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Association between serum inflammatory biomarkers and atrial low voltage in patients with atrial fibrillation: A phase 1 FIB-MARK study

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A B S T R A C T

Background: The mechanisms leading to atrial fibrosis in patients with atrial fibrillation (AF), especially in relation to inflammation, remain unclear.
Methods and Results: Forty biomarkers were measured in peripheral blood samples collected prior to catheter ablation, and the association with left atrial (LVZ) was evaluated in 16 consecutive patients. The median %LVZ was 17%. In Pearson's correlation analysis, interleukin(IL)-17A and interferon(IFN)-γ showed the most significant positive and negative correlations with %LVZ ($R = 0.35$ and 0.43, $P < 0.001$). Furthermore, the IL-17A/IFN-γ ratio was significantly associated with %LVZ ($R = 0.65$, $P = 0.007$), as was the macrophage inflammatory protein (MIP)-1δ/IFN-γ ratio ($R = 0.73$, $P = 0.001$). The area under the receiver operator characteristics curves of the IL-17A/IFN-γ and MIP-1δ/IFN-γ ratios for detecting severe LVZ (%LVZ ≥ 10% as a reference standard) were 0.88 and 0.90, respectively. The IL-17A/IFN-γ ratio was significantly higher in patients with severe LVZ than those without (1.41 versus 0.97, $P = 0.01$). Furthermore, the sensitivity, specificity, and accuracy for detecting severe LVZ were 60%, 100%, and 75.0%, respectively, at a cut-off value of 1.3.
Conclusions: Among inflammatory biomarkers, the serum IL-17A/IFN-γ ratio was associated with severe left atrial LVZ in patients with AF. However, further studies are needed to clarify the role of inflammatory biomarkers in the development and progression of atrial fibrosis in patients with AF.

1. Introduction

Atrial fibrillation (AF) is a progressive disease that increases in prevalence with age. The majority of cases of AF are thought to originate from arrhythmogenic pulmonary veins, and highly frequent atrial contractions during AF promote atrial fibrosis and predisposes to arrhythmogenicity, which is known as "AF begets AF" [1,2]. The severity of left atrial (LA) fibrosis, detected as delayed enhancement on contrast magnetic resonance imaging (MRI), is associated with cardiovascular events such as heart failure and cerebrovascular events in patients with AF [3–5]. In addition, it is also an important predictor for refractory arrhythmia even after catheter ablation procedures for AF [6]. Fibrosis, mediated by inflammatory cytokines and the renin-angiotensin-aldosterone system, plays an important role in the development and progression of AF, as reported in several studies [7,8]. However, the key inflammatory biomarker for the development and progression of atrial fibrosis in AF is still unknown. The FIbrosis Biomarker Mirroring Atrial fibRillation severity as a Key of aging (FIB-MARK) study is a prospective study to identify the key inflammatory biomarker associated with severe atrial fibrosis in patients with AF and to reveal the mechanism of myocardial fibrosis advancement with age by regularly measuring the biomarker over a long-term period (jRCT1050200007). The aim of the current study, a phase 1 study of the FIB-MARK study, was to clarify the key inflammatory biomarker for atrial fibrosis measured as a low voltage zone (LVZ), which demonstrates decreased electrical activity and is correlated with delayed enhancement on MRI, [9] prior to catheter ablation for AF. Furthermore, we evaluated the prognostic impact of the identified inflammatory biomarker on outcomes after catheter ablation.

2. Methods

2.1. Study design

The current study enrolled 16 consecutive patients with AF for whom the LVZ of the LA had been measured during catheter ablation procedures in Mitsubishi Kyoto Hospital between May and August 2019. Patients with AF aged 20–90 years who had undergone catheter ablation

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for the first time for AF, were clinically suspected of having extensive LA fibrosis, or had undergone voltage mapping prior to ablation were eligible for the current study. We excluded patients for whom voltage mapping during constant atrial pacing was not obtained, those who had previously received catheter ablation or a MAZE procedure for AF, and those with renal (estimated glomerular filtration ratio < 30 mL/min/1.73 m^2) or hepatic impairment; inflammatory disease; acute infection; intake of steroids; recent myocardial infarction within 90 days before the procedure; life expectancy<1 year; or the inability to adhere to the study procedures. For the study patients, 40 biomarkers were measured in peripheral blood samples, and their association with the LA LVZ and outcomes after ablation were assessed. The current study protocol was approved by the ethics committee in Kyoto University Graduate School and Faculty of Medicine and the institutional review board of Mitsubishi Memorial Kyoto Hospital. Written informed consent was obtained from all the patients.

2.2. Measurement of biomarkers

Before the catheter ablation procedure, peripheral blood samples were collected. After centrifugation, the plasma was frozen and stored at −80 °C until required. Forty inflammatory biomarkers (Supplemental Appendix 1) were measured using a commercially available human inflammation antibody array (RayBio® C-series; RayBiotech, Norcross, GA; Fig. 1). Intensities were quantified using free image processing software ImageJ (developed by Wayne Resband) [10]. To compare the results of multiple arrays, the intensities of the positive control signals on each membrane were used to normalize the signals as per the manufacturer's manual. The experiments were performed in duplicate, and means of the data were calculated. The plasma concentration of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured by enzyme immunoassay (Alere NT-proBNP, Abbott, Chicago, IL; Chemilumi BNP, Siemens Healthineers, Erlangen, Germany).

