

Association between reactive hyperemia peripheral arterial tonometry index and atrial fibrillation recurrence after catheter ablation

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ABSTRACT

Background: Vascular endothelial function has recently been recognized as an independent predictor of cardiovascular events. However, studies investigating its association with atrial fibrillation (AF) are lacking. This study aimed to examine association with AF recurrence and vascular endothelial function as assessed using natural logarithmic transformation of reactive hyperemia peripheral arterial tonometry index (LnRHI).

Methods: Ninety-nine consecutive AF patients who underwent catheter ablation (CA) at Shinshu University Hospital between September 2015 and April 2017 were enrolled. LnRHI was measured 48 to 72 h before CA using the EndoPAT system. The primary outcome was AF recurrence beyond 3 months post-ablation.

Results: A total of 30 (30.3%) patients experienced AF recurrence after CA over a median follow-up period of 210 days (range: 93–764 days). Female sex and low LnRHI were significantly associated with AF recurrence. In multivariate analysis, LnRHI was an independent predictor of AF recurrence (hazard ratio: 0.087, 95% confidence interval 0.015–0.51, $p = 0.007$). In comparison in Kaplan-Meier analysis of high LnRHI ($\text{LnRHI} \geq 0.52$, $n = 52$) and low LnRHI ($\text{LnRHI} < 0.52$, $n = 47$) groups, AF recurrence rate was significantly higher in the low LnRHI group (log-rank test, $p = 0.043$). A negative correlation was observed between LnRHI and AF duration, whereby LnRHI was significantly decreased when the duration of AF events exceeded 1 year.

Conclusion: Decreased LnRHI was associated with AF recurrence after CA and prolonged AF duration.

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1. Introduction

The effectiveness of catheter ablation (CA) for atrial fibrillation (AF) has recently been established [1], especially that of extensive encircling pulmonary vein isolation (EPPVI) [2]. With the advent of three-dimensional mapping and balloon ablation (BA), EPPVI outcomes are rapidly improving. Superior vena cava (SVC) isolation [3], creation of a block line to the cavo-tricuspid isthmus (CTI), and complete left atrial posterior wall isolation (Box isolation) [4,5] are other options for AF ablation. However, AF can recur even after successful CA [6]. Several factors have been associated with the recurrence of AF [7–11], with electrical and structural remodeling of the left atrium also considered to be involved [9,10].

In recent years, the vascular endothelial function has attracted attention as a factor related to AF [12]. The vascular endothelium plays a key

role in regulating the function of the cardiovascular system, paracrine and endocrine signaling, and local inflammatory responses [13,14]. Vascular endothelial function is often assessed by the reactive hyperemia peripheral artery tonometry index (RHI) using the EndoPAT 2000 device (Itamar Medical Ltd., Caesarea, Israel). RHI is a good predictor of prognosis and cardiovascular events, especially for patients with coronary artery disease [15,16] and congestive heart failure [17,18].

Vascular endothelial dysfunction has been associated with an increased risk of AF [12,19]. Irregular pulsatile blood flow due to AF impairs the vascular endothelial response to shear stress and increases pro-inflammatory responses. Accordingly, long-term AF decreases vascular endothelial function [13,15], thus implying that endothelial dysfunction is both a cause and result of AF [20]. However, reports on the correlation between the vascular endothelium and AF recurrence after CA are scarce [19,21].

This study evaluated the relationships between vascular endothelial function and the recurrence of AF after CA as well as the duration of AF. And we aimed to investigate of association with AF recurrence and vascular endothelial function based on the natural logarithmic transformation of RHI (LnRHI).

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2. Methods

2.1. Patient population

Patients who underwent CA for AF at Shinshu University Hospital between September 2015 and April 2017 were retrospectively enrolled (Fig. 1). Inclusion criteria were symptomatic, drug-refractory AF, which included both paroxysmal AF (pAF) and persistent AF. Exclusion criteria were any cancer, severe chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease class 2 or more), hemodialysis and peripheral artery disease including upper extremities. Vascular endothelial function in all patients was examined before CA, as described below. The study protocol was approved by the ethics committee of Shinshu University Hospital (The registration number was 4199). Informed consent was obtained from the patients as much as possible due to the limitations of a retrospective study design.

