


Correlation of the peak oxygen consumption and ventilatory aerobic threshold by cardiopulmonary exercise testing with atrial fibrillation recurrences after ablation in patients with paroxysmal atrial fibrillation

Daiki Yamashita PT¹ | Shigeshi Kamikawa MD²  | Ryou Tanaka PT¹ |
Natsumi Tabita ET¹ | Saori Nishimura ET¹ | Miyuki Mitsuoka Ns¹ |
Shunich Higashiya MD³ | Hirosuke Yamaji MD² | Takashi Murakami MD¹ |
Kazuyoshi Hina MD² | Shozo Kusachi MD²

¹Division of Cardiovascular Rehabilitation, Okayama Heart Clinic, Okayama, Japan

²Cardiovascular Center, Okayama Heart Clinic, Okayama, Japan

³Heart Rhythm Center, Okayama Heart Clinic, Okayama, Japan

Correspondence

Shigeshi Kamikawa, Cardiovascular Center, Okayama Heart Clinic, Takeda 54-1, Naka-Ku, Okayama 703-8251, Okayama, Japan.
Email: s-kamikawa@okayama-heart.com

Abstract

Background: The cardiopulmonary function is hypothesized to be associated with atrial fibrillation/atrial tachyarrhythmia (AF/AT) recurrence after AF ablation.

Purpose: To clarify the relationship between the cardiopulmonary function after successful ablation and AF/AT recurrence.

Methods: We examined 31 patients with paroxysmal AF who underwent AF ablation. Cardiopulmonary exercise testing (CPET) was performed at 1 month after the ablation. A continuously increasing loading method on a bicycle ergometer was employed for the CPET.

Results: No adverse events, including AF/AT recurrence, occurred during the CPET. Among 31 patients, AT/AF recurrence was observed in seven (23%). The ventilatory anaerobic threshold (VAT) and peak oxygen consumption (VO₂) were significantly higher in patients without AF/AT recurrence than in those with AT/AF recurrences (peak VO₂ 23.6 ± 5.7 vs 17.2 ± 4.1 mL/kg/min; VAT, 16.7 ± 2.8 vs 13.8 ± 2.7 mL/min/kg). The areas under the receiver operating characteristic curve for the peak VO₂ and VAT were 0.786 ($P < .01$) and 0.789 ($P < .01$), respectively. Both indices had a sensitivity of 70%–80% and specificity of 70%–80% for predicting AT/AF recurrence. Similar results were obtained for the percent values of the predicted peak VO₂ and VAT.

Conclusions: The present pilot study found that CPET can be performed safely at approximately 1 month after AF ablation. The peak VO₂ and VAT were significantly associated with AT/AF recurrence. The peak VO₂ and VAT were thought to provide helpful information regarding AT/AF recurrence.

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KEYWORDS

cardiopulmonary function, exercise, irrigated catheter, outcome, percutaneous catheter treatment, radiofrequency energy, reoccurrence, supraventricular tachyarrhythmia

1 | INTRODUCTION

Cardiopulmonary exercise testing (CPET) has been applied for evaluating the prognosis and risk stratification of pathological conditions in various heart diseases.^{1,2} The concept, methodology, and physiologic basis have been well established.³ Among the various indices obtained by CPET, the peak oxygen uptake (Peak VO₂) and ventilatory anaerobic threshold (VAT) have been widely used for the evaluation of the pathophysiology of various heart diseases as well as the physical activity in healthy individuals.

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a significant impact on the morbidity and mortality.⁴ Catheter ablation is now widely applied for the treatment of AF, and the number of ablation methods is increasing.^{5,6} Although for symptomatic paroxysmal AF patients, pulmonary vein isolation (PVI) has provided a high success rate and is generally accepted, AF and atrial tachyarrhythmia (AT) recur in certain patients.⁴ AF/AT recurrence is thus still a major problem associated with AF ablation.