2.3. Electrophysiologic study and ablation protocol

Ten-pole electrodes were placed in the upper right atrium and coronary sinus adjacent to the bilateral femoral vein approach. Before pulmonary vein isolation (PVI), bipolar voltage mapping of the LA was acquired with a 20-pole high-density catheter (PentaRay; Biosense Webster, Inc., Diamond Bar, CA) during constant pacing (heart rate, 100 beats/min) from the upper right atrium. When AF was persistent at the time of the procedure, electrical cardioversion was performed, and we waited a few minutes until recovery of stable sinus excitation before bipolar voltage mapping.

After voltage mapping, extensive encircling pulmonary vein or single-ring posterior wall isolation was performed by point-by-point ablation with a 3.5-mm tip irrigation catheter (ThermoCool SmartTouch catheter; Biosense Webster, Irwindale, CA), and the double circular catheter method was followed by placing two 20-pole circular-shaped catheters (Lasso; Biosense Webster or Orbiter PV; C.R. Bard Electrophysiology, Lowell, MA). The operators decided whether to perform PVI or posterior wall isolation from the anatomical position of pulmonary veins. Tricuspid valve isthmus ablation was routinely performed regardless of the presence of typical atrial flutter with an 8-mm tip ablation catheter (Fantasista; Japan Lifeline, Tokyo, Japan and NAVISTAER; Biosense Webster). When AF was easily induced and sustained after extensive encircling PVI, sites with LVZ < 0.5 mV were ablated for homogenization [11]. Mitral isthmus linear ablation was only performed for sustained atrial tachycardia.

Antiarrhythmic drugs were discontinued before admission. Flecainide or bepridil was administered for 1 month after the procedure and then discontinued in all patients. Thereafter, antiarrhythmic drugs were restarted only when recurrent atrial tachyarrhythmia was detected. When recurrent atrial tachyarrhythmia was detected after the blanking period of 3 months, a second procedure was recommended for the patient. Recurrent atrial tachyarrhythmia was defined as documented AF and/or atrial tachycardia lasting for > 30 s or requiring a repeat ablation procedure. A 12-lead electrocardiogram was routinely measured at each clinical visit and 24-h or 1-week Holter monitoring was recommended at

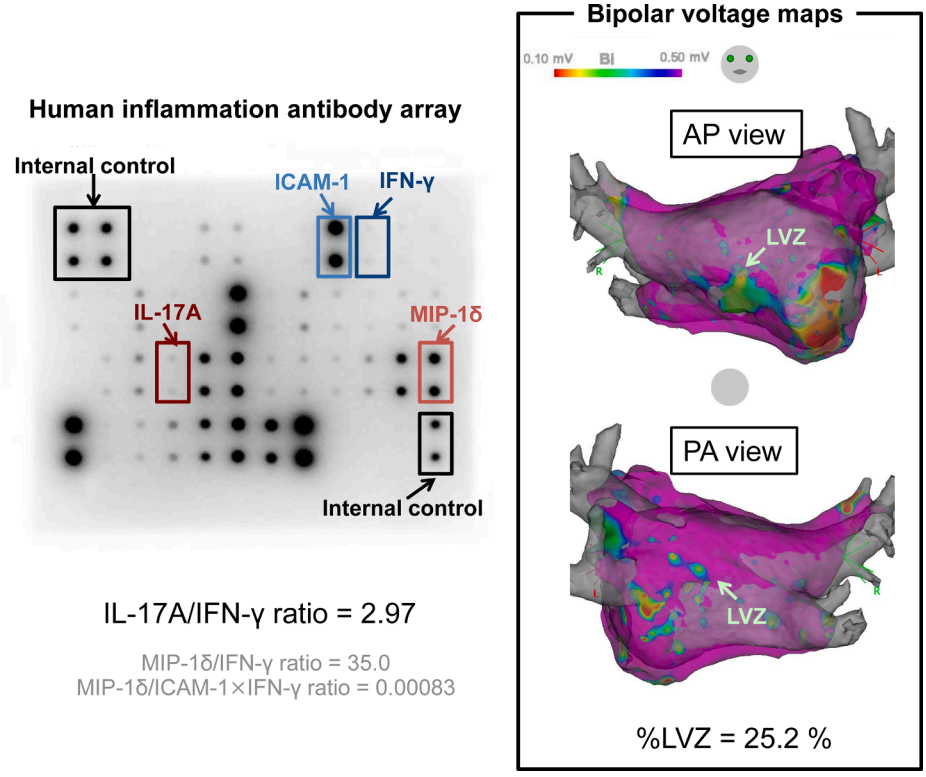

Fig. 1. Representative sample A 77-year-old patient with non-paroxysmal atrial fibrillation had severe low voltage in bipolar voltage maps. A human inflammation antibody array of a peripheral blood sample showed a high IL-17A/IFN-γ ratio of 2.97. He was free from recurrent atrial tachyarrhythmia for 680 days after pulmonary vein isolation and tricuspid valve isthmus ablation without substrate modification. AP = anteroposterior; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; MIP = macrophage inflammatory protein; PA = posteroanterior; %LVZ = % low voltage zone.

6–12 months. Additional 24-h Holter monitoring and/or an ambulatory electrocardiogram were recorded when patients had symptoms. A second catheter ablation procedure was usually recommended for patients with recurrent atrial tachyarrhythmia after the blanking period of 3 months.