2.2. Catheter ablation

EEPVI was performed via radiofrequency CA (RFA) using an irrigated catheter with contact force (ThermoCool; Biosense Webster, CA, USA) or BA including a cryoballoon (Arctic Front Advance; Medtronic, MN, USA) or HotBalloon (SATAKE HotBalloon; Toray Industries, Tokyo, Japan). A three-dimensional mapping system was employed to simulate the geometry of the left atrium and pulmonary veins in all CA sessions. CTI block line ablation was performed if common atrial flutter was found before CA or induced during CA. SVC isolation was performed if patients did not have sinus node dysfunction, with no cases of complete left atrial posterior wall isolation, complex fractionated atrial electrogram ablation, or linear ablation of the mitral isthmus. The procedural endpoints were defined as follows: the entrance and exit blocks between each pulmonary vein and the left atrium were confirmed; no induction of sustained AF by atrial rapid pacing and 1- μ g isoproterenol infusion after EEPVI; and no documented adenosine triphosphate-induced dormant conduction between the pulmonary veins and left atrium. All patients received oral anticoagulant therapy for at least 4 weeks prior to CA and continued treatment for at least 12 months.

2.3. Vascular endothelial function

Vascular endothelial function was assessed using the EndoPAT 2000 device, which is widely used because it provides reproducible findings and is automated, objective, and convenient [17].

Measurement of RHI was performed 48 to 72 h before CA. All evaluations were performed in a quiet room. The patients discontinued vasoactive medications 24 h before and fasted for 4 h before the examination. This method has been validated and described in previous studies on patients with AF [22,23].

The study protocol for vascular endothelial function has been validated in other populations [17,24]. First, a dedicated probe was attached to a finger on the arm undergoing hyperemia testing (right hand), and a second probe was attached to the contralateral index finger (left hand). Thereafter, the baseline blood flow volume of the fingertip of both arms was measured for 5 min. Next, a blood pressure cuff wrapped around the right arm was inflated to 60 mmHg above the baseline systolic blood pressure or a maximum of 200 mmHg for 5 min. After the 5-minute occlusion, the cuff was deflated. The changes over time of blood flow volume into the fingertips in response to reperfusion stimulation after arm compression were recorded. Finally, RHI was calculated by dividing the increased rate of the volume pulse waves in the compressed arm by the increased rate in the control arm.

LnRHI was evaluated in this study due to the skewed distribution of patient data. Endothelial function was presented as LnRHI based on a previous report [24], since it showed good reproducibility in another investigation [25].

2.4. Follow-up and endpoint

All patients were monitored periodically after CA. Data of 12 lead electrocardiography (ECG) or Holter monitoring ECG were obtained at follow-up visits every 3 months post-CA for all patients. AF duration was defined as the period from the first documented AF on ECG or Holter monitoring ECG until LnRHI measurement. AF recurrence was defined as AF lasting 30 s or more as confirmed by ECG or Holter monitoring ECG after CA. The 3-month period immediately following CA was excluded as a blind period. Therefore, the endpoint was recurrence of AF after CA beyond 3 months post-ablation.

2.5. Statistical analysis

Quantitative variables were presented as medians with interquartile range and categorical variables were expressed as the number and percentage. Quantitative variables were compared using Mann-Whitney test. Categorical variables were compared by means of the chi-squared test or Fisher's exact test. A p-value of ≤ 0.05 was considered statistically significant. Pearson correlation coefficient was calculated to determine the relationship between LnRHI and AF duration. A Cox proportional hazards model with forward-backward stepwise selection was used to identify predictors of AF recurrence. Receiver-operating characteristic (ROC) curve analysis was conducted to assess the optimal cut-off value of LnRHI for AF recurrence. The Kaplan-Meier method was employed to estimate cumulative event rates for AF recurrence. All analyses were performed using SPSS statistical software, version 24.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics and AF recurrence

A total of 99 patients were enrolled in this study. AF recurrence after CA occurred in 30 patients among all patients (30.3%) over a median follow-up period of 210 days (range: 93–764 days). Table 1 summarizes the baseline characteristics of the cohort divided into 2 groups by the presence or absence of AF recurrence.

