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【 ORIGINAL ARTICLE 】

In Paroxysmal Atrial Fibrillation Patients, the Neutrophil-to-lymphocyte Ratio Is Related to Thrombogenesis and More Closely Associated with Left Atrial Appendage Contraction than with the Left Atrial Body Function

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Abstract:

Objective The neutrophil-to-lymphocyte ratio (NLR) is an inflammation marker that can be used to detect atrial inflammatory changes, which may contribute to a reduced left atrial (LA) function and thrombosis. Our study aimed to determine whether or not the association of NLR with the LA appendage (LAA) function in relation to thrombogenesis differs from the association with the LA body function in paroxysmal atrial fibrillation (PAF) patients.

Methods A total of 183 PAF patients were studied. The LA volume index, mitral flow velocity (A), and mitral annular motion velocity (A') were examined using transthoracic echocardiography. The LAA area, LAA wall motion velocity, and presence of spontaneous echo contrast (SEC) were examined using transesophageal echocardiography.

Results The NLR of patients with cerebral embolism was significantly greater than in patients without the disorder. A cut-off point of 2.5 for the NLR had a sensitivity of 71% and a specificity of 74% in predicting cerebral embolism. The patients with an NLR ≥2.5 had a higher CHADS2 score and greater LA volume index or LAA area than those with an NLR <2.5. The NLR was an independent risk factor for SEC and was significantly correlated with the LAA wall motion velocity (r=-0.409) in 153 patients without SEC and with the LAA wall motion velocity and LAA area (r=-0.583, r=0.654, respectively) in 30 patients with SEC, but not with the LA volume index, A, or A' in either group.

Conclusion In PAF patients, a high NLR indicates thrombogenesis with a high degree of certainty and is associated with reduced LAA contraction rather than with the LA body function.

Key words: neutrophil-to-lymphocyte ratio, left atrial appendage function, paroxysmal atrial fibrillation, spontaneous echo contrast

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Introduction

Atrial fibrillation (AF) is a disease with serious clinical implications that can contribute to cerebral embolism. Hohnloser et al. reported that patients with paroxysmal AF (PAF) have a similar risk for thromboembolic events as those with sustained AF (1). Several histopathological studies of AF have revealed extensive fibrosis in the enlarged atrium (2-4). In AF, fibro-inflammatory changes in the left atrial (LA) tissue may lead to dysfunction of the LA and LA appendage (LAA).

The neutrophil-to-lymphocyte ratio (NLR) is an inflammation marker that is elevated in patients with certain diseases (e.g. thromboembolic stroke, acute coronary syndrome, aortic valve stenosis) (5-7). Yalcin et al. reported that

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the NLR was related to the presence of LA thrombus in AF (8), and Kaya et al. reported that it was associated with spontaneous echo contrast (SEC) in patients with mitral stenosis (9). However, the association of NLR with the LAA or LA function has not yet been fully investigated in relation to thrombogenesis in PAF patients, although thrombosis is more often detected in the LAA than in the LA body.

In the present study, we examined whether or not the association of the NLR with the LAA function in relation to thrombogenesis differs from the association with the LA body function in non-valvular PAF patients.

Materials and Methods

Participants

This retrospective, non-randomized study was conducted at a single medical facility. The study population comprised 183 non-valvular PAF patients (mean age 64±9 years; 69% men). The patients were scheduled for pulmonary vein isolation and had undergone transesophageal and transthoracic echocardiography on the same day from April 2014 to March 2016 at Hiroshima University Hospital (Table 1). PAF patients were defined as those with AF spontaneously switching to a sinus rhythm within seven days from the onset. All patients with PAF underwent echocardiography during sinus rhythm.

Cerebral embolism was diagnosed according to a typical sudden onset of neurological symptoms, specific findings resulting from tests conducted by neurologists and radiological imaging, and hospital or radiological records of confirmed previous stroke. Exclusion criteria were acute cerebral infarction within one month of initiation of the study, significant congestive heart failure, valvular heart disease, myocardial infarction, or prior AF ablation. Patients with concomitant etiologies that might affect the NLR values, such as hematological disease, malignancy, infectious disease, systemic inflammation, and a white blood cell count of >12,000 cells/μL or <4,000 cells/μL, were also excluded from the study. Warfarin or non-vitamin K dependent anticoagulants had been administered in 181 of the 183 patients before the echocardiographic examinations.

