

### Table 2B Multivariate logistic regression analysis of risk factor for POAF when the patients divided into a loop diuretic group and a non-loop diuretic group

| Subjects                                | Odds ratio | 95% CI       | p value |
|-----------------------------------------|------------|--------------|---------|
| Age                                     | 1.064      | 0.997–1.134  | 0.060   |
| P wave duration                         | 0.998      | 0.986–1.010  | 0.695   |
| LA EAT/Total EAT ratio                  | 106.775    | 1.061–10750.407 | 0.047* |

LA: left atrial; POAF: postoperative atrial fibrillation; EAT: epicardial adipose tissue; CI: confidence interval

### Table 3 Univariate analysis comparing the patients with and without preoperative diuretics

| Subjects                                | Diuretic use (n = 24) | No diuretic use (n = 53) | p value |
|-----------------------------------------|------------------------|--------------------------|---------|
| BNP (pg/mL)                             | 85.8 (30.6, 280.0)     | 57.8 (26.5, 135.0)       | 0.008*  |
| EF (%)                                  | 65.5 (59.1, 73.2)      | 63.6 (58.7, 73.1)        | 0.847   |
| Left atrial dimension (mm)              | 37.7 (34.8, 45.9)      | 37.0 (33.8, 41.4)        | 0.001*  |
| Left atrial volume (mL)                 | 123.6 (87.9, 156.7)    | 105.0 (76.1, 131.9)      | 0.005*  |

*p < 0.05. BNP: brain natriuretic peptide; EF: ejection fraction

### Table 4 EAT revised with BSA and LA volume, and surgery types and LA EAT/Total EAT ratio

| EAT revised with BSA and LA volume     | POAF group (n = 21) | non-AF group (n = 56) | p value |
|----------------------------------------|---------------------|-----------------------|---------|
| Total EAT/BSA ratio                    | 93.8 (12.4, 149.4)  | 92.7 (56.9, 139.1)    | 0.740   |
| LA EAT/BSA ratio                       | 31.5 (0.39, 44.2)   | 23.1 (12.8, 37.3)     | 0.701   |
| LA EAT/LA volume ratio                 | 0.34 (0.50, 0.54)   | 0.31 (0.16, 0.44)     | 0.639   |

| Surgery types and LA EAT/Total EAT ratio | POAF group | non-POAF group | p value |
|-----------------------------------------|------------|----------------|---------|
| CABG                                    | 0.30 (0.20, -) | 0.23 (0.21, 0.30) | 0.590   |
| Valve surgery                           | 0.30 (0.25, 0.36) | 0.22 (0.18, 0.30) | 0.031   |
| Aortic surgery                          | 0.31 (0.26, 0.37) | 0.32 (0.21, 0.55) | 1.000   |

Values are the mean ± SD, median (25th, 75th interquartile range) or n (%). *p < 0.05. AF: atrial fibrillation; BSA: body surface area; CABG: coronary artery bypass grafting; LA: left atrial; POAF: postoperative atrial fibrillation; EAT: epicardial adipose tissue
LA EAT and the echocardiographic LA dimension (Pearson’s correlation coefficient: 0.266, \( p = 0.029, \alpha = 0.05 \)) while LA EAT and LA volume were not correlated. These results suggested that LA EAT increases around the free wall of the left atrium rather than circumferentially. Though Total EAT and LA EAT tend to increase with systemic obesity, LA enlargement only increases LA EAT. Our results and previous reports\(^{20–22}\) suggest that an increase in the LA EAT/Total EAT ratio is associated with chronic inflammation and fibrosis, leading to POAF.

**LA EAT and adipocytokines**

Echahidi et al.\(^{18}\) reported that metabolic syndrome and obesity were independent risk factors for POAF after CABG. Excessive EAT (cardiac obesity) may also be associated with POAF. In 2014, Drossos et al.\(^{21}\) reported that EAT was strongly associated with POAF after CABG. In their multivariate analysis, pericardial fat was the strongest independent factor, with a volume of 129.5 mL being suitable for CABG. This study included patients undergoing various types of cardiac surgery although there was only one patient with congenital heart disease. We found no significant difference of Total EAT and LA EAT between the POAF and non-POAF groups, possibly because adipose tissue showed a variable distribution. However, our study suggested that the LA EAT/Total EAT ratio was the second strongest risk factor for POAF and a higher ratio was associated with POAF.

Adipose tissue is an endocrine organ that secretes two types of adipocytokines, which either have insulin-sensitizing or anti-inflammatory properties or else induce insulin secretion. Insulin sensitizers include tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)), resistin, and free fatty acids while adiponectin induces insulin secretion. Mazurek et al.\(^{20}\) reported that EAT is a source of adipocytokines and Chatterjee et al.\(^{21}\) reported that excess adipose tissue surrounding vascular tissue promotes inflammation. Therefore, if LA EAT around the left atrium increases inflammation, this may become the basal substrate of POAF. The LA EAT/Total EAT ratio may be increased when the left atrium is exposed to stress such as chronic heart failure, mitral valve disease, and hypertension while LA overload leads to hypertrophy and fibrosis of the LA myocardium. Past articles reported that mice with metabolic syndrome due to a high fat diet show significant downregulation of adiponectin.\(^{24–27}\) In this mouse model, adiponectin supplementation reverses insulin resistance and hyperlipidemia. Adiponectin inhibits vascular endothelial dysfunction, suggesting that reduction of adiponectin by metabolic syndrome and obesity might promote arteriosclerosis. Expression of adiponectin is regulated by the serotonin receptor cascade, and increased serotonin receptor expression by enlarged adipocytes possibly contributes to a decrease in adiponectin.\(^{28}\) Hypertrophy of adipocytes also leads to chronic inflammation and fibrosis of adipose tissue, which inhibits the production of adipocytokines.\(^{22}\)