LnRHI was significantly lower in AF recurrence group. Approximately 40% of patients had atrial fibrillation at the time of LnRHI measurement, but there was no difference in recurrence rate compared with patients who were in sinus rhythm at LnRHI measurement. The median AF duration overall was 10.6 months, with a minimum of one month and a maximum of 122 months. AF duration was significantly longer in AF recurrence group. Female, hypertension (HT) and diabetes (DM) were not statistically significant but tended to be more frequent in the AF recurrence group. There were no significant differences in CHA₂DS₂-Vasc score, left atrial diameter (LAD) and left atrial volume index (LAVI) between the two groups. No significant differences in the frequency of ablation methods, such as RFA or BA, were seen. And there was no difference in recurrence rates between the two groups, patients with PVI alone or patients who added SVC isolation and/or CTI block lines.

3.2. Association with LnRHI and AF recurrence

The conditions during LnRHI measurement were summarized in Table 2. Sixty-one patients were sinus rhythm and 38 were AF rhythm during LnRHI measurements. The value of LnRHI and blood pressure did not differ between sinus rhythm and AF rhythm, but heart rate was significantly faster in AF rhythm patient. In addition, there was no difference in AF recurrence between the two groups.

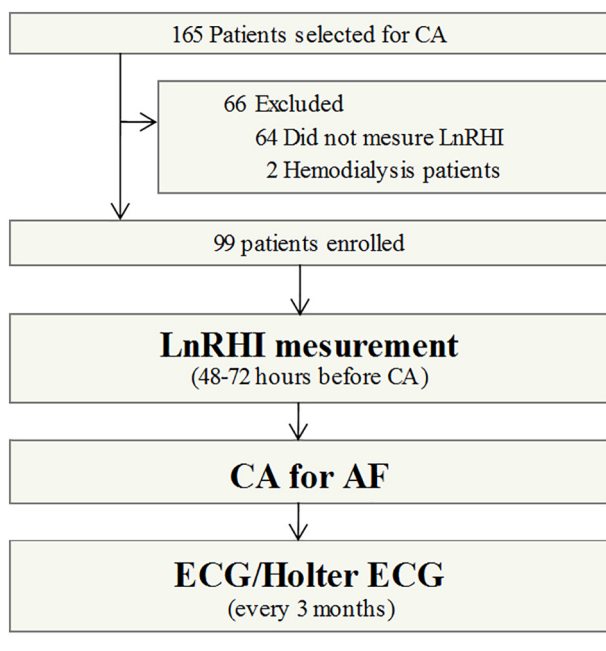


Fig. 1. Flow chart of the study participants. A total of 165 AF patients received catheter ablation for atrial fibrillation between September 2015 and April 2017. Finally, 99 AF patients were enrolled in this study. CA: catheter ablation, LnRHI: the natural logarithmic transformation of reactive hyperemia peripheral arterial tonometry index, AF: atrial fibrillation, ECG: electrocardiogram.

Table 1
Baseline characteristics.