The study was approved by the Hiroshima University Hospital Institutional Review Board. Informed consent was obtained from all subjects.

Echocardiographic apparatus

The Vivid 7 ultrasound system (General Electric Healthcare, Milwaukee, USA) was used for the echocardiographic examinations. The corresponding measurements for transesophageal tissue Doppler imaging were as follows: frame rate, 78 frame/s; frequency, 3.9 MHz; and sampling volume width, 3.2 mm (10).

Transthoracic echocardiography

The LA dimension (LAD) was measured by a conventional method using M-mode echocardiography. The modified biplane Simpson rule was used to measure the maximum LA volumes in the apical four- and two-chamber views at end-ventricular systole. The LA volume was divided by the body surface area and expressed in terms of the LA volume index as a measure of LA remodeling. Pulsed Doppler echocardiographic recording allowed for the analysis of the peak mitral flow velocity during atrial contraction (A) wave as an index of the LA body contractile function. The peak mitral annular motion velocity during atrial contraction (A') as another index of the LA body contractile function was measured using tissue Doppler imaging. The ratio of peak mitral flow velocity during early diastole (E)/peak mitral annular motion velocity during early diastole (E') was calculated as E divided by E'.

Transesophageal echocardiography

The maximum LAA area as an index of LAA remodeling and the peak LAA flow velocity during atrial contraction as an index of the LAA contractile function were measured based on the long-axis view of the LAA. The LAA flow velocity was assessed using pulsed Doppler, with the sample volume placed in proximity to the LAA orifice, and peak velocities of flow originating from the LAA were measured. The LAA wall motion velocity as an index of the LAA contractile function at the tip of the LAA during atrial contraction was obtained using pulsed tissue Doppler imaging. The LAA wall motion velocity was calculated as the average of the maximum positive peak wave velocity within each R-R interval over three cardiac cycles. We examined the presence of SEC in the LAA as an index of LAA thrombogenesis. In this study, we defined the presence as positive if SEC was visible when the gain settings were adjusted to distinguish background noise (11). The acquired images were analyzed by two sonographers blinded to the patients' clinical information.

Hemodynamic measurements

A double transseptal puncture approach was adopted for catheter access to the left atrium. The LA pressure was immediately measured after transseptal puncture using a catheter inserted into the left atrium via a long sheath (Schwartz Left 1; St. Jude Medical, Minnetonka, USA). The peak LA pressure (at the v wave) and mean LA pressure were analyzed. The aortic pressure was measured via a femoral artery sheath.

Common blood counting parameters

All blood samples were drawn from the antecubital vein before the transesophageal echocardiography examination. Hematologic parameters were measured using an automated blood counter (Sysmex XE-5000; Sysmex Corporation, Kobe, Japan). The NLR was computed using the absolute neutrophil count divided by the absolute lymphocyte count.

Table 1. Patients' Characteristics according to NLR.

