RESEARCH LETTER

Association between interleukin 17A levels and left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation

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Introduction The presence of left atrial spontaneous echo contrast (LASEC) and left atrial thrombus (LAT) in patients with atrial fibrillation (AF) increases the risk of thromboembolic events.[1] Oral anticoagulant therapy, left atrial appendage (LAA) closure, and radiofrequency ablation are the standard regimens for the prevention of thromboembolic events in AF; however, there is still a risk of bleeding and recurrence of AF. Accumulating evidence has revealed that chronic inflammatory responses play an important role in the pathogenesis of LASEC.[2] The changes of AF and hemodynamics stimulate the cardiovascular system to undergo a biological transformation to an inflammatory response, which can cause LASEC and LAT. Identification of some inflammatory biomarkers that reflect the initiation of chronic inflammatory response may enhance the discriminatory ability to evaluate the efficacy of anticoagulation, which could be highly beneficial in terms of reducing the risk of thromboembolic events in patients with AF.

In our previous studies we showed that interleukin (IL) 17A was involved in the pathogenesis of AF by promoting cardiac fibrosis and remodeling.[3] However, it remains unclear whether IL-17A is associated with the development of LASEC and LAT. In the present study, we assessed serum levels of IL-17A and other AF-related cytokines in patients with nonvalvular AF and investigated the relationship between these cytokines and cardiac fibrosis in the pathogenesis of LASEC and LAT.

Patients and methods A total of 179 consecutive patients with nonvalvular AF who underwent transesophageal echocardiography (TEE) were prospectively enrolled. All the patients with persistent AF were treated with an oral anticoagulant (warfarin). As this was an observational study, the diagnostic procedure and treatment were not interfered with. Informed consent was obtained from every participant, and the study was approved by the Ethics Committee of the Affiliated Hospital of Jiangsu University (approval no. SWYXLL20200121-2). The exclusion criteria were as follows: valvular heart disease or a history of cardiac surgery, malignant disease, any contraindication to TEE, heart failure, myocardial infarction, or poor-quality echocardiographic images.

The eligible patients were divided into 2 groups according to the results of TEE: the LAT/LASEC group, that is, patients with LAT or LASEC found on TEE (n = 53), and the non-LAT/LASEC group, comprising LAT- or LASEC-negative individuals (n = 126).

Serum expression levels of IL-17A, IL-6, IL-10, IL-23, transforming growth factor β1, matrix metalloproteinase 9 (MMP-9), procollagen type I, and procollagen type III were determined using commercial biotin / avidin-based enzyme-linked immunosorbent assay (ELISA) kits (eBiosciences, San Diego, California, United States).

Statistical analysis Descriptive data were expressed as mean (SD), or as median with interquartile range in the case of a skewed distribution. Continuous variables were compared using the analysis of variance (ANOVA) or the Mann–Whitney test, as appropriate. Spearman rank correlation tests were adopted to investigate bivariate correlations. The receiver operating characteristic (ROC) curves were plotted. The optimal prognostic cutoff value (Youden index) of IL-17A was derived from the area under the curve (AUC) assessed at baseline. The optimal cutoff point was calculated according to the following formula: Sensitivity + Specificity – 1. Multivariable logistic regression was used to assess the independent effect of IL-17A on the occurrence of LAT/LASEC. Three multivariable-adjusted models were constructed accordingly.