Much evidence has shown that the cardiopulmonary function is correlated with the disease severity in connection with patients' prognosis.^{7,8} We hypothesized that the cardiopulmonary function evaluated by CPET, especially the peak VO₂, VAT, minute ventilation-carbon dioxide production relationship (VE/VCO₂) at VAT, and VO₂-work rate relationship ($\Delta\text{VO}_2/\Delta\text{WR}$) may be associated with AF recurrence after ablation. There have, however, been no reports that have examined relationships between these indices of CPET and the AF ablation outcomes. Accordingly, we performed CPET after AF ablation in patients with paroxysmal AF and determined the association of the CPET results with AF/AT recurrence.

2 | METHODS

2.1 | Patients

A single-center, retrospective study was conducted at the Okayama Heart Clinic, Okayama, Japan. We performed CPET in 31 consecutive paroxysmal AF patients (69 ± 10 years; men 24, women 7) who underwent their first AF ablation from September 2016 to November 2017. The examination procedure complied with the rules of the Declaration of Helsinki, and the study was approved by the Institutional Ethics Committee of Okayama Heart Clinic for Human Research. Written informed consent for the use of clinical data without personal information was obtained from the patients.

2.2 | Ablation

The methods of PVI were described elsewhere in detail.^{9,10} PVI was performed with the double Lasso technique using an electroanatomical integration mapping system (Ensite-NavX System, Abbott Laboratories). Ablation was carried out using an open-irrigated ablation catheter (CoolFlex™/FlexAbility™, Abbott Laboratories) via a steerable sheath. Irrigated radiofrequency (RF) energy was delivered point by point for 20 s until the maximal local electrogram amplitude decreased by 70% with a target temperature of 43°C, a maximal power limit of 35 W (20–30 W for the posterior wall ablation and 30–35 W for the anterior wall ablation), and an infusion rate of 13 mL/min via the irrigated ablation catheter. The endpoint of PVI was defined as follows: (a) elimination of the pulmonary vein (PV) potentials recorded by the two ring catheters within the ipsilateral PVs and the lack of left atrial (LA) capture during intra-PV, isthmus, and PV atrium pacing and (b) no recurrence of PV spikes within all the PVs after an intravenous bolus administration of 20–40 mg of adenosine triphosphate during sinus rhythm or coronary sinus pacing at least 30 minutes after the isolation. PVI was finally established.

After PVI, we performed the provocation test for the non-PV foci in all patients. A high dose of isoproterenol (10 mg/min) was intravenously infused. If the non-PV focus was not provoked, rapid atrial pacing (20 beats, 300–180 ms) from the left and right atrium was performed under isoproterenol. Non-PV focus was defined as the atrial ectopic beat that initiated AF or more than three consecutive short-run atrial ectopic beats. In case of induction of the non-PV focus, additional ablation was performed. The criteria for the successful ablation of the non-PV focus were the elimination of the atrial ectopic beats during ablation, non-induction of AF/AT under isoproterenol, and rapid atrial pacing after ablation.

2.3 | CPET

All patients underwent symptom-limited CPET on a bicycle ergometer (StrangthErgo8, Mitsubishi Electric Engineering Co., Ltd.). CPET was carried out at 1 month after the ablation when the patients visited our outpatient clinic for their second arrhythmia check and another medical status. CPET was performed at 9:30–10:30 AM or 2:30–4:00 PM essentially according to the scientific statement in a purpose-designed room.^{1,3} Using a bicycle ergometer, the exercise intensity was continuously increased by 5, 7, or 10 watts/min of the ramping up rate after 5, 7, and 10 watts, respectively, for a 4 minutes warm-up period. The exercise program depended on the patient's condition in addition to age, sex, and body weight. The exercise was planned to be completed within

8-12 minutes. The bicycle pedal rotation speed was set at 60 cycles/min. The minute ventilation (VE), oxygen uptake (VO₂), and carbon dioxide production (VCO₂) were monitored continuously using a respiratory mass spectrometer with a breath-by-breath method (CPex1, OG Wellness). The moving average of the VO₂ for 8 seconds was continuously calculated from the instantaneously detected VO₂. Surface standard 12-lead electrocardiography was also continuously monitored (cardimax8 FX-8800, Fukuda Denshi). The forearm blood pressure was determined every 15 minutes by the Cuff-Oscillometric Method with Korotkoff Sound Technique (TangoM2, SunTach Medical, respectively). The termination criteria for the CPET were (a) intolerance of exercise and (b) slowing down of pedal rotation speed to 55 cycle/min by the patient.