Variables	All n=183	NLR<2.5 n=122	NLR ≥2.5 n=61	p value
Male, n (%)	127 (69)	83 (68)	44 (72)	0.569
Age, year	64 ± 9	63 ± 9	66 ± 9	0.076
CHADS2 score	1.3 ± 1.1	1.1 ± 0.9	1.6 ± 1.3	0.010*
CHA2DS2-VASc score	2.1 ± 1.5	1.9 ± 1.3	2.6 ± 1.6	0.011*
Cardiovascular risk factors , n (%)				
Hypertension	119 (65)	76 (62)	43 (70)	0.270
Hyperlipidemia	71 (39)	45 (37)	26 (43)	0.454
Diabetes mellitus	39 (21)	21 (17)	18 (30)	0.060
Congestive heart failure	8 (4)	5 (4)	3 (5)	0.800
Stroke	24 (13)	11 (9)	13 (21)	0.024*
Cerebral embolism	14 (8)	5 (4)	9 (15)	0.014*
Medications, n (%)				
Sodium channel blockers	42 (23)	31 (25)	11 (18)	0.256
Multichannel blockers	46 (25)	31 (25)	15 (25)	0.904
Beta blockers	65 (35)	43 (35)	22 (36)	0.913
Warfarin	49 (27)	30 (25)	19 (31)	0.349
NOAC	132 (72)	91 (75)	41 (67)	0.298
Biochemical tests				
C-reactive protein, mg/dL	0.06 (0.03-0.10)	0.06 (0.02-0.09)	0.06 (0.03-0.11)	0.366
Triglycerides, mg/dL	121 ± 88	122 ± 99	119 ± 61	0.335
Low-density lipoprotein, mg/dL	118 ± 23	119 ± 25	114 ± 18	0.091
Common blood counting parameters				
Hemoglobin, g/dL	14.0 ± 1.5	14.1 ± 1.5	14.0 ± 1.7	0.941
Platelet count,$\times 10^3/\mu L$	210 ± 46	213 ± 44	203 ± 50	0.147
White blood cell count,$\times 10^3/\mu L$	5.81 ± 1.52	5.38 ± 1.33	6.28 ± 1.71	<0.001*
NLR	2.2 ± 0.9	1.7 ± 0.4	3.3 ± 0.6	<0.0001*
PT-INR	1.45 ± 0.53	1.41 ± 0.51	1.53 ± 0.57	0.057
Echocardiographic parameters				
LAD, mm	38 ± 6	38 ± 6	39 ± 7	0.227
LA volume index, mL/m^2	39 ± 11	37 ± 11	41 ± 11	0.039*
LAA area, cm^2	4.5 ± 1.4	4.3 ± 1.2	5.0 ± 1.7	0.007*
LAA flow velocity, cm/s	63 ± 19	64 ± 18	61 ± 20	0.422
LAA wall motion velocity, cm/s	14.1 ± 4.8	15.6 ± 4.4	11.0 ± 3.9	<0.0001*
A, cm/s	55 ± 21	53 ± 21	58 ± 20	0.103
E', cm/s	7.2 ± 2.1	7.3 ± 2.1	6.7 ± 2.0	0.084
A', cm/s	8.0 ± 1.9	8.0 ± 1.7	8.2 ± 2.1	0.604
E/E'	10.0 ± 3.6	9.7 ± 3.2	11.1 ± 4.3	0.071
LVEDD, mm	48 ± 5	49 ± 4	48 ± 5	0.576
LVEDVI, mL/m^2	51 ± 11	51 ± 11	50 ± 12	0.315
LVEF, %	61 ± 6	61 ± 6	62 ± 5	0.101
SEC, n (%)	30 (16)	14 (11)	16 (26)	0.013*
Hemodynamic parameters				
Systolic aortic pressure, mmHg	139 ± 17	140 ± 18	139 ± 17	0.673
Diastolic aortic pressure, mmHg	74 ± 12	76 ± 12	71 ± 11	0.123
Peak LA pressure, mmHg	18 ± 5	18 ± 5	19 ± 6	0.545
Mean LA pressure, mmHg	12 ± 5	12 ± 5	13 ± 5	0.408

Values are expressed as mean ± SD, n (%), or median (IQR). NOAC: non-vitamin K dependent anticoagulant, NLR: neutrophil-to-lymphocyte ratio, PT-INR: international normalized ratio of prothrombin time, LAD: left atrial dimension, LA volume index: maximal left atrial volume index, LAA area: maximal left atrial appendage area, LAA flow velocity: left atrial appendage flow velocity during atrial contraction, LAA wall motion velocity: left atrial appendage wall motion velocity during atrial contraction, A: transmitral flow velocity during atrial contraction, E': mitral annular motion velocity during early diastole, A': mitral annular motion velocity during atrial contraction, E: transmitral flow velocity during early diastole, LVEDD: left ventricular end-diastolic dimension, LVEDVI: left ventricular end-diastolic volume index, LVEF: left ventricular ejection fraction, SEC: spontaneous echo contrast, *: Statistically significant

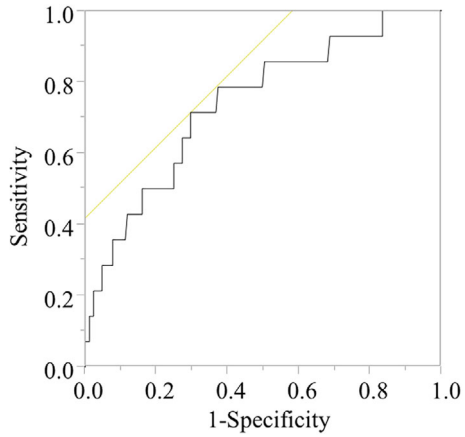

Figure 1. Receiver operating characteristic curve for the NLR as a predictor of cerebral embolism. The optimum cut-off point was 2.5, with a sensitivity of 71% and specificity of 74%. The area under the curve was 0.740. The abbreviations are the same as those in Table 1.