2.4. Definition, endpoints, and statistical analysis

AF was classified into paroxysmal (lasting < 7 days) and non-paroxysmal (lasting ≥ 7 days). %LVZ was defined as the ratio of the LVZ, with a cutoff value of < 0.5 mV, to the LA surface area.

Categorical variables, presented as numbers and percentages, were compared using the chi-square test or Fisher's exact test whenever appropriate. Continuous variables, presented as means with standard deviations or medians with interquartile ranges, were compared using the Student's *t*-test or the Wilcoxon rank sum test based on their distributions. The main outcome measure of the current study was the correlation between the quantified intensity of each biomarker and % LVZ, which was assessed using Pearson's correlation coefficient. Diagnostic performance of the key biomarker was assessed using the area under the receiver operator characteristics curve (AUC) for detecting severe LVZ (%LVZ $\geq$ 10% as a reference standard). The recurrence of atrial tachyarrhythmia was defined as documented AF and/or atrial tachycardia lasting for $\geq$ 30 sec or requiring a repeat ablation procedure. Event-free survival from the recurrence of atrial tachyarrhythmia within 90 days after procedure (early recurrence) and past the 90-day blanking period were assessed.

All statistical analyses were two-tailed and performed using JMP Pro 14 (SAS Institute Inc, Cary, NC) software. P-values < 0.05 were considered statistically significant.

3. Results

3.1. Study population

The study population had a mean age of 72.4 years and a low proportion of female patients (31.3%; Table 1). Overall, 62% of the patients had non-paroxysmal AF and median AF for a duration of 0.5 years. The LA was mildly dilated, and the median %LVZ was 17.0% (5.0–22.8%). Both baseline BNP and NT-pro BNP were elevated at the time of the procedures at 144 and 945 pg/dL, respectively.

3.2. Association between inflammatory biomarkers and LA LVZ

The correlation coefficients between the quantified intensities of each biomarker and %LVZ are shown in Fig. 2. The most significant and next-most significant positive correlations with %LVZ were observed in the quantified intensities of interleukin (IL)-17A and macrophage inflammatory protein (MIP)-1δ (R = 0.35 and 0.30, P < 0.001; Fig. 3), while interferon (IFN)-γ and intercellular adhesion molecule (ICAM)-1 had the most significant and next-most significant negative correlations with %LVZ (R = 0.43 and 0.42, P < 0.001). Furthermore, there was a significant correlation between the IL-17A/IFN-γ ratio of the quantified intensities and %LVZ (R = 0.65, P = 0.007), although the MIP-1δ/IFN-γ and MIP-1δ/ICAM-1 × IFN-γ ratios correlated most significantly with % LVZ (R = 0.73). All of the inflammatory biomarker ratios were significantly higher in patients with severe LVZ than those without (1.41 versus 0.97, P = 0.01; 27.6 versus 14.8, P = 0.01; 0.00072 versus 0.00033, P = 0.01, respectively; Fig. 4A and Supplemental Fig. 1A and B).

The AUC of the IL-17A/IFN-γ ratio for detecting severe LVZ was 0.88, and the optimal cut-off value of the receiver operator characteristics curve was 1.3 (Fig. 4B). The sensitivity, specificity, and accuracy of an IL-17A/IFN-γ ratio $\geq$ 1.3 were 60%, 100%, and 75.0%, respectively. Baseline characteristics, including AF duration and the prevalence of non-paroxysmal AF, were not significantly different between patients with and without an IL-17A/IFN-γ ratio $\geq$ 1.3 (Table 1). Patients with an IL-17A/IFN-γ ratio $\geq$ 1.3 had higher %LVZ (20% versus 6.9%, P = 0.09; Fig. 4C).

Table 1
Patient characteristics.

	Overall N = 16	IL-17A/IFN-γ ratio ≥ 1.3 N = 6	IL-17A/IFN-γ ratio < 1.3 N = 10	P value
Age (years old)	72.4 ± 8.4	70.7 ± 9.0	73.5 ± 8.3	0.53
Female	5 (31.3%)	2 (33.3%)	3 (30.0%)	0.65
Body weight	66.0 ± 13.5	64.3 ± 20.8	67.0 ± 8.0	0.72
AF duration (years)	0.5 (0.3–4.1)	0.4 (0.3–2.0)	1.1 (0.4–7.6)	0.30
Non-paroxysmal AF	10 (62.5%)	5 (83.3%)	5 (50.0%)	0.22
Hypertension	10 (62.5%)	3 (50.0%)	7 (70.0%)	0.39
Diabetes	2 (12.5%)	1 (16.7%)	1 (10.0%)	0.63
CHA_2DS_2-VASc score	3.2 ± 2.4	2.7 ± 2.0	3.5 ± 2.7	0.52
Echocardiography findings				
Left ventricular ejection fraction (%)	65.6 ± 12.5	63.8 ± 15.6	66.6 ± 11.1	0.68
Left atrial diameter (mm)	39.8 ± 3.2	41.0 ± 3.6	39.1 ± 2.9	0.27
Laboratory findings				
Cre	1.1 ± 0.4	1.0 ± 0.3	1.1 ± 0.3	0.56
eGFR (ml/min/1.73 m^2)	52.4 ± 12.8	56.3 ± 13.0	50.0 ± 12.7	0.36
BNP (pg/dL)	144 (89–288)	195 (111–334)	121 (75–262)	0.36
NT-pro BNP (pg/dL)	945 (455–2767)	980 (630–2839)	912 (296–3065)	0.55
Electrophysiological findings				
%Low voltage zone (%)	17.0 (5.0–22.8)	20.3 (17.1–25.7)	6.9 (3.0–20.9)	0.09
Severe low voltage zone (>10%)	10 (62.5%)	6 (100%)	4 (40.0%)	0.63

Categorical variables are presented as number (percentage). Continuous variables are presented as mean ± SD or median and interquartile range.
AF = atrial fibrillation; BNP = brain natriuretic peptide; eGFR = estimated glomerular filtration rate; IFN = interferon; IL = interleukin.