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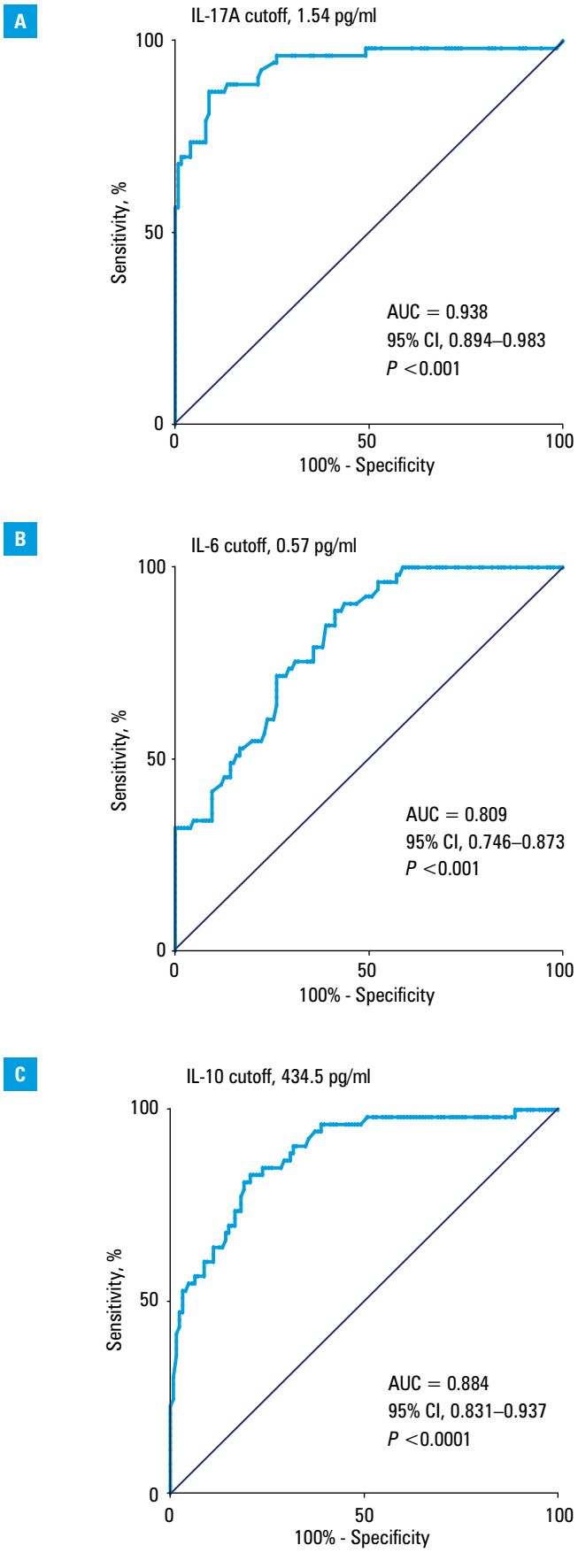

FIGURE 1 Associations between atrial fibrillation (AF)-related cytokines and left atrial spontaneous echo contrast (LASEC) in patients with nonvalvular AF; **A–C** – receiver operating characteristic curves for predicting left atrial thrombus/LASEC occurrence using the levels of AF-related cytokines
Abbreviations: AUC, area under the curve; IL, interleukin

Model 1 included age, race, hyperlipidemia, and persistent AF; Model 2 comprised all variables included in Model 1 plus prothrombin time–international normalized ratio (PT-INR), N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, left atrial diameter (LAD), and left ventricular ejection fraction (LVEF); and Model 3 comprised all variables included in Model 2 plus left atrial emptying fraction (LAEF) and left atrial appendage flow velocity (LAAFV). The Akaike information criterion, Bayes information criterion, and Harrell *C* index were used to compare the models. All analyses were performed using the SPSS software (v. 11.5, SPSS, Chicago, Illinois, United States). A *P* value below 0.05 was considered significant.

Results In comparison with patients without LAT or LASEC, individuals from the LAT/LASEC group more frequently had a history of coronary artery disease (CAD), prior heart failure, CHA_2DS_2-VASc score above 2, and persistent AF. The NT-proBNP level and LAD were greater in the LAT/LASEC group than in the non-LAT/LASEC group. On the other hand, LAEF, LAAFV, and PT-INR were lower in the LAT/LASEC group than in the non-LAT/LASEC group (Supplementary material, *Tables S1* and *S2*).

We found that the levels of IL-17A and IL-6 were elevated in the patients with LAT or LASEC, as compared with the non-LAT/LASEC group. The level of IL-10 was lower in the patients with LAT or LASEC than in the non-LAT/LASEC group (Supplementary material, *Table S3*). Based on the ROC curves, we observed that IL-17A, IL-6, and IL-10 showed a significant AUC. Moreover, IL-17A showed the highest diagnostic accuracy in predicting the occurrence of LAT or LASEC (FIGURE 1A–1C).