The peak VO₂ was obtained from the VO₂ (mL/min) curve to the exercise time curve, and the AT points were determined by established methods using criteria.^{11,12} The percent values of the predicted peak VO₂ and VAT were also obtained from the reported age- and sex-matched healthy population.¹³ The VE/VCO₂ at the VAT and $\Delta\text{VO}_2/\Delta\text{WR}$ were also used for the analyses.

2.4 | Postablation care and follow-up, and the definition of AT/AF recurrence

The complications were checked during the ablation and postablation. All previously ineffective antiarrhythmic drugs were withdrawn just after the ablation. After the procedure, anticoagulation therapy was continued for at least 3 months after the AF ablation in both groups. After discharge, follow-up was performed at our clinic at 2 weeks and 1, 3, and 12 months after the AF ablation in all patients. Thereafter, a check-up was performed every 6 months in all patients. During the follow-up, the surface electrocardiograms and transthoracic echocardiography were performed. Furthermore, all patients wore a telemetry electrocardiogram recording device (Omron Co., Ltd.) after every follow-up to monitor symptomatic arrhythmias or to transfer the electrocardiogram once a week if asymptomatic. AF/AT recurrence was defined as any supraventricular tachycardia (AF and/or AT) lasting >30 seconds.

2.5 | Statistical analysis

The statistical analyses were performed using R version 3.2.2 (R Foundation for Statistics Computing). The Student t test was used to compare the data between the AF nonrecurrence and recurrence groups. In accordance with the sample size, a Shapiro-Wilk test and histogram were used to determine whether the distribution pattern involved a normal probability distribution including the AF recurrence group. A Smirnov-Grubbs test was performed for the outlier detection in each group's data. The homogeneity of variance was checked using the F-test. Fisher exact tests with 2 × 2 tables, with a two-tailed test for categorical variables, were used to compare the two groups. The area under the curve (AUC) was obtained by analyses of the receiver operating characteristic

(ROC) curves to determine the CPET indices for distinguishing between AF/AT recurrence and nonrecurrence. The optimum cutoff point was determined as the value that minimized the distance from the upper left corner of the plot frame. The data are expressed as means ± 1 standard deviation. Differences with $P < .05$ were considered significant.

3 | RESULTS

3.1 | Ablation

All patients assessed met the ablation completion criteria. Hypotension and/or bradycardia that suggested ganglionated plexi ablation did not occur in both groups. The procedural time, fluoroscopic time, and RF energy delivery durations were 103 ± 19, 36.1 ± 8.1, and 21.4 ± 7.4 minutes, respectively. In two patients, the non-PV focus was elicited. The non-PV focus was located at the LA septum and anterior wall of the LA, provoked by rapid pacing, and successfully ablated. No major complications, such as thromboembolic or major bleeding, occurred. No AF recurred in any of the patients during the CPET, and all patients completed the CPET without any notable adverse events.

3.2 | Data distribution

A normal data distribution in each group, especially in the AF/AT recurrence group, was confirmed by a Shapiro-Wilk test. No outliers were detected by the Smirnov-Grubbs test in either of the two groups.

3.3 | Comparison of background characteristics between patients with and without AF recurrence

Among the 31 patients, AF/AT recurrence was observed in 7 (23%). Table 1 summarizes the results of the comparison of the clinical and echocardiographic features evaluated before ablation during sinus rhythm between the AF/AT nonrecurrence and recurrence groups. There were no significant differences in either the clinical and echocardiographic features between the two groups. Two patients with extra-PV focus were not associated with AF/AT recurrence.

3.4 | Comparison of CPET indices between patients with and without AF/AT recurrence

Comparisons of the CPET indices between the AF/AT nonrecurrence and recurrence groups are summarized in Table 2. The typical results of the peak VO₂ and VAT are shown in Figure 1.