Statistical analyses

Continuous variables were presented as the mean ± standard deviation, median, and interquartile range. Categorical variables were expressed as the number and percentage. The chi-squared test, unpaired Student's t-test, Mann-Whitney U-test, and Kruskal-Wallis test were performed where appropriate for comparisons between the groups. To calculate the correlations, Pearson's correlation coefficient was used as appropriate. Cut-off values for the NLR were estimated using a receiver operating characteristic (ROC) curve analysis to predict SEC or emboli with corresponding sensitivity and specificity. Potential predictors with p <0.10 on a univariate analysis were included in a multivariate regression analysis. A multivariate regression analysis was used to identify the independent predictors of SEC. A p value <0.05 was considered significant, and the confidence interval (CI) was set at 95%. The JMP Ver. 11 statistical software package (SAS Institute, Tokyo, Japan) was used for all statistical tests.

Results

NLR and thrombogenesis

The baseline characteristics of the study participants are shown in Table 1. The ROC curve for NLR as a predictor of cerebral embolism showed an area under the curve of 0.74 (95% CI: 0.92-1.91, p <0.001) (Fig. 1). A cut-off point of 2.5 for NLR had a sensitivity of 71% and a specificity of 74% in predicting cerebral embolism. Of the 14 patients with cerebral embolism, 9 had an NLR ≥2.5 and 5 had an NLR <2.5 (p=0.014). The patients with an NLR ≥2.5 had a higher CHADS2 or CHA2DS2-Vasc score than those with an NLR <2.5 (1.6±1.3 vs. 1.1±0.9, p=0.010, 2.6±1.6 vs. 1.9 ±1.3, p=0.011, respectively). The NLR of the patients with cerebral embolism or SEC was significantly greater than in those without the disorders (3.0±1.0 vs. 2.2±0.9, p=0.003; 2.7±1.0 vs. 2.2±0.8, p=0.006, respectively). According to the univariate analysis, diabetes, NLR, and peak LA pressure were identified as potential risk factors for SEC. In the multivariate analysis, NLR was an independent risk factor for SEC in PAF patients (Table 2). There were no significant differences in the C-reactive protein (CRP) levels between the patients with and without cerebral embolism or SEC (0.07 vs. 0.05, p=0.086; 0.06 vs. 0.05, p=0.532, respectively). There were no significant differences in type of anticoagulation therapy between patients with and without SEC (warfarin: p=0.192, non-vitamin K dependent anticoagulant: p=0.250).

Association of NLR with the LA body and LA appendage function

The patients with an NLR ≥2.5 had a greater LA volume index, LAA area, and less LAA wall motion velocity than those with an NLR <2.5 (41±11 vs. 37±11, p=0.039; 5.0± 1.7 vs. 4.3±1.2, p=0.007; 11.0±3.9 vs. 15.6±4.4, p <0.0001, respectively). The mitral flow velocity A and mitral annular motion velocity A' did not differ markedly between the patients with an NLR ≥2.5 and those with an NLR <2.5. Correlations between the NLR and echocardiographic and hemodynamic parameters in patients with or without SEC are shown in Table 3. In the 153 patients without SEC, the NLR had a significant inverse correlation with the LAA wall motion velocity alone (r=-0.409) but had no significant correlation with the LAD, LA volume index, mitral flow velocity A, or mitral annular motion velocity A'. In the 30 patients with SEC, the NLR was more closely correlated with the LAA wall motion velocity and LAA area than in the patients without SEC (r=-0.583 and 0.654, respectively) (Fig. 2). However, the NLR did not correlate with the LAD, LA volume index, mitral flow velocity A, or mitral annular motion velocity A' in these patients (Fig. 3).

Discussion

In histological studies of AF patients, inflammatory cells, such as monocytes and macrophages, infiltrate the subendocardium or the myocardium (12, 13). Inflammatory cell infiltration was also confirmed in the LAA (14). Cytokines, which are secreted from inflamed cells and the endothelium, cause electrostatic destabilization of the myocardiocytes, activate fibroblasts, and ultimately induce fibrosis of the extracellular matrix. NLR is an inflammation marker that is elevated in acute coronary syndrome or aortic stenosis (6, 7). One study examined the NLR in AF patients with thromboembolic stroke (5). Saliba et al. reported that the hazard ratio for a first stroke in AF patients was 1.11 (0.91-1.35) for an NLR 1.71-2.29, 1.25 (1.03-1.51) for an NLR 2.29-3.15, and 1.56 (1.29-1.88) for an NLR >3.15 (15). The NLR is associated with the presence of LA thrombus in AF patients or SEC in patients with mitral stenosis (8, 9).

