Clinical impact of right ventricular-pulmonary artery uncoupling on predicting the clinical outcomes after catheter ablation in persistent atrial fibrillation patients

Masamichi Yano, Yasuyuki Egami, Kohei Ukita, Akito Kawamura, Hitoshi Nakamura, Yutaka Matsuhiro, Koji Yasumoto, Masaki Tsuda, Naotaka Okamoto, Yasuharu Matsunaga-Lee, Masami Nishino*, Jun Tanouchi

Division of Cardiology, Osaka Rosai Hospital, 3-1179 Nagasonecho, kita-ku, Sakai, Osaka 591-8025, Japan

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ABSTRACT

Background: Right ventricular (RV)-pulmonary artery (PA) uncoupling is associated with poor outcomes in heart failure patients. We aimed to elucidate the relationship between RV-PA uncoupling and late arrhythmia recurrence after ablation in persistent atrial fibrillation (PerAF) patients whose phenotypes have impaired right ventricular function and pulmonary hypertension.

Methods: The present study included 203 PerAF patients from the Osaka Rosai Atrial Fibrillation ablation (ORAF) registry who underwent an initial ablation. We assigned the patients based on the value of tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio that could predict late recurrence of AF/atrial tachycardia (LRAF) as an indicator of RV-PA uncoupling. We evaluated the following factors: the difference in the relationship between TASPE/PASP before ablation and incidence of LRAF among the 2 groups stratified by TAPSE/PASP based on the above cut-off value and TAPSE/PASP change from before to one-year after ablation.

Results: A receiver operating characteristic curve analysis revealed a good accuracy of predicting LRAF by TAPSE/PASP ratio with a cutoff of 0.57. The patients with TAPSE/PASP ratios ≤0.57 had a significantly greater LRAF risk than TAPSE/PASP ratios > 0.57. A multivariate Cox proportional hazards analysis showed that TAPSE/PASP (HR 0.12, 95% CI; 0.019–0.724, p = 0.026) was independently and significantly associated with LRAF. The TAPSE/PASP significantly improved more one-year after the ablation than before (p = 0.016).

Conclusion: RV-PA uncoupling was independently associated with LRAF, independent of left atrial function, and significantly improved more one-year after the ablation than before in PerAF patients.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is associated with considerable morbidity and mortality [1]. Pulmonary vein isolation (PVI) has become widely established as a standard therapy for patients with drug-refractory paroxysmal atrial fibrillation (PAF) and short lasting persistent atrial fibrillation (PerAF) [2–3]. PerAF accounts for approximately 50% of all atrial fibrillation (AF) cases and is associated with a higher stroke and mortality risk than those with PAF [4–5]. AF and heart failure with preserved ejection fraction (HFpEF) are age-related conditions that are increasing in prevalence, commonly coexist, and share clinical features [6–7]. HFpEF is a heterogeneous syndrome with diverse etiologies and pathophysiological factors, and those phenotypes have impaired right ventricular dysfunction, pulmonary hypertension (PH) and high AF burden. PH related to left heart diseases, such as HFpEF, is the most common form, classified as post-capillary or Group 2 PH, and PH is associated with AF occurrence and paradoxical embolism [8–9]. When AF becomes permanent, afflicted patients display severe atrial dysfunction and abnormal right ventricular–pulmonary vascular coupling as compared to patients with HFpEF in sinus rhythm [10–11]. While left atrium (LA) compliance and mechanics progressively decline with increasing AF burden in HFpEF patients and these changes promote the development of right heart failure and worsening pulmonary vascular disease. Tricuspid annular
plane systolic excursion (TAPSE) / pulmonary artery systolic pressure (PASP) assessed with echocardiography is a useful clinical index of right ventricular (RV) function [12–13]. In the present study, we aimed to elucidate the relationship between RV-pulmonary artery (PA) uncoupling and the clinical outcomes after post-ablation in persistent AF (PerAF) patients who are mainly classified as Group 2 PH.