The levels of IL-17A, IL-6, and IL-10 were associated with an increased risk for the occurrence of LAT or LASEC in an unadjusted analysis. After adjustment for age, race, hyperlipidemia, PT-INR, LAD, LVEF, LAEF, and LAAFV (Model 3), IL-6 and IL-10 were no longer significant. However, the level of IL-17A (odds ratio, 1.35; 95% CI, 1.12–1.64; $P = 0.003$) was still significantly associated with an increased risk for the occurrence of LAT or LASEC in Model 3 (Supplementary material, *Table S4*).

We also analyzed the correlations between IL-17A and fibrotic parameters (MMP-9, procollagen type I, and procollagen type III). The serum level of IL-17A positively correlated with the levels of MMP-9 ($R = 0.38$; $P < 0.001$), procollagen type I ($R = 0.58$; $P < 0.001$), and procollagen type III ($R = 0.47$; $P < 0.001$) (Supplementary material, *Figure S1*).

Among the 53 patients with LAT/LASEC, 17 individuals underwent TEE at least twice. These patients were divided into 2 groups according to the cutoff value of IL-17A: Group 1 comprised patients with IL-17A values below 1.54 pg/ml (n = 6), and Group 2 consisted of individuals with

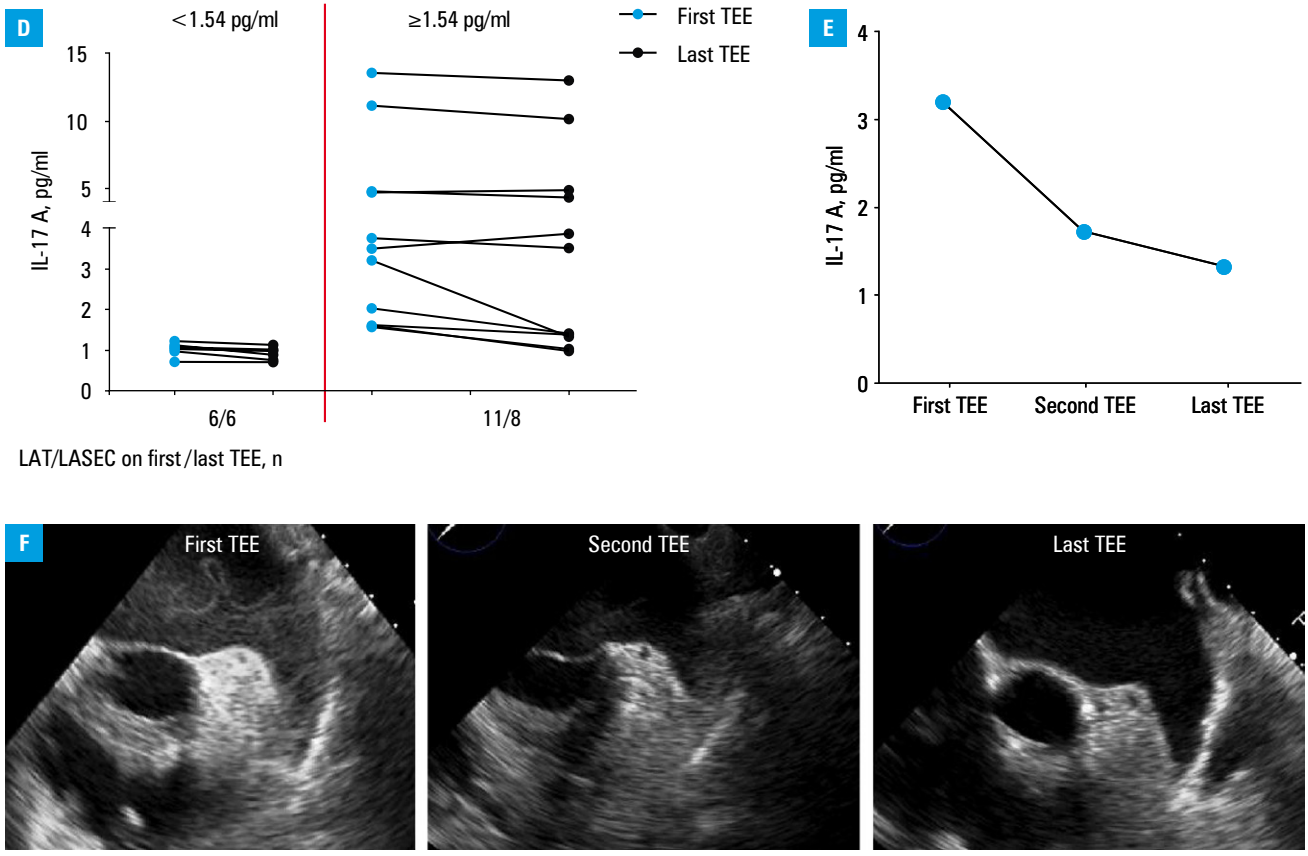

FIGURE 1 Associations between atrial fibrillation (AF)-related cytokines and left atrial spontaneous echo contrast in patients with nonvalvular AF; **D** – serum IL-17A levels at the time of baseline and follow-up transesophageal echocardiography (TEE) in 17 patients who underwent TEE ≥2 times; **E** – serum IL-17A levels of a 69-year-old woman at the time of baseline and 2 follow-up TEEs; **F** – ultrasound images of the 3 TEEs performed in the abovementioned woman

Abbreviations: AUC, area under the curve; IL, interleukin

IL-17A values of 1.54 pg/ml and greater (n = 11). All the 17 patients underwent a follow-up TEE after at least 3 months whilst on warfarin, with INR in the therapeutic range. In Group 1, no LAT or LASEC was detected in any of the patients in the follow-up. In Group 2, only 3 patients showed no LAT or LASEC on the follow-up TEE, and the cure rate was 23%, which was much lower than in Group 1 (P = 0.40) (FIGURE 1D).

In Group 2, the 3 patients in whom LAT or LASEC was not present on the follow-up TEE showed a decrease in the expression of IL-17A during the treatment process. One of these patients, a 69-year-old woman, underwent TEE 3 times (FIGURE 1E and 1F). Her first TEE showed severe spontaneous echo contrast (SEC) and intense echo density with a very slow swirling pattern in the left atrium (LA) and LAA, and microthrombosis in the LAA was not ruled out. The second TEE showed moderate SEC and a dense swirling pattern in the LA and LAA, and the microthrombosis in the LAA still could not be excluded. The final TEE showed no SEC or LAT in the LA and LAA. Overall, her IL-17A level decreased along with the disappearance of LAT/LASEC.