The MIP-1δ/IFN-γ and MIP-1δ/ICAM-1 × IFN-γ ratios also had high AUC values (0.90) for detecting severe LVZ at cut-off values of 22.2 and 0.00053, respectively (Supplemental Fig. 1 C, D, E and F). Using these cut-off values provided high sensitivity, specificity, and accuracy for the inflammatory biomarker ratios at 80%, 100%, and 87.5%, respectively. Moreover, patients with a high inflammatory biomarker ratio had higher %LVZ (21.7% versus 5.5%, P = 0.004).

3.3. Prognostic impact of the inflammatory biomarker ratio on arrhythmia recurrence after an ablation procedure

Extensive encircling PVI and single-ring posterior wall isolation were respectively performed in 12 (75.0%) and four patients (25.0%) according to the anatomical position of pulmonary veins (Supplemental Table1). All patients received tricuspid valve isthmus ablation. Mitral isthmus linear ablation for sustained *peri*-mitral atrial tachycardia was performed in three patients (18.8%). LVZ ablation was required in three patients (18.8%) whose AF was easily induced and sustained even after PVI.

Event-free survival from early recurrence after a procedure did not significantly differ between patients with and without an IL-17A/IFN-γ ratio $\geq$ 1.3 (83.3% versus 40.0%, P = 0.15; Supplemental Fig. 2A). However, patients with an IL-17A/IFN-γ ratio $\geq$ 1.3 had a significantly higher event-free survival rate from the recurrence of atrial tachyarrhythmia with a blanking period of 90 days than those without (83.3% versus 30.0% at 2 years, P = 0.04; Supplemental Fig. 2B). The arrhythmia recurrence-free rate was comparable between patients with

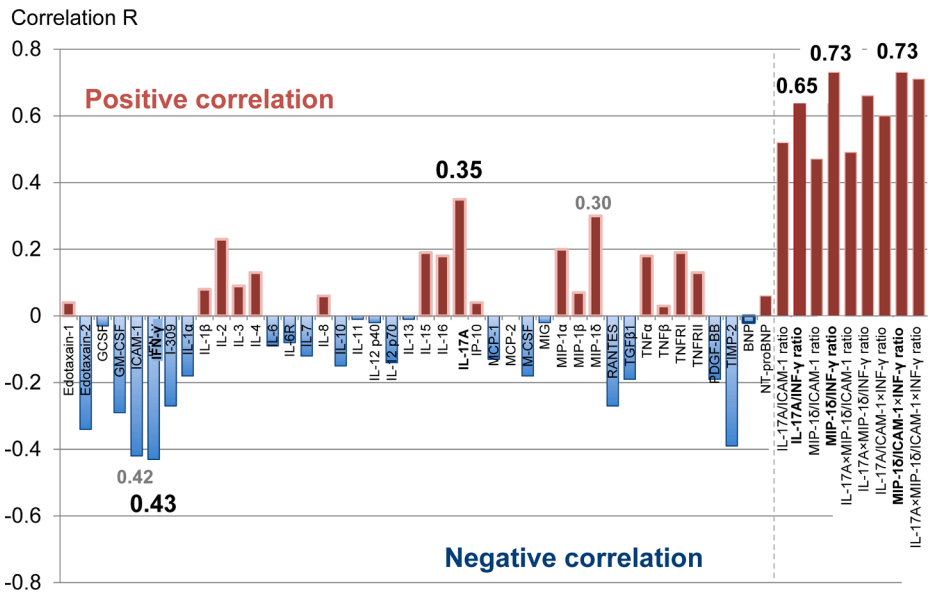

Fig. 2. Correlation coefficients between biomarkers and left atrial low voltage (%LVZ). BNP = brain natriuretic peptide; GM-CSF = granulocyte macrophage-colony stimulating factor; GSCF = granulocyte colony-stimulating factor; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; IP = interferon-γ inducible protein; M−CSF = macrophage-colony stimulating factor; MCP = monocyte chemoattractant protein; MIG = monokine induced by interferon-γ; MIP = macrophage inflammatory protein; NT-proBNP = N-terminal pro-brain natriuretic peptide; PDGF = platelet-derived growth factor; R = receptor; RANTES = regulated on activation, normal T cell expressed and secreted; TGF = transforming growth factor; TIMP = tissue inhibitor of metalloproteinase; TNF = tumor necrosis factor.

and without severe LVZ (60.0% versus 33.3% at 2 years, P = 0.40), but an IL-17A/IFN-γ ratio ≥ 1.3 was associated with a higher arrhythmia-free rate even in patients with severe LVZ (Supplemental Fig. 2C, D). On the other hand, the arrhythmia recurrence-free rate was comparable between patients with and without higher MIP-1δ/IFN-γ or MIP-1δ/ICAM-1 × IFN-γ ratios (Supplemental Fig. 2E, F).