2. Methods

2.1. Study population

PerAF patients who underwent an initial ablation were enrolled between May 2017 and September 2020 from the ORAF (Osaka Rosai Atrial Fibrillation ablation) registry [14–16]. In the present study, PerAF was defined as AF persisting for more than 1 week. All patients received a detailed informed consent and the study protocol was approved by the hospital’s institutional review board. The procedure was in accordance with the ‘Declaration of Helsinki’ and the ethical standards of the responsible committee on human experimentation. This study was granted an exemption from requiring ethics approval by Osaka Rosai Hospital Ethics Committee because this study was a retrospective observational study and the permission for using the clinical data were obtained from all study patients on admission.

2.2. Echocardiography study

All patients underwent transthoracic echocardiography (TTE) before catheter ablation. The TTE was performed with a 2.5 MHz multplane probe and live images were interpreted by experienced physicians who were blinded to the outcome of the ablation. Comprehensive echocardiographic examinations were performed by trained cardiac sonographers according to the American Society of Echocardiography guidelines [17]. The LA volume (LAV) was measured by the modified Simpson method and LAEF was calculated as (LA end-diastolic volume [LAEDV] – LA end-systolic volume [ LAESV]) / LAEDV × 100. LAV index (LAVI) was calculated as LAV/body surface area. The right ventricular fractional area change (FAC) and TAPSE measurements were acquired from the left apical 4-chamber view. The TAPSE measurement was obtained from 2D cine loops by drawing a line from the lateral tricuspid valve annulus to the right ventricular apex at end-diastole. For the FAC calculation, measurements of right ventricle area were obtained by tracing the right ventricular endomyocardial border at end-diastole and end-systole, excluding the papillary musculature. PASP was calculated as follows: 4 × [peak velocity of tricuspid regurgitation (TR)]² + [estimated right atrial pressure], with the pressure measurement based on the inferior vena cava diameter and collapsibility. The details of the measurement of TAPSE/PASP in our group have been published previously [18]. Patients without noticeable TR signal or lacking either inspiratory/expiratory phases of inferior vena cava diameters were excluded. Echocardiographic parameters during AF rhythm were acquired where the two preceding cardiac cycles had similar R-R intervals and preferably where the average heart rate was < 100 beats per minute. Transesophageal echocardiography prior to the ablation was performed to exclude any LA or LA appendage thrombi.

2.3. Ablation procedure

All antiarrhythmic drugs (AADs) were discontinued for at least 3 weeks before the ablation. Anticoagulation therapy was started at least 3 weeks before the ablation procedure. Details of the catheter ablation in our laboratory have been published previously [14–16]. One circular mapping catheter was deployed in the superior and inferior pulmonary veins and the left-sided then right-sided ipsilateral pulmonary veins (PVs) were circumferentially ablated guided by three-dimensional left atrium mapping (CARTO3, Biosense-Webster, Diamond Bar, CA, USA). The PVI was performed with a 3.5 mm ablation catheter with an externally-irrigated tip (ThermoCool® SmartTouch® Catheter, Biosense-Webster, Diamond Bar, CA, USA). The ablation procedures performed between May 2017 and July 2018 were contact force (CF)-guided, whereas those between August 2018 and September 2020 were ablation index (AI)-guided. After the PV isolation, the induction of non-PV triggers was performed using iso-proterenol and/or adenosine triphosphate. Reproducible non-PV triggers were ablated. Additional ablation, including left atrial posterior wall isolation or superior vena cava isolation, was performed at the operator’s discretion. At the end of the procedure, dormant conduction of the PVs was examined with a rapid injection of 40 mg of adenosine triphosphate. Additional ablation at the dormant conduction site was performed if necessary.