Discussion Recent studies have generated a significant interest in exploring the potential role of chronic inflammatory response, including fibrosis and thrombogenesis, in the pathogenesis of AF.[4-6] In the present study, we showed that IL-17A could be used to identify patients with AF who are at an increased risk for the occurrence of LAT and LASEC.

We aimed to clarify the underlying molecular mechanism of LASEC and LAT in AF, which would help identify and implement an efficient treatment strategy regarding anticoagulant management of patients with AF. Left atrial enlargement is a consequence of AF with the advancing electrical and structural abnormalities, and reflects the impaired LA function. Chronic inflammatory response could contribute to LA enlargement by stimulating the expression of proteins and fibrogenic mediators that induce cardiac fibrosis.[7-9]

The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study[10] showed that a multi-blood-biomarker score, including elevated levels of factor VIII, NT-proBNP, IL-6, and cystatin C, is strongly associated with an increased risk of stroke in AF. We were interested in the inflammatory response of LAT/LASEC in AF, which was established to contribute to stroke. In the present study, we showed that IL-17A might be a critical marker affecting the pathogenesis of cardiac fibrosis. The patients

with underlying diseases received regular therapy, and the diseases were well controlled. At the same time, regular therapy of the underlying diseases did not affect the risk for LAT or LASEC occurrence. However, the sample size of the current study was too small to allow definite conclusions. Moreover, the prevalence of hypertension was greater in the LAT/LASEC group than in the non-LAT/LASEC group, and Th17 responses also contributed to cardiac hypertrophy and remodeling in essential hypertension, which may have affected the expression of IL-17A in patients with AF.

Overall, the level of IL-17A was strongly associated with the occurrence of LAT or LASEC in the patients with AF, which promoted cardiac fibrosis and remodeling. IL-17A could be used as a potential inflammatory biomarker to reflect LA remodeling in the pathogenesis of AF.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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