4. Discussion

As a phase 1 study of the FIB-MARK study, we validated the key inflammatory biomarkers for atrial fibrosis as measured as LVZ in the LA with AF. The main findings in the current study were as follows (Supplemental Fig. 3): (1) serum IL-17A/IFN-γ and MIP-1δ/IFN-γ ratios showed significant correlations with %LVZ in the LA among 40 inflammatory biomarkers and BNP; (2) the optimal cut-off value for the IL-17A/IFN-γ ratio for detecting severe LVZ, defined as %LVZ ≥ 10%, was 1.3, and the accuracy of an IL-17A/IFN-γ ratio ≥ 1.3 was 75%; (3) an IL-17A/IFN-γ ratio ≥ 1.3 was associated with higher event-free survival from arrhythmia recurrence after ablation for AF, even in patients with severe LVZ.

An atrial cardiomyopathy is considered as any complex of structural, architectural, contractile, or electrophysiological changes that affect the atria and with the potential to produce clinically-relevant manifestations such as AF [12]. Previous studies have reported that atrial myocardial inflammation plays an important role in the development of atrial cardiomyopathy, contributing to the initiation and progression of AF. Ozcab et al. reported that serum inflammatory parameters, such as CRP, IL-6, and tumor necrosis factor (TNF)-α in LKB1 knockout mice were elevated along with the ultrastructural and electrophysiological changes in the atrial myocardium [13]. Furthermore, animal models overexpressing TGF-β1, which is increased by heart failure, show profound atrial fibrosis and AF.[14–16], and serum TGF-β1 elevation is associated with atrial fibrosis and refractory AF after ablation procedures [16]. Likewise, several studies have reported that inflammatory biomarkers such as IL-6 and fibroblast growth factor-23 are associated with the development of AF and the clinical prognosis of patients with AF [17,18]. In the current study, we demonstrated that the serum IL-17A/IFN-γ and MIP-1δ/IFN-γ ratios are key biomarkers that are associated with severe LVZ in the LA. However, we found TGF-β1 to be negatively associated with atrial LVZ with a poor correlation, which is discordant with previous studies. One possible cause of this discordance is that LVZ does not always accurately represent fibrotic tissue detected using other analytical techniques, such as MRI or biopsy [19]. Also, the small number of study patients and measurement errors may have caused bias in our results. Therefore, caution is needed when attempting to directly generalize the results of the current study to the mechanism of atrial fibrosis.

IL-17A, along with IL-17F, IL-21, IL-22, and TNF-α, is secreted by Th17 cells, which are a novel lineage of effector $CD4^+$ T helper lymphocytes, and is linked to the pathogenesis of several inflammatory and autoimmune disease, including autoimmune and dilated cardiomyopathies, by promoting the migration of cardiac fibroblasts [20]. High IL-17 levels are reported in the acute phase of cardiomyopathy, and patients with dilated cardiomyopathy show increased IL-17 levels compared with healthy donors [21,22]. In addition, IL-17 levels were reported to be inversely correlated with favorable prognosis [23,24]. On the other hand, IFN-γ is secreted by natural killer cells, natural killer T-cells, $CD8^+$ cells, and Th1 cells, contributing to the initiation of inflammatory processes along with IL-17A, although its role in cardiomyopathy is still controversial [20]. While several studies have reported increased IFN-γ levels in myocardial inflammation, it has also been shown that enhanced IFN-γ levels are associated with a lower severity of autoimmune cardiomyopathy [25,26]. Although the direct interaction between IL and 17A and IFN-γ has been reported, previous studies have reported increased IFN-γ production in IL-17A knockout mice [27] and differences between IFN-γ and IL-17A production in p35 knockout mice [28]. These studies suggest that the balance between IL and 17A and IFN-γ is important for the development and progression of cardiomyopathy. The MIP-1δ/C-C motif chemokine ligand 15/leukotactin-1 is produced by endothelial cells and likely plays a regulatory role in mediating transmigration of fibrocytes. However, the role of this complex in the progression of cardiomyopathy or cardiac fibrosis is unclear. The current study suggests that the serum IL-17A/IFN-γ and MIP-1δ/IFN-γ ratios are important for the development of atrial fibrosis in patients with AF.

Regarding the association between serum inflammatory biomarker ratios and prognosis of AF after ablation procedures, event-free survival from arrhythmia recurrence after a procedure was higher in patients with a high serum IL-17A/IFN-γ ratio than those with a high serum MIP-1δ/IFN-γ ratio or severe %LVZ. The discordance of our results with previous studies on refractory AF with severe LVZ may have been caused by our relatively mild cut-off value of %LVZ (10%) and tailored ablation strategy [29,30]. The small number of enrolled patients and unadjusted baseline risks might preclude any definitive conclusion about association between inflammatory biomarkers and prognosis after ablation