	All patients (n = 99)	AF Recur (+) (n = 30)	AF Recur (-) (n = 69)	p-value
Age (years)	66 [56, 70]	65 [58, 71]	66 [54, 70]	0.39
Female	27 (27.3)	11 (36.7)	16 (23.2)	0.22
Body mass index (kg/m ²)	24.1 [21.9, 27.2]	24.5 [21.6, 27.6]	23.7 [21.8, 27.0]	0.68
Systolic blood pressure (mmHg)	122 [114, 136]	123 [110, 134]	121 [115, 136]	0.64
Diastolic blood pressure (mmHg)	74 [66, 82]	76 [65, 82]	73 [68, 80]	0.71
Heart rate (bpm)	63 [55, 75]	63 [57, 79]	63 [52, 74]	0.44
Hypertension	43 (43.4)	15 (50.0)	28 (40.6)	0.51
Congestive heart failure	13 (13.1)	3 (10.0)	10 (14.5)	0.75
Diabetes mellitus	14 (14.1)	5 (16.7)	9 (13.0)	0.75
Old cerebral infarction	10 (10.1)	2 (6.7)	8 (11.6)	0.71
Coronary artery disease	7 (7.8)	2 (6.7)	5 (7.2)	0.64
CHA ₂ DS ₂ -Vasc score	1 [1, 2]	1 [1, 2]	1 [1, 2]	0.85
AF Duration (month)	10.6 [4.4, 42.9]	30.0 [7.0, 60]	7.2 [4.1, 26]	0.025
Hemoglobin A1c (%)	5.7 [5.6, 6.2]	5.8 [5.5, 6.1]	5.7 [5.6, 6.2]	0.57
BNP (pg/ml)	63.5 [27.5, 121]	68.8 [33.3, 148]	53.8 [22.7, 106]	0.45
LAD (cm)	3.82 [3.3, 4.3]	3.84 [3.07, 4.31]	3.82 [3.40, 4.30]	0.43
LAVI (ml/m ²)	33.5 [26.4, 42.7]	33.5 [24.7, 45.0]	32.9 [27.0, 42.1]	0.92
Ankle brachial index	1.16 [1.11, 1.23]	1.16 [1.12, 1.23]	1.16 [1.09, 1.23]	0.60
LnRHI	0.52 [0.39, 0.73]	0.43 [0.32, 0.55]	0.57 [0.47, 0.75]	0.023
SR in Measurement	61 (61.6)	16 (53.3)	45 (65.2)	0.27
AF in Measurement	38 (38.4)	14 (46.7)	24 (34.8)	
Medication at admission				
Class I antiarrhythmic drug	31 (31.3)	9 (30.0)	24 (34.8)	0.82
Beta blocker	46 (46.5)	13 (43.3)	33 (47.8)	0.83
Calcium antagonist	23 (23.2)	7 (23.3)	16 (23.2)	1.00
Warfarin	16 (16.2)	6 (20.0)	10 (14.5)	0.56
Direct oral anticoagulants	83 (83.8)	24 (80.0)	59 (85.5)	
pAF	81 (81.8)	25 (83.3)	56 (81.2)	0.52
psAF	18 (18.2)	5 (16.7)	13 (18.8)	
RFCA	55 (55.6)	15 (50.0)	40 (58.0)	0.51
Balloon ablation	44 (44.4)	15 (50.0)	29 (42.0)	
PVI only	56 (56.6)	14 (46.7)	42 (60.9)	0.11
PVI + SVCI	25 (25.3)	6 (20.0)	19 (27.5)	0.62
PVI + CTI block line	28 (28.3)	10 (33.3)	18 (26.1)	0.48
PVI + SVCI+CTI block line	13 (13.1)	3 (10.0)	10 (14.5)	0.75

AF, atrial fibrillation; Recur, recurrence; BNP, brain natriuretic peptide; LAD, Left atrial diameter; LAVI, Left atrial volume index; LnRHI, natural logarithmic transformation of reactive hyperemia peripheral arterial tonometry index; SR, sinus rhythm; pAF, paroxysmal atrial fibrillation; psAF, persistent atrial fibrillation; RFCA, radiofrequency catheter ablation; PVI, pulmonary vein isolation; SVCI, superior vena cava isolation; CTI, cavo tricuspid isthmus.

A negative correlation was found between the value of LnRHI as a whole and systolic blood pressure, diastolic blood pressure and hemoglobin A1c, respectively (correlation coefficient, p-value; $r = -0.21$, $p = 0.039$, $r = -0.32$, $p = 0.002$, $r = -0.26$, $p = 0.009$).

Cox proportional hazards analysis was performed on factors related to AF recurrence, including LnRHI (Table 3). Female sex and low LnRHI were significantly associated with AF recurrence, and RFCA tended to be higher in the patients with AF recurrence. AF duration was not associated with AF recurrence significantly. In the multivariate analysis adjusted for female sex, AF duration and LnRHI revealed that LnRHI remained an important factor associated with AF recurrence after CA (hazard ratio 0.087, 95% CI 0.015–0.51, $p = 0.007$).