The AF/AT nonrecurrence group had a significantly higher peak VO₂, VAT, % peak VO₂, and % VAT than the AF/AT recurrence

TABLE 1 Comparison of clinical characteristics and echocardiographic parameters between patients with and without AF recurrence

	AF nonrecurrence	AF recurrence	P	Total
n	24	7		31
Age	68.2 ± 9.6	67.3 ± 10.3	0.843	67.9 ± 9.6
Sex (female:male)	5:19	3:04	0.335	8:23
Body height	168.1 ± 8.3	160.5 ± 12.1	0.064	166.5 ± 9.6
Body weight	69.6 ± 13.2	62.0 ± 9.0	0.167	67.9 ± 12.6
BMI	24.4 ± 3.0	24.0 ± 2.1	0.775	24.3 ± 2.8
Smoking habit n (%)	2 (8)	1 (14)	0.550	3 (10)
Diabetes mellitus n (%)	5 (21)	1 (14)	1.000	6 (19)
Hypertension n (%)	17 (71)	2 (29)	0.076	19 (61)
Hyperlipidemia n (%)	7 (29)	1 (14)	0.642	8 (26)
Ischemic heart disease n (%)	1 (4)	0 (0)	1.000	1 (3)
Cerebrovascular disease n (%)	2 (8)	1 (14)	0.550	3 (10)
Hyperuricemia n (%)	4 (17)	0 (0)	0.550	4 (13)
Respiratory disease	0 (0)	0 (0)	1.000	0 (0)
LA	40.3 ± 6.9	37.8 ± 8.7	0.440	39.7 ± 7.2
LAVI (mL/m ²)	31.6 ± 11.5	31.1 ± 12.7	0.929	31.5 ± 11.5
E/e'	11.9 ± 3.6	12.7 ± 3.4	0.639	12.1 ± 3.5
DCT (ms)	232 ± 54	198 ± 48	0.142	224 ± 52
LVEF	66.2 ± 8.5	66.5 ± 9.4	0.440	66.3 ± 8.6
ACEI/ARB n (%)	7 (29)	3 (43)	0.652	10 (14)
Ca blocker n (%)	10 (42%)	2 (29)	0.676	12 (39)
β blocker n (%)	5 (21)	2 (29)	0.642	7 (23)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; DCT, deceleration time; LA, left atrium; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction.

TABLE 2 Comparison of CPX indices between patients with and without AF recurrence

	AF nonrecurrence	AF recurrence	P	Total
n	24	7		31
Peak VO ₂ (mL/kg/min)	23.6 ± 5.7	17.2 ± 4.1	.009	22.2 ± 6.0
Percent of predicted peak VO ₂	98.0 ± 19.3	75.7 ± 20.4	.013	93.0 ± 21.4
VAT (mL/kg/min)	16.7 ± 2.8	13.8 ± 2.7	.022	16.0 ± 3.0
Percent of predicted VAT	115.2 ± 17.0	96.0 ± 20.2	.017	110.9 ± 19.2
VE/VCO ₂ at VAT	26.8 ± 6.4	28.5 ± 3.8	.508	27.2 ± 5.9
ΔVO ₂ /ΔWR	11.8 ± 2.0	10.2 ± 2.0	.070	11.4 ± 2.0

Abbreviations: VAT, ventilatory anaerobic threshold; VCO₂, carbon dioxide production; VE, minute ventilation; VO₂, oxygen uptake; WR, work rate.

group. There were no significant differences in the VE/VCO₂ at the VAT and ΔVO₂/ΔWR between the two groups.

3.5 | ROC analysis

The results of the ROC curve analyses are summarized in Table 3. The ROC curve for the peak VO₂ and VAT are shown in Figure 2. The AUC for the peak VO₂, % peak VO₂, VAT, and %VAT exhibited a similar area, 0.78-0.83 (standard error [SE] 0.07-0.11; 95% confidence interval [CI], 0.5-0.99; P < .001), which indicated that these

indices can be useful for distinguishing AF/AT recurrence from nonrecurrence. The specificity-sensitivity curve indicated that a 70%-85% specificity and 67%-80% sensitivity were obtained with each cutoff for distinguishing recurrence from nonrecurrence.