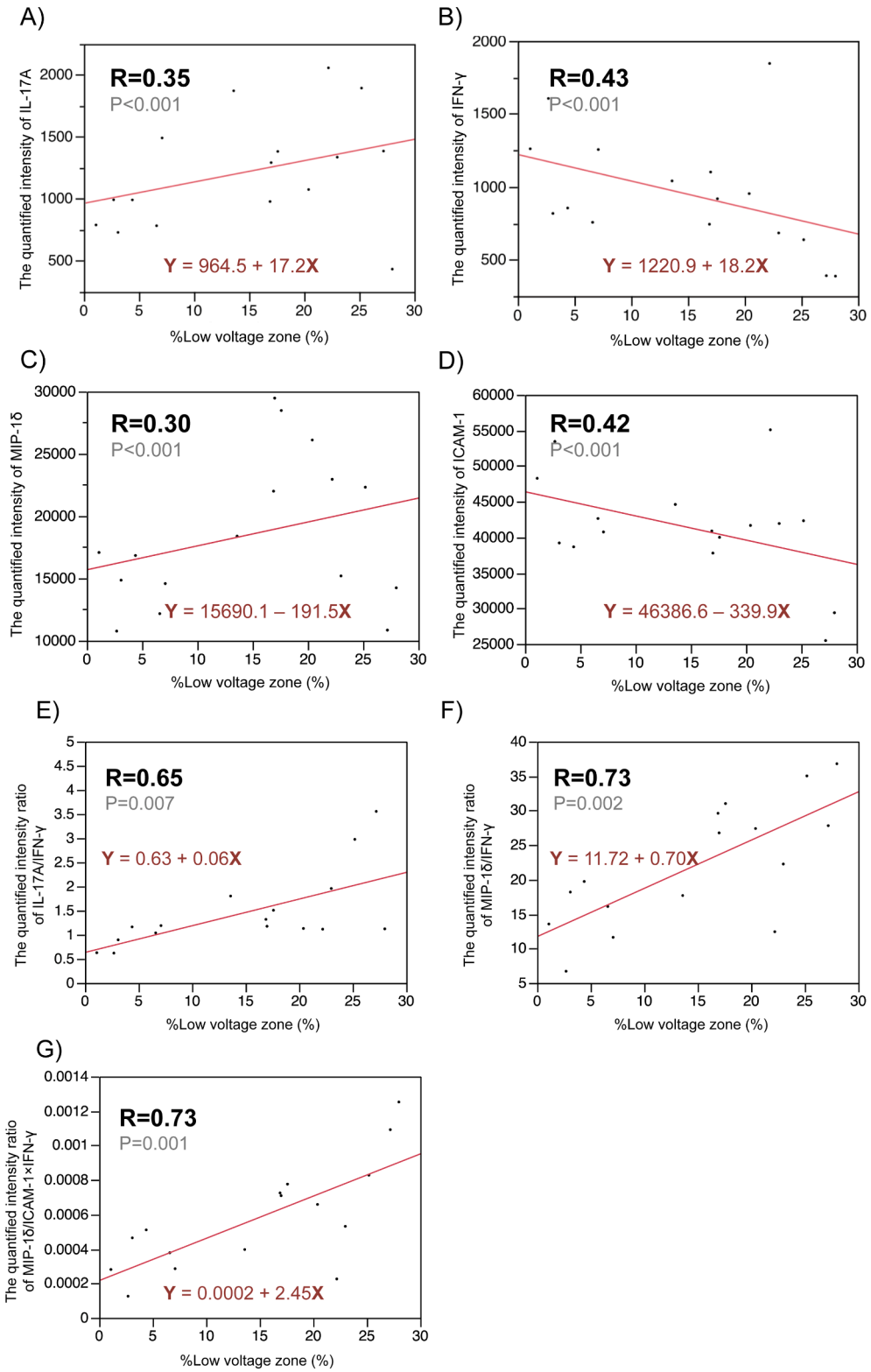

Fig. 3. Correlation between left atrial low voltage (%LVZ) and the quantified intensities of the biomarkers. (A) IL-17A, (B) IFN-γ, (C) MIP-1δ, (D) ICAM-1, (E) IL-17A /IFN-γ, (F) MIP-1δ/IFN-γ, and (G) MIP-1δ/ICAM-1 × IFN-γ. ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; MIP = macrophage inflammatory protein; %LVZ = % low voltage zone.

procedure.

4.1. Limitations

There are several important limitations to this study. The first and most important limitation was the small number of enrolled patients. Although our results showed that the serum IL-17A/IFN-γ and MIP-1δ/IFN-γ ratios are associated with severe LVZ in the LA and are key biomarkers for atrial LVZ in patients with AF, the correlation coefficient is low, especially for a single biomarker. The limited number of subjects