When correlations between adiponectin and adipose tissue parameters were evaluated, negative correlations were found between adiponectin and body mass index (Pearson’s correlation coefficient \(-0.266, \ p = 0.021, \alpha = 0.05\)), adiponectin and Total EAT (Pearson’s correlation coefficient \(-0.303, \ p = 0.014, \alpha = 0.05\)), and adiponectin and LA EAT (Pearson’s correlation coefficient \(-0.263, \ p = 0.033, \alpha = 0.05\)). These findings suggest that down-regulation of adiponectin is not only due to systemic obesity but also an increase in Total EAT and LA EAT, so LA EAT might be one risk factor for POAF.

**Surgery**

CABG was associated with the lowest frequency of POAF. When the odds ratio of CABG was set as 1 in multivariate analysis, the odds ratio was 0.525 for valve surgery and 4.079 for aortic surgery (Table 2A). While there were no significant differences because of the small sample size, the surgical procedure seems to be associated with the incidence of POAF. We also performed univariate analysis of the LA EAT/Total EAT ratio among different types surgery. As shown in Table 4, the LA EAT/Total EAT ratio was significantly higher in the POAF group than the non-POAF group among patients undergoing valve surgery. This difference may have arisen because valvular heart disease imposes much greater mechanical stress on the left atrium than coronary artery disease or aortic disease. The stresses associated with POAF are reported to include mitral valve disease, congestive heart failure, LA overload caused by hypertension, LA myocardial hypertrophy, and fibrosis,\(^{14,19}\). However, it is unclear whether POAF occurs after valve surgery because of preoperative factors or the surgical procedure itself, and further research is required to determine which is the stronger risk factor.

**Aging and fibrosis**

In our univariate analysis, aging and prolonged P wave duration were associated with POAF, as already
Almost all authors agree that aging is associated with POAF. P wave duration is also related to POAF and is useful for detecting susceptibility to paroxysmal AF, with the risk of paroxysmal AF being increased if the P wave duration is prolonged or shortened. Hayashida et al. reported that a prolonged P wave duration predicts POAF if patients are elderly and have LA enlargement. Mathew et al. reported that the risk of POAF increases with age and that an age over 70 years is a high risk factor. This is because aging is related to atrial enlargement with atrial degeneration, inflammatory changes, and fibrosis. It has also been suggested that atrial fibrosis caused by aging is associated with POAF. Nakai et al. reported that aging leads to atrial fibrosis and that occurrence of POAF after CABG increases along with the fibrosis ratio. Sezai et al. reported that POAF is related to aging and to elevation of serum fibrosis markers such as KL-6 or I-CTP. Considering the present findings and these reports, aging promotes atrial fibrosis and thus increases susceptibility to POAF.

**Prediction and prevention of POAF**

Based on our results, 3D-CT can be used to assist with prevention of POAF. However, we do not think that 3D-CT should be performed in all patients, taking into account radiation exposure and medical expenses versus the potential benefits. Instead, we recommend that patients with a higher risk of developing POAF should undergo 3D-CT, such as the elderly or those with a longer P wave duration.

For prevention of POAF, the 2014 AHA/ACC/HRS guideline recommends preoperative administration of amiodarone in patients undergoing cardiac surgery (Class IIa, Evidence level A). Although amiodarone is used globally for prophylaxis of POAF, it is not popular in Japan because of side effects such as interstitial pneumonia and long QT syndrome. However, we hope that experience with using amiodarone will increase in Japan. Regarding CABG, the 2011 ACCF/AHA guideline recommends administration of a β-blocker at least 24 hours before surgery (Class I, Evidence level B). Our institution has reported that the combination of a short-acting intravenous β-blocker preoperatively and oral bisoprolol postoperatively can significantly reduce POAF. Although the short-acting β-blocker with little influence on hemodynamics is currently only approved in Japan, we recommend perioperative administration of a β-blocker.

**Study limitations**

This study included patients with various types of heart disease, including 40% with valve disease, almost all of whom took oral diuretics, which might have led to bias.

In addition, we focused on LA EAT, but histological examination was performed in the right atrium. Furthermore, our analysis was based on one random slice of the right atrium. Finally, this study included morphological analyses but not functional analyses.

**Conclusion**

The use of loop diuretics showed the strongest association with POAF. Although the association was not significant, logistic regression analysis suggested that a high LA EAT/Total EAT ratio had the second strongest association with POAF.

**Disclosure Statement**

We all have no conflict of interest.

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