ROC curve analysis showed that the optimal cut-off value for LnRHI was determined as 0.52 (area under the curve: 0.67, 95% confidence interval [CI] 0.55–0.79, $p = 0.044$). The specificity and sensitivity of the cut-off value were 58% and 67%, respectively. Favorable endothelial function was considered to exist in the high LnRHI group (LnRHI ≥ 0.52 , $n = 52$), whereas the low LnRHI group (LnRHI < 0.52 , $n = 47$) was considered to have impaired endothelial function. Unexpectedly, this value was identical to the median LnRHI value in this study.

Fig. 2 showed the AF recurrence free curve divided into the high LnRHI group and low LnRHI group. Even during long-term observation, the high LnRHI group had less AF recurrence ($p = 0.043$, log-rank test) than the low LnRHI group.

Table 2
Heart rhythm during LnRHI measurement.

	All patients (n = 99)	SR (n = 61)	AF (n = 38)	p-value
Age	66 [56, 70]	67 [56, 71]	64 [56, 69]	0.65
Systolic blood pressure	122 [114, 136]	125 [110, 130]	120 [117, 130]	0.45
Diastolic blood pressure	74 [66, 82]	76 [70, 80]	70 [70, 80]	0.76
Heart rate	63 [55, 75]	59 [51, 64]	76 [64, 81]	< 0.001
LnRHI	0.52 [0.39, 0.73]	0.53 [0.40, 0.79]	0.51 [0.39, 0.69]	0.57
pAF	81 (81.8)	61 (100)	20 (52.6)	< 0.001
psAF	18 (18.2)	0 (0.0)	18 (47.4)	
AF recurrence	30 (30.3)	17 (27.9)	13 (34.2)	0.50

LnRHI, natural logarithmic transformation of reactive hyperemia peripheral arterial tonometry index; SR, sinus rhythm; AF, atrial fibrillation; pAF, paroxysmal atrial fibrillation; psAF, persistent atrial fibrillation.

Table 3
A Cox proportional hazards analysis.

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.99 (0.95–1.03)	0.54		
Female	2.28 (1.08–4.82)	0.031	3.06 (1.35–6.93)	0.007
Body mass index	1.03 (0.94–1.13)	0.47		
Hypertension	1.47 (0.62–3.44)	0.39		
Congestive heart failure	1.84 (0.56–6.10)	0.32		
Diabetic mellitus	1.39 (0.53–2.08)	0.51		
Old cerebral infarction	1.72 (0.23–12.8)	0.60		
Coronary artery disease	1.31 (0.31–5.50)	0.71		
CHA ₂ DS ₂ -Vasc score	1.00 (0.74–1.34)	0.98		
AF Duration	1.01 (1.00–1.02)	0.18	1.00 (0.99–1.01)	0.95
Brain natriuretic peptide	1.00 (1.00–1.00)	0.72		
Left atrial diameter	0.81 (0.50–1.44)	0.42		
LAVI	0.99 (0.96–1.02)	0.99		
Ankle brachial index	1.06 (0.017–67.8)	0.98		
LnRHI	0.13 (0.023–0.71)	0.018	0.087 (0.015–0.51)	0.007
psAF	1.67 (0.64–4.38)	0.30		
RFCA	2.04 (0.98–4.24)	0.055		

HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; LAVI, Left atrial volume index; LnRHI, natural logarithmic transformation of reactive hyperemia peripheral arterial tonometry index; psAF, persistent atrial fibrillation; RFCA, radiofrequency catheter ablation.

3.3. Relationship between LnRHI and AF duration

AF duration of the low LnRHI group was significantly longer and a negative correlation was seen for LnRHI and AF duration (correlation coefficient = 0.217, $p = 0.031$), in that LnRHI decreased as the duration of AF increased. LnRHI based on AF duration comparisons are shown in Fig. 3. To obtain similar group sizes, patients were divided into the following two groups according to the length of AF duration: short group (<12 months) and long group (≥ 12 months). Significant differences was observed between two groups ($p = 0.005$). Thus, vascular