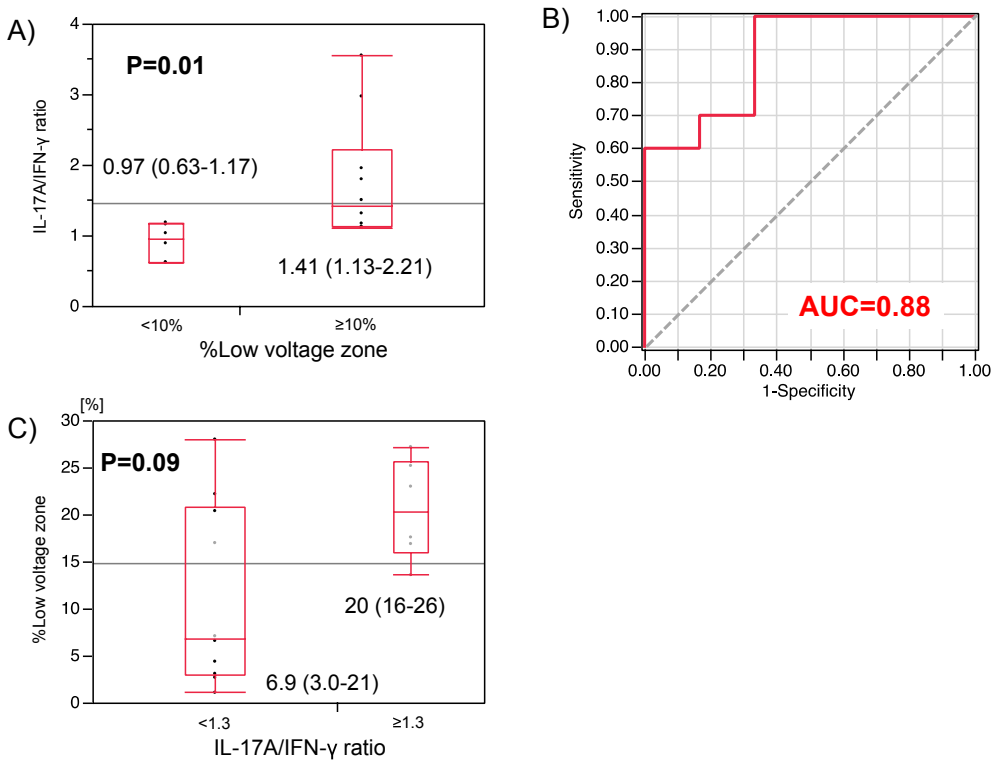

Fig. 4. Correlation between the IL-17A/IFN-γ ratio and left atrial low voltage. (A) IL-17A/IFN-γ ratio between %LVZ < 10% and ≥ 10%, (B) Area under the receiver operator characteristics curve (AUC) of the IL-17A/IFN-γ ratio for detecting %LVZ ≥ 10%, (C) %LVZ between IL and 17A/IFN-γ ratio < 1.3 and ≥ 1.3. IFN = interferon; IL = interleukin; %LVZ = % low voltage zone.

means that these findings should be interpreted with caution. Second, as mentioned above, we used LVZ, defined as a voltage < 0.5 mV during SR, and not atrial fibrosis itself as the reference standard, which was based on the assumption of the concordance between atrial LVZ and fibrosis. Furthermore, we did not take into consideration myocardial fibrosis in the right atrium or ventricles, which constitute a large proportion of the myocardial volume. Third, the pathophysiology of AF is complex, and the IL-17A/ IFN-γ and MIP-1δ/IFN-γ ratios are just two possibilities out of a complex combination of inflammatory cytokines.

5. Conclusions

Among inflammatory biomarkers, the serum IL-17A/IFN-γ ratio was associated with severe LA low voltage in patients with AF. Further studies are needed to clarify the role of the balance between IL and 17A and IFN-γ in the development and progression of atrial fibrosis in patients with AF.

Disclosures

This study was supported by JSPS KAKENHI grant Number JP19K17594.

Ethical approval

The current study protocol was approved by the ethics committee in Kyoto University Graduate School and Faculty of Medicine and the institutional review board of Mitsubishi Memorial Kyoto Hospital.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data availability statement

All relevant data are within the manuscript.

What is already known on this subject?

- Atrial fibrillation (AF) promotes atrial fibrosis, increasing arrhythmogenicity, which is known as AF begets AF.
- Several inflammatory biomarkers such as transforming growth factor (TGF)-β1, interleukin (IL)-6, and fibroblast growth factor (FGF)–23 were reported to predict left atrial fibrosis and high incidence of cardiovascular events in AF patients.

What might this study add?

- The serum IL-17A/interferon (IFN)-γ ratio showed significant correlation with %low voltage zone (LVZ) in the left atrium.
- The optimal cut-off value of the IL-17A/IFN-γ ratio for detecting severe LVZ, defined as %LVZ ≥ 10%, was 1.3, and the accuracy of IL-17A/IFN-γ ratios ≥ 1.3 was 75%.
- An IL-17A/IFN-γ ratio ≥ 1.3 was associated with higher event-free survival from arrhythmia recurrence after ablation for AF.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100904.

References

[1] M. Haïssaguerre, P. Jaïs, D.C. Shah, et al., Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins, New Engl J Med. 339 (1998) 659–666.

[2] M.C. Wijffels, C.J. Kirchhof, R. Dorland, Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 92(1995)1954-1968.

[3] M. Daccarett, T.J. Badger, N. Akoum, et al., Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation, J Am Coll Cardiol. 57 (2011) 831–838.

[4] J.B. King, P.N. Azadani, P. Suksaranjit, et al., Left atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation, J Am Coll Cardiol. 70 (2017) 1311–1321.

[5] P.N. Azadani, J.B. King, M. Kheirkhahan, et al., Left atrial fibrosis is associated with new-onset heart failure in patients with atrial fibrillation, Int J Cardiol. 248 (2017) 161–165.

[6] N.F. Marrouche, D. Wilber, G. Hindricks, et al., Association of atrial tissue fibrosis identified by delayed enhancement mri and atrial fibrillation catheter ablation, JAMA 311 (2014) 498.