However, to our knowledge there have been no studies of

Table 2. Independent Predictors of SEC.

Variables	Univariate OR 95% CI	p value	Multivariate OR 95% CI	p value
Age	1.02 (0.98-1.07)	0.430		
Hypertension	1.31 (0.58-3.19)	0.528		
Diabetes	2.13 (0.88-4.98)	0.092	1.47 (0.55-3.72)	0.431
Congestive heart failure	3.29 (0.64-14.22)	0.140		
NOAC	0.61 (0.27-1.43)	0.250		
C-reactive protein	0.32 (0.03-1.06)	0.677		
Serum creatinine	0.96 (0.43-1.08)	0.192		
Hemoglobin	0.90 (0.70-1.16)	0.407		
White blood cell count	1.16 (0.90-1.48)	0.244		
NLR	1.91 (1.25-2.97)	0.003*	1.86 (1.20-2.92)	0.006*
peak LA pressure	1.08 (1.01-1.16)	0.023*	1.07 (0.99-1.16)	0.119

NOAC: non-vitamin K dependent anticoagulant, NLR: neutrophil-to-lymphocyte ratio

Table 3. Correlations between NLR and Echocardiographic and Hemodynamic Parameters in Patients with and without SEC.

Variables	All n=183 Correlation Coefficients	p value	With SEC n=30 Correlation Coefficients	p value	Without SEC n=153 Correlation Coefficients	p value
Echocardiographic parameters						
LAD	0.121	0.102	0.052	0.785	0.069	0.395
LA volume index	0.205	0.005*	0.195	0.302	0.150	0.064
LAA area	0.296	<0.001*	0.654	<0.001*	0.077	0.343
LAA flow velocity	-0.159	0.032*	-0.211	0.264	-0.069	0.396
LAA wall motion velocity	-0.477	<0.001*	-0.583	0.001*	-0.409	<0.001*
A	0.057	0.444	-0.040	0.833	0.114	0.159
E'	-0.177	0.017*	-0.513	0.004*	-0.094	0.247
A'	0.038	0.607	0.101	0.595	0.049	0.551
E/E'	0.221	0.003*	0.375	0.041*	0.127	0.117
LVEDD	-0.055	0.459	0.059	0.758	-0.077	0.347
LVEDVI	-0.058	0.445	-0.041	0.832	-0.022	0.787
LVEF	0.071	0.339	0.160	0.398	0.088	0.281
Hemodynamic parameters						
Systolic aortic pressure	-0.012	0.873	-0.304	0.102	0.061	0.458
Diastolic aortic pressure	-0.121	0.102	-0.197	0.298	-0.121	0.136
Peak LA pressure	0.064	0.388	-0.070	0.714	0.055	0.499
Mean LA pressure	0.026	0.733	-0.033	0.862	-0.004	0.959

SEC: spontaneous echo contrast, LAD: left atrial dimension, LA volume index: maximal left atrial volume index, LAA area: maximal left atrial appendage area, LAA flow velocity: left atrial appendage flow velocity during atrial contraction, LAA wall motion velocity: left atrial appendage wall motion velocity during atrial contraction, A: transmitral flow velocity during atrial contraction, E': mitral annular motion velocity during early diastole, A': mitral annular motion velocity during atrial contraction, E: transmitral flow velocity during early diastole, LVEDD: left ventricular end-diastolic dimension, LVEDVI: left ventricular end-diastolic volume index, LVEF: left ventricular ejection fraction

NLR with respect to the LA and LAA function in non-valvular PAF patients. In PAF patients, frequent instances of AF can cause not only a temporary decline in the LAA function due to LAA stunning but also a sustained decline in the LAA function due to LAA inflammation and/or fibrosis. We showed that the NLR was significantly higher in non-valvular PAF patients with SEC or cerebral embolism than in those without the disorders. The ROC curve for the NLR as a predictor of cerebral embolism showed an area under the curve of 0.74 (95% CI: 0.92-1.91, p <0.001). A cut-off point of 2.5 for NLR had a sensitivity of 71% and a specificity of 74% in predicting cerebral embolism. The patients with an NLR ≥2.5 had a higher CHADS2 or CHA2DS2-Vasc score compared to the patients with an NLR <2.5. These results show that a high NLR indicates thrombogenesis or thromboembolic risk in non-valvular PAF patients with a high degree of certainty. We decided on a cut-off point of 2.5 based on our analysis of the ROC curve