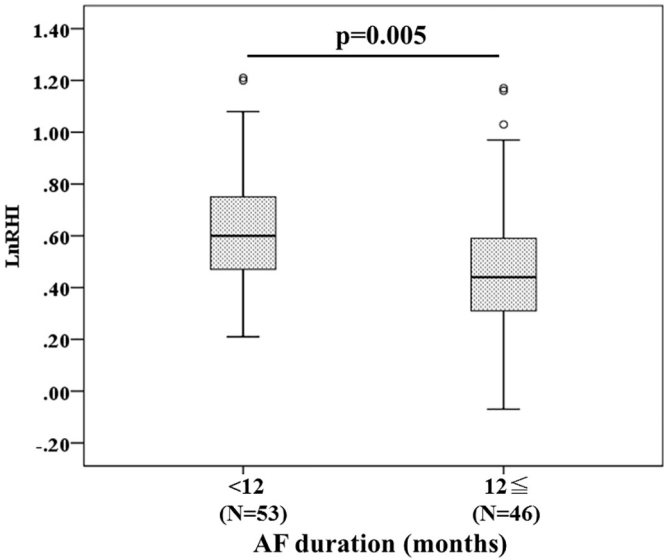


Fig. 3. Comparison of LnRHI according to atrial fibrillation duration. Horizontal lines represent the median, boxed areas are the interquartile range, and vertical whiskers represent the 10%–90% range. LnRHI: the natural logarithmic transformation of reactive hyperemia peripheral arterial tonometry index, AF: atrial fibrillation.

endothelial function became significantly decreased when AF duration exceeded 1 year.

4. Discussion

4.1. Major findings

This study showed that declined LnRHI was independently associated with AF recurrence after CA. In addition, LnRHI correlated significantly with the duration of AF and decreased with longer duration. Our results suggested that it was possible the prolonged AF duration reduced vascular endothelial function and increases AF risk after CA.

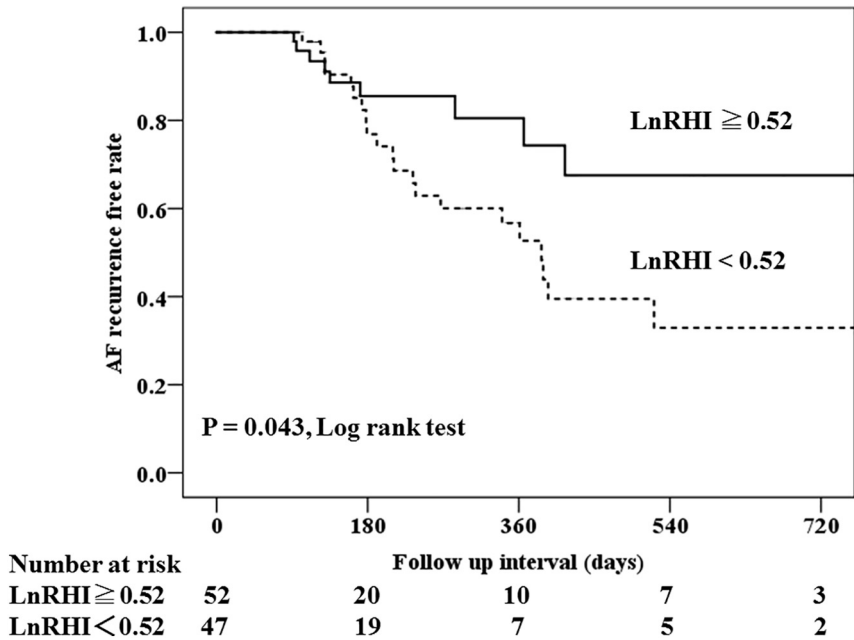


Fig. 2. Kaplan–Meier analysis for the probability of atrial fibrillation recurrence after catheter ablation according to baseline LnRHI. LnRHI: the natural logarithmic transformation of reactive hyperemia peripheral arterial tonometry index.

4.2. Vascular endothelial function and AF recurrence

Vascular endothelial dysfunction has been linked to an increased risk of AF occurrence [12,22], although their pathophysiological relationship remains unclear. LnRHI might suggest a premature dysfunctional vasculature because LnRHI had a negative correlation with blood pressure and hemoglobin A1c. Abnormal vascular endothelial function promotes local inflammation, with the resulting oxidative stress preventing the relaxation of vascular smooth muscle [26]. Such an increase in vascular resistance may overload the heart to cause AF.