2.4. Follow-up and clinical outcomes

The patients underwent continuous electrocardiogram (ECG) monitoring for approximately 3 days (until discharge) after the ablation. They visited private clinics or our cardiology clinic every 2–4 weeks after the ablation. Patients were encouraged to have smartphone or tablet applications and check their pulse rate and rhythm every day and to visit our hospital if they experienced palpitations or other symptoms. The follow-up visits included a clinical interview, ECG, blood examination, 24 h Holter monitoring or portable ECG (2 week cardiac event recording), and TTE. Patients with palpitations or other chest symptoms underwent a portable ECG. Late recurrence of AF / atrial tachycardia (LRAF, 3 months after the ablation) was defined as AF/AT documented on the ECG or AF/AT continuing longer than 30 s on the Holter or portable ECG.

The following factors were investigated. 1) The cut-off value of TAPSE/PASP for predicting LRAF was determined by receiver operating characteristic (ROC) curve analysis. 2) The difference in the relationship between TAPSE/PASP before ablation and the incidence of LRAF among the 2 groups stratified by TAPSE/PASP based on the above cut-off value. 3) The change in the echocardiographic parameters including TAPSE/PASP measured from before to one-year after ablation.

2.5. Statistical analysis

JMP 15 statistical software (SAS Institute Inc., Cary, North Carolina, USA) was used for the statistical analysis. Continuous variables were expressed as median [interquartile range]. Normality test was done for continuous variables by Shapiro-Wilk W test. Normal distribution was not confirmed in all variables. Two-group comparisons were analyzed by Mann-Whitney U test for continuous variables. Paired data was analyzed by Wilcoxon signed-rank test. Categorical data were expressed as the number (percentage) and were compared using the chi-square test or Fisher’s exact test for categorical variables. Kaplan-Meier curves were used for the incidence of the LRAF and the statistical significance was determined using the Log-rank test. A Cox proportional hazards analysis was performed to compare the hazard ratio of LRAF after ablation between the two groups. It was performed using covariates of the clinical importance as follows: age, gender, brain natriuretic peptide (BNP), LAVI, E/e’, and TAPSE/PASP. The hazard ratios per one unit increase are presented in continuous variables (age, BNP, LAVI, septal E/e’ and TAPSE/PASP). A value of p < 0.05 was considered to be statistically significant.

3. Results

3.1. Patient and procedural characteristics

This study population included a total of 203 patients from the ORAF registry who underwent an initial ablation using a RFCA for PerAF. The ROC analysis revealed a good accuracy of predicting LRAF by TAPSE/PASP ratio with a cutoff of 0.57 for the TAPSE/PASP sensitivity of 37.5% and specificity of 85.2% (Fig. 1). The study flowchart showed in
Fig. 2. The patients without noticeable TR signal or lacking either inspiratory/expiratory phases of the inferior vena cava diameters in pre-ablation TTE were excluded. The clinical characteristics of the enrolled patients are shown in Table 1. Age, BNP and septal E/e’ were significantly higher, and BMI was significantly lower in the patients with TAPSE/PASP ≤ 0.57 than in those with TAPSE/PASP > 0.57 (p < 0.001, p < 0.001, < 0.001, p = 0.020, respectively). The ratio of females and history of chronic heart failure were significantly higher in the patients with TAPSE/PASP ≤ 0.57 than in those with TAPSE/PASP > 0.57 (p = 0.009, p = 0.024, respectively). The procedural characteristics of the patients are shown in Table 1. No significant differences in the details of the ablation and complications were observed.

3.2. The relationship between TAPSE/PASP and LRAF

Kaplan-Meier analysis demonstrated that the patients with TAPSE/PASP ratios ≤ 0.57 had a significantly greater risk of LRAF than those with TAPSE/PASP ratios > 0.57 (Fig. 3). Multivariate Cox proportional hazards analysis showed that TAPSE/PASP (HR 0.12, 95% CI; 0.019–0.724, p = 0.026) was independently and significantly associated with LRAF (Table 2).