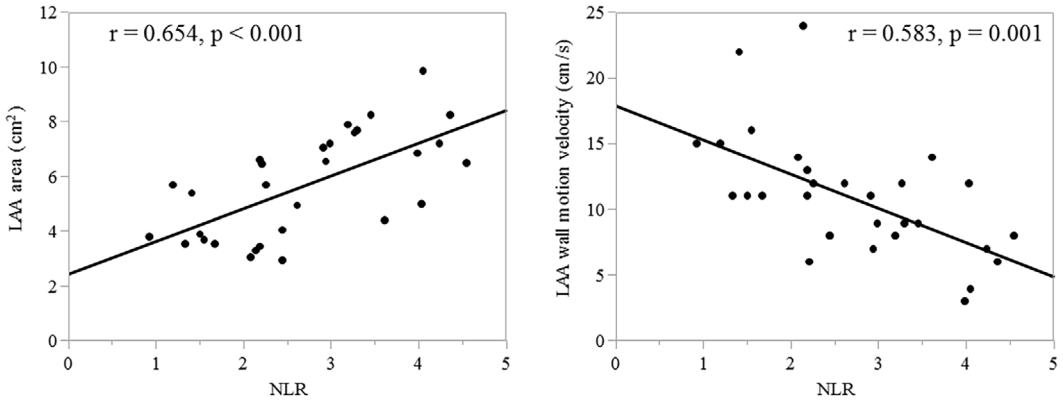

Figure 2. **Correlations between the NLR and the LAA function in patients with SEC. Significant correlations were noted between the NLR and the LAA area (left panel) or LAA wall motion velocity (right panel). The abbreviations are the same as those in Table 1.**

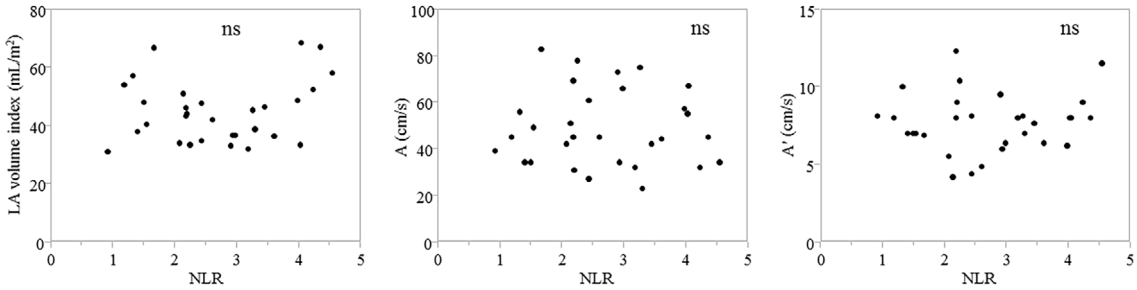

Figure 3. **Correlations between the NLR and the LA body function in patients with SEC. No significant correlations were noted between the NLR and the LA volume index (left panel), mitral flow velocity A (center panel), or mitral annular motion velocity A' (right panel). The abbreviations are the same as those in Table 1.**

for the NLR as a predictor of cerebral embolism. Forget et al. reported that the mean NLR was 1.69±1.37 in healthy volunteers (16). Yalcin et al. showed a cut-off value of 2.59 for LAA thrombus in non-valvular AF patients (8). Akil et al. showed a cut-off value of 2.6 for previous cerebral ischemic stroke (17). These results are concordant with our results. Regarding the issue of CRP as another inflammatory marker, some previous studies of AF have shown an association between the CRP level and SEC (9, 18). However, we detected no such association in the present study. This discrepancy may be due to differences in the study patient's characteristics, as we examined only non-valvular PAF patients in our study. The previous studies also included valvular AF patients. In addition, the NLR is not only an inflammation marker but also a fibrosis marker, and it therefore may not always be concordant with the CRP level.