It was also known that prolonged periods of AF affect vascular endothelial function. Okawa et al. described that persistent AF decreased RHI [21], which was corroborated by our finding of diminished LnRHI over longer durations of AF. LnRHI was significantly lower especially in patients with AF duration over 1 year than in those with shorter durations. Hence, it is conceivable that vascular endothelial function and AF are both the cause and result of each other.

4.3. Clinical advantage of LnRHI

Lerman et al. proposed RHI ≤ 1.67 (LnRHI ≤ 0.51) as a cut-off for the presence of vascular endothelial disorder based on clinical trials. However, the normal range of LnRHI remains unknown [27]. In this study, we defined LnRHI ≤ 0.52 as vascular endothelial dysfunction. This threshold was supported by the ROC curve analysis for the prediction of AF recurrence.

It is controversial for using EndoPAT to assess vascular endothelial function during AF. Previously, Okawa et al. measured RHI before and after cardioversion in 30 identical AF patients and reported that their values changed little [21]. In this study, as shown in Table 2, there was no difference in baseline LnRHI values between patients who were sinus rhythm at LnRHI measurement and those who were AF rhythm. Thus, patients with AF rhythm at RHI measurement were also analyzed using baseline LnRHI.

Previous studies have proposed other clinical indicators of AF recurrence. Winkle et al. reported that age, coronary artery disease, and LAD were predictive factors of AF events after ablation [28]. Kosiuk et al. described that DM, LAD ≥ 45 mm, and age ≥ 65 years were associated with left atrial low-voltage areas [29]. These clinical indicators may also be important in predicting the recurrence of AF.

There is also a method of measuring flow-mediated dilatation (FMD) as an evaluation of vascular endothelial function, and it was reported that recurrence rate of AF after CA was low in patients with maintained FMD [20]. However, FMD measurement requires techniques to visualize arteries with echoes. Since there are variations in measurement results among examiners, long-term training is needed to obtain good reproducibility [30]. In that respect, RHI measurement by EndoPAT 2000 device only requires to attach the dedicated probe at the fingertip, so no special training for the examiner is required and stable reproducibility can be obtained. Therefore, RHI measurement is considered to be an available test in many medical institutions.

4.4. Limitations

This study had several limitations. First, this was a small observational study that might have included a sampling bias. Therefore, in multivariate Cox regression analysis, items such as HT, DM, AF duration and LAD did not become predictors of AF recurrence; validation is needed in a larger cohort. Second, it was still unclear if EndoPAT actually evaluate endothelial or micro vascular physiology strictly. If biomarkers such as nitric oxide, endothelin, and vascular endothelial growth factor, which were suggestive of vascular endothelial dysfunction, had been evaluated, it might be considered that decline in RHI was associated with vascular endothelial dysfunction [31]. Third, whether EndoPAT can be used to assess vascular endothelial function during AF as well as during sinus rhythm has not been verified. Wong et al. reported

that although the peripheral arterial tonometry (PAT) values were uneven in short-time measurement during AF, the coefficient of variation of the value becomes smaller if recording ≥ 1 min [23]. As the PAT measurement was performed for 5 min after the cuff was released in this study, we considered that the LnRHI value could be determined as in sinus rhythm. Fourth, LnRHI was measured only once. If vascular endothelial function had also been evaluated after CA, the effects of CA might have been more evident by comparing the values of AF and non-AF recurrence cases. Fifth, quantitative data on exercise tolerance of patients before and after catheter ablation were not collected. Changes in exercise tolerance due to maintenance of sinus rhythm might affect vascular endothelial function. Lastly, several ablation methods were used in this study. In the case of BA, only EEPVI was performed and ablation targeting non-pulmonary vein foci was not included. However, in all cases, the same conditions were eventually estimated at the end of the procedure, as AF was not induced by isoproterenol administration and atrial burst pacing after ablation.

5. Conclusion

This study showed that AF recurrence after CA was associated with LnRHI decline. Specifically, LnRHI decreased significantly when AF duration exceeded 1 year. Our results indicate that a significant relationship between AF recurrence after CA and that vascular endothelial dysfunction based on LnRHI measurement, and that long duration of AF affects vascular endothelial function.

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Declaration of Competing Interest

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