[7] M.S. Dzeshka, G.Y. Lip, V. Snezhitskiy, et al., Cardiac fibrosis in patients with atrial fibrillation: Mechanisms and clinical implications, J Am Colle Cardiol. 66 (2015) 943–959.

[8] A. Xintarakou, S. Tzeis, S. Psarras, et al., Atrial fibrosis as a dominant factor for the development of atrial fibrillation: Facts and gaps, Europace 22 (2020) 342–351.

[9] N.A. Qureshi, S.J. Kim, C.D. Cantwell, et al., Voltage during atrial fibrillation is superior to voltage during sinus rhythm in localizing areas of delayed enhancement on magnetic resonance imaging: An assessment of the posterior left atrium in patients with persistent atrial fibrillation, Heart rhythm. 16 (2019) 1357–1367.

[10] C.A. Schneider, W.S. Rasband, K.W. Eliceiri, Nih image to imagej: 25 years of image analysis, Nat Methods. 9 (2012) 671–675.

[11] T. Yamaguchi, T. Tsuchiya, S. Nakahara, et al., Efficacy of left atrial voltage-based catheter ablation of persistent atrial fibrillation, J Cardiovasc Electrophysiol. 27 (2016) 1055–1063.

[12] H. Calkins, G. Hindricks, R. Cappato, et al., HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation, Europace. 20 (2018) (2017) e1–e160.

[13] C. Ozcan, E. Battaglia, R. Young, et al., LKB1 knockout mouse develops spontaneous atrial fibrillation and provides mechanistic insights into human disease process, J Am Heart Assoc. 4 (2015), e001733.

[14] S.K. Kim, J.H. Park, J.Y. Kim, et al., High plasma concentrations of transforming growth factor-beta and tissue inhibitor of metalloproteinase-1: Potential non-invasive predictors for electroanatomical remodeling of atrium in patients with non-valvular atrial fibrillation, Circ J. 75 (2011) 557–564.

[15] C.H. Wu, Y.F. Hu, C.Y. Chou, et al., Transforming growth factor-beta1 level and outcome after catheter ablation for nonparoxysmal atrial fibrillation, Heart rhythm. 10 (2013) 10–15.

[16] U. Canpolat, A. Oto, T. Hazirolan, et al., A prospective de-mri study evaluating the role of tgf-beta1 in left atrial fibrosis and implications for outcomes of cryoballoon-based catheter ablation: New insights into primary fibrotic atriocardiomyopathy, J Cardiovasc Electrophysiol. 26 (2015) 251–259.

[17] J. Aulin, A. Siegbahn, Z. Hijazi, Interleukin-6 and c-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. *Am Heart J*. 170 (2015)1151-1160.

[18] W. Chua, Y. Purmah, V.R. Cardoso, et al., Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation, Eur Heart J. 40 (2019) 1268–1276.

[19] T. Yamaguchi, A. Fukui, K. Node, Bipolar voltage mapping for the evaluation of atrial substrate: Can we overcome the challenge of directionality? J Atr Fibrillation. 11 (2019) 2116.

[20] E. Kurtenbach, C.G. Martinez, IFN-γ versus IL-17: A battle during cardiac autoimmunity evolution, Intech Open. (2017), https://doi.org/10.5772/66986.

[21] G.C. Baldeviano, J.G. Barin, M.V. Talor, et al., Interleukin-17a is dispensable for myocarditis but essential for the progression to dilated cardiomyopathy, Circ Res. 106 (2010) 1646–1655.

[22] V. Nindl, R. Maier, D. Ratering, et al., Cooperation of th1 and th17 cells determines transition from autoimmune myocarditis to dilated cardiomyopathy, Eur J Immunol. 42 (2012) 2311–2321.

[23] T. Simon, S. Taleb, N. Danchin, et al., Circulating levels of interleukin-17 and cardiovascular outcomes in patients with acute myocardial infarction, Eur Heart J. 34 (2013) 570–577.

[24] J.M. Myers, L.T. Cooper, D.C. Kem, et al., Cardiac myosin-th17 responses promote heart failure in human myocarditis, JCI insight. 1 (2016), e85851.

[25] M. Afanasyeva, Y. Wang, Z. Kaya, et al., Interleukin-12 receptor/stat4 signaling is required for the development of autoimmune myocarditis in mice by an interferon-gamma-independent pathway, Circulation 104 (2001) 3145–3151.

[26] S.P. Levick, P.H. Goldspink, Could interferon-gamma be a therapeutic target for treating heart failure? Heart Fail Rev. 19 (2014) 227–236.

[27] D.L. Sacks, J. Tosello Boari, M.C. Amezcua Vesely, et al., IL-17ra signaling reduces inflammation and mortality during trypanosoma cruzi infection by recruiting suppressive il-10-producing neutrophils, PLoS Pathog. 8 (2012), e1002658.

[28] C.A. Murphy, C.L. Langrish, Y. Chen, et al., Divergent pro- and antiinflammatory roles for il-23 and il-12 in joint autoimmune inflammation, J Exp Med. 198 (2003) 1951–1957.

[29] X.-h. Wang, Z. Li, J.-l. Mao, Low voltage areas in paroxysmal atrial fibrillation: The prevalence, risk factors and impact on the effectiveness of catheter ablation. *Int J Cardiol*. 269(2018)139-144.

[30] N.F. Marrouche, C. Sohns, Atrial fibrillation and cardiac fibrosis, Eur Heart J. 41 (2020) 1123–1131.