4 | DISCUSSION

To the best of our knowledge, the present pilot study is the first to report that cardiopulmonary function achieved after successful AF ablation was significantly associated with AF/AT recurrence.

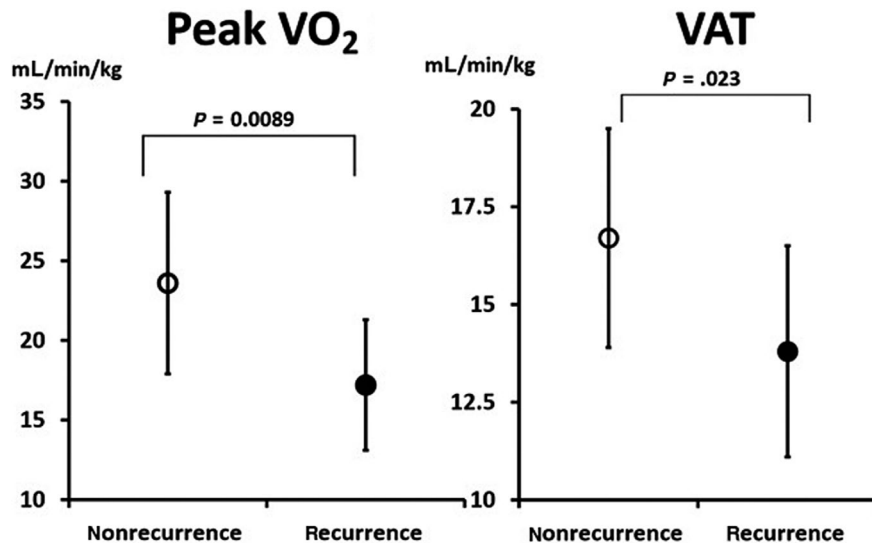


FIGURE 1 Comparison of the VAT and peak VO₂ between the patients with and without AF/AT recurrence. The error bars indicate one standard deviation. AF, atrial fibrillation; peak VO₂, peak oxygen consumption; VAT, ventilatory anaerobic threshold

TABLE 3 Results of receiver operating characteristic curve (ROC) analyses

Measurements	AUC	SE	95% confidence interval		P	Sensitivity	Specificity	Cut-off value
			Lower limit	Upper limit				
Peak oxygen content (PVo ₂)	0.839	0.074	0.694	0.985	<.001	0.857	0.75	21.2
Percent PVo ₂	0.786	0.105	0.58	0.992	.00066	0.714	0.75	83
Peak VO ₂ /BMI	0.827	0.076	0.68	0.975	<.001	0.857	0.703	0.87
Ventilatory anaerobic threshold (VAT)	0.789	0.069	0.614	0.964	.0012	0.86	0.67	16.5
Percent VAT	0.765	0.111	0.547	0.983	.0171	0.714	0.792	104
Minute ventilation/carbon dioxide output ratio (VE/Vco ₂) at VAT					NS (.106)			
ΔVO ₂ /ΔWR	0.744	0.106	0.536	0.952	.0213	0.714	0.337	11.25

Abbreviations: AUC, area under the curve; P, probability value; SE, standard error.