It is well known that an enlarged size or reduced emptying function of the LA and LAA are related to thrombosis or thrombogenesis in AF patients. Recently, the LAA wall motion velocity, a measure of the LAA contraction function, obtained by tissue Doppler echocardiography was postulated as a new noninvasive tool for evaluating the LAA function. Machino-Ohtsuka et al. reported that the LAA wall motion velocity at baseline predicts both the maintenance of sinus rhythm and LA reverse remodeling after catheter ablation for AF (19). A relationship between the LAA wall motion velocity and thrombotic tendency among patients with AF has also been reported (10, 20). In the present study's non-valvular PAF patients with SEC, the NLR had a significant inverse correlation with the LAA wall motion velocity and a positive correlation with the LAA area. In non-valvular PAF patients who did not have SEC, the NLR also had significant inverse correlation with the LAA wall motion velocity. In contrast, the NLR did not correlate with the LA volume index or LAD, which indicates the LA body size. The NLR also did not correlate with the mitral flow velocity A or mitral annular motion velocity A', which are used as LA body function parameters during atrial contraction.

Several authors have noted that fibrosis in the LAA and LA body is similar to that observved in patients with chronic AF (2, 4, 21, 22). In contrast, however, Agmon et al. reported that the LAA function does not always parallel the LA function (23). One pathological study showed that LA fibrosis is ubiquitous (24). Since the LA and LAA differ in terms of embryological development, they may possess different structural characteristics, such as with respect to myocardial cell distribution and the density of endothelial cells (25). These different histological changes may result in

a different degree of development from inflammation to fibrosis. Our findings in non-valvular PAF patients, particularly those with SEC, suggest that the NRL was more closely correlated with the LAA contractile function than the LA body function, indicating that the transient inflammation effect may differ between the LA body and LAA. There is no definitive explanation for why the localized inflammation in the smaller-sized LAA, versus the LA body, is correlated with the NLR in the peripheral blood sample. Because the LAA is smaller than the LA body and consists of thick pectinate muscle, LAA fibrosis may precede LA body fibrosis. The endocardial distribution of nerve bundles was higher in the LAA than in the LA body (26). These differences between the LAA and LA body may be related to the peripheral blood sample NLR, reflecting the LAA fibro-inflammatory status. A similar situation is observed in serum human atrial natriuretic peptide (HANP) values. HANP may be released mainly from the LAA rather than the LA body and is found to be elevated in the peripheral blood samples of patients with heart failure.

Since the LAA is a common site of thrombus formation, the association of the NLR with the LAA function and size has the potential to be an exciting finding. The LAA function ranges from normal to low in PAF patients (27). In the present study, the NLR also ranged from normal to high and was associated with the LAA wall motion velocity in the non-valvular PAF patients with SEC. We found that the NLR was more strongly correlated with the LAA wall motion velocity than with the LAA flow velocity, although the reason for this difference is unclear at present. While the LAA wall motion velocity was directly assessed based on the LAA wall contractile performance as measured by tissue Doppler echocardiography, the blood flow velocity in the LAA generally depends not only on the LAA contraction but also on the LAA size. As such, in cases of identical LAA wall motion velocities, the LAA flow velocity may be slower in an enlarged LAA than in a normal-sized LAA. We therefore speculate that the LAA wall motion velocity in persistent AF patients is generally concordant with the LAA flow velocity, but that is not the case in some PAF patients. This may be one of the reasons for the difference in the NLR between the LAA wall motion velocity and flow velocity.

Limitations

Several limitations associated with the present study warrant mention. First, this was a retrospective study that included a relatively small number of patients. Subjects were examined before catheter ablation for AF, and a few stroke patients were included; thus, a selection bias may exist. Second, we determined the LA volume using two-dimensional echocardiography. Three-dimensional (3D) echocardiography may provide more accurate measurement of LA volume, but clear 3D LA images are often difficult to obtain. Third, we did not determine the LA and LAA function using recently developed echocardiographic strain imaging. Finally, the NLR blood sampling time was considerably delayed after the onset of cerebral embolism, and thus the NLR values may have fluctuated. Such issues may have caused data variations and rough correlations between NLR and echocardiographic variables. The detection of high-risk PAF patients for thromboembolism based on the NLR alone was not convincingly accurate given our present data. With this in mind, further studies using larger subject cohorts are considered necessary in the future.

Conclusion

The NLR is higher in non-valvular PAF patients with thrombogenesis than in those without thrombogenesis and it also has a stronger association with the LAA contractile function than with the LA body function.

The authors state that they have no Conflict of Interest (COI).

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