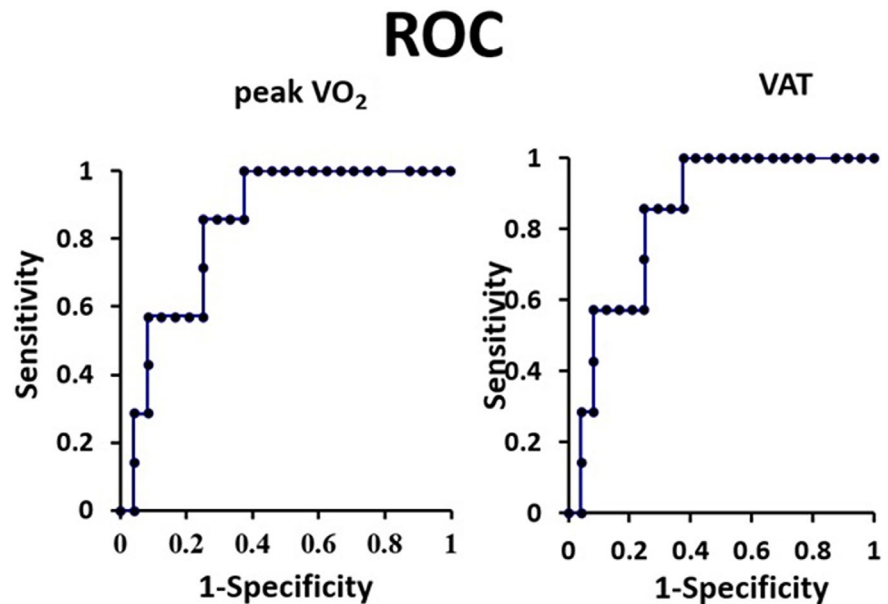
The present method of AF ablation has been well established.⁴ Our procedural ablation parameters; the procedural times, RF energy delivery time and fluoroscopy time, were within acceptable ranges.⁹ Furthermore, the AF/AT recurrence rate was acceptably low. The CPET was performed with well-established methods essentially in accordance with the CPET guidelines.^{2,3} We increased the load continuously, not stepwisely, with a ramp-up manner to obtain smooth VO₂ and VCO₂ curves. Those considerations enabled further discussion.

All patients completed the CPET in the present study. To the best of our knowledge, there have been no reports regarding CPET after AF ablation, and the present results cannot be compared to previously reported findings. Much evidence has shown that the autonomic nervous function plays a significant role in AF pathogenesis, including paroxysmal AF.^{14,15} It is well known that the parasympathetic nervous tone rapidly decreases, and sympathetic nervous activity conversely increases and reaches the maximal tone in response to a workload.¹⁶ It can be assumed that AF/AT recurrence may occur during CPET with an increase in the

sympathetic nervous tone after AF ablation. However, AF/AT did not recur during CPET in any patient at 1 month after ablation. AF ablation may affect the autonomic function. Numerous autonomic nerves are present in the PV-LA junction. Strong colocalization of adrenergic and cholinergic nerves has been demonstrated there.¹⁴ Because of the colocalization of both nerves, PVI did not result in the selective sympathetic or parasympathetic nerve ablation. These reported findings indicate that PVI may not affect the balance of the sympathetic and parasympathetic autonomic function. In addition, PVI was confirmed by electrophysiologic determination. The present results of the nonrecurrence of AF/AT during the CPET indicated that reconnections through the ablation lines did not occur because of an increment in the sympathetic nervous tone during the CPET. Furthermore, the present study firstly showed that CPET can be performed safely at 1 month after AF ablation.

We found a significant correlation between the peak VO₂ and VAT and AF/AT recurrences. The present study did not primarily deal with the mechanisms of the significant relationship between the reduced cardiopulmonary function and AF/AT recurrence, and

FIGURE 2 Results of the ROC analysis for the % peak VO₂ and VAT to distinguish patients with AF/AT recurrence from those without. AF, atrial fibrillation; AU, area under the curve; peak VO₂, peak oxygen consumption; ROC, receiver operating characteristic curve; VAT, ventilatory anaerobic threshold



the mechanisms were thus unclear. There has been much evidence that inflammatory processes play a significant role in the development of AF.¹⁷ The mechanism of AF recurrence is complicated and still under clarification. PVI performed by electrical energy applications evokes tissue damage, and causes systemic and local inflammatory processes.¹⁸ The inflammatory processes in response to tissue injury have been reported to be associated with AF/AT recurrence.¹⁹ Furthermore, the exercise capacity has been well demonstrated to be inversely correlated with the inflammatory severity in many diseases.^{20,21} These lines of evidence suggest that a preserved exercise capacity may, at least, partly account for the inverse correlation with the AF/AT recurrence after the ablation observed in the present study.

The ROC analyses showed the AUC for the peak VO₂ and VAT was >0.75 with a sensitivity and specificity of about 70%. The results indicated that the peak VO₂ and VAT could be clinically useful for the prediction of AF/AT recurrences after AF ablation. Again, no previous studies have studied the cardiopulmonary function using the CPET for the prediction of AF/AT recurrences after AF ablation for comparison with the present results. However, LA function and volume have been extensively evaluated with respect to AF/AT recurrence by analyses of images obtained by cardiac ultrasound methods, computed tomography, and magnetic resonance.²²⁻²⁶ Substantial differences in the predictive value of the LA volume and indices among the reported studies have been noted. The present study did not find any significant differences in the cardiac ultrasound indices between the patients with AF/AT nonrecurrence and recurrence. The reasons for the disagreement were obscure. LA diameter and volume index as well as LV ejection fraction in the patients examined showed a relatively narrow distribution. Furthermore, these indices were within the normal ranges in a large proportion of the patients. These would account for this disagreement. Nevertheless, the present study suggested

that the cardiopulmonary function obtained by CPET was thought to have similar or superior predictive values for AF/AT recurrence after ablation.

The Framingham heart study found that advanced age, female sex, diabetes mellitus, hypertension, congestive heart failure, and valvular disease are risk factors for AF. The cardiopulmonary function is thought to be reduced in association with these pathological conditions. It can be presumed that CPET may be sensitive for evaluating the pathophysiological conditions of these risk factors for AF. This assumption may thus partly account for the relationships between the indices involving the CPET, peak VO₂ and VAT, and AF/AT recurrence. The present study did not find significant correlations between hypertension or hyperlipidemia and AF/AT recurrence. The small number of patients examined and treatment intervention with lifestyle modification may make these correlations reported by Framingham's study obscure. Nevertheless, the present results indicated that the cardiopulmonary function was associated with AF/AT recurrence after ablation.

We performed CPET at 1 month after AF ablation, not before ablation. CPET initially induces reduction in parasympathetic nerve function followed by an increase in sympathetic nerve activity, and the activity plateaus.¹⁶ Enhancement of sympathetic nervous activity is known to evoke AF occurrence. Therefore, maximal exercise by CPET is considered inadequate for paroxysmal AF patients. When CPET induces AF, accurate evaluation of peak VO₂ as well as VAT is impossible. On the basis of these reasons, we did not perform CPET before ablation. As described above, strong colocalization of adrenergic and cholinergic nerves in the LA-PV junction and PVI may not affect the balance between sympathetic and parasympathetic autonomic function. These considerations indicated that CPET performed at 1 month after ablation can be analyzed.

5 | LIMITATIONS

The present study had several limitations. First, it included a relatively small number of patients. We performed statistical analyses carefully. Furthermore, the uniform ablation technique and CPET procedures performed with experience and skill in a single center may have addressed this limitation. However, the present results warrant the need for further studies with a greater number of patients to confirm the present results. Second, as aforementioned, CPET could not be performed before ablation, so we could not provide information about preoperative cardiopulmonary reserve. Cardiac swelling caused by ablation, which correlates with underlying histological changes, recovers within 1 month after ablation.^{27,28} Thus, CPET measured at 1 month after ablation is thought to be available to clarify the relationship between CPET indices and AF/AT recurrence. We found a positive relationship between CPET indices obtained within 1 month after ablation and AF/AT recurrence. In addition, the lack of preablation CPET did not affect the present study's results. Hence, we do not consider the lack of data of CPET before ablation as a deficit of the present study.

6 | CONCLUSIONS

The present study first found that CPET can be performed safely at approximately 1 month after AF ablation. The cardiopulmonary function, peak VO₂, and VAT determined after a successful AF ablation were significantly associated with AF/AT recurrence. The VO₂ and VAT were thought to provide useful information regarding AF/AT recurrence.

CONFLICT OF INTEREST

The authors declare no conflict of interests for this article.

ORCID

Shigeshi Kamikawa  <https://orcid.org/0000-0002-4801-0246>

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