3.3. Changes in TAPSE/PASP after ablation

There were 160 patients (78.8%) that underwent TTE one-year after ablation and TR had disappeared in 31 patients (15.3%). The LV ejection fraction (LVEF), LAEF, FAC, TAPSE and TAPSE/PASP significantly more increased (p = 0.003, p < 0.001, p = 0.046, p < 0.001 and p = 0.016, respectively) and LA diameter, LAVI significantly more decreased one-year after the ablation than before (p < 0.001 and p < 0.001, respectively) (Table 3).

4. Discussion

4.1. Main findings

The main findings of the present study are that (1) the patients with TAPSE/PASP ratios ≤ 0.57 had a significantly greater risk of LRAF than those with TAPSE/PASP ratios > 0.57. (2) TAPSE/PASP ≤ 0.57 was independently and significantly associated with LRAF. (3) The TAPSE/PASP significantly more increased one-year after the ablation than before. These results suggested RV-PA uncoupling was a useful factor for LRAF after ablation.

4.2. TAPSE/PASP value in PerAF patients

RV dysfunction and AF are common in patients with HFrEF. They frequently coexist and are independently associated with a poor prognosis [19]. RV dysfunction is characterized by decreased TAPSE on Doppler echocardiography [17]. However, TAPSE/PASP is thought to be a more accurate indicator of the disease severity than either TAPSE or PASP alone [20]. Previous reports showed that average TAPSE/PASP was decreased both in HFrEF and HFrEF patients (median value = 0.54 and 0.55, respectively) than in healthy controls (median value = 0.83), and the TAPSE/PASP < 0.48 was associated with the composite endpoint of all-cause death and HF hospitalization in HF patients [20]. In the patients with severe pulmonary hypertension TAPSE/PASP < 0.31 had a significantly worse prognosis than those with higher TAPSE/PASP [13]. In the present study, our enrolled patients were mainly classified as post-capillary or Group 2 PH and the TAPSE/PASP cutoff value of 0.57 was shown to be a useful surrogate marker as a predictor of

![Fig. 1. ROC curve analysis for predicting the LRAF with TAPSE/PASP. The prognostic predictability of the continuous variable of TAPSE/PASP ratio for the LRAF was evaluated with ROC curve analysis. AUC, area under curve; LRAF, late recurrence of atrial fibrillation/atrial tachycardia; PASP, pulmonary artery systolic pressure; ROC, receiver operating characteristic; TAPSE, tricuspid annular plane systolic excursion.](image)

![Fig. 2. Flow chart of the study patients. Among 531 PerAF patients, we finally studied 203 patients. PAF, paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; TR, tricuspid regurgitation.](image)
Table 1
Baseline patient characteristics.

| Overall population | TAPSE/ ≥ PASP | TAPSE/ > PASP | p value |
|--------------------|---------------|---------------|---------|
| (n = 203)          | 0.57          | 0.57          |         |
| (n = 41)           |               |               |         |
| (n = 162)          |               |               |         |

Clinical data
Age, years
70 [66, 76] 75 [70, 79] 69 [65, 75] <0.001
Female
52 (25.7) 17 (41.5) 35 (21.6) 0.009
BMI, kg/m²
24 [22,27] 23 [20,25] 24 [22,27] 0.020
Hypertension
116 (57.1) 24 (58.5) 92 (56.8) 0.840
Diabetes
38 (18.7) 9 (22.0) 29 (17.9) 0.553
Chronologic heart failure
35 (17.2) 12 (29.3) 23 (14.3) 0.024
Stroke
16 (7.9) 6 (14.6) 10 (6.2) 0.072
Dyslipidemia
58 (28.6) 11 (26.8) 47 (29.0) 0.782
CHADS² VASc score
0.120

Laboratory data
Creatinine, mg/dL
0.9 [0.7, 1.0] 0.9 [0.7, 0.9] 0.94
CRP, mg/dL
0.1 [0.1, 0.2] 0.1 [0.1, 0.1, 0.2] 0.37
BNP, pg/ml.
148 [80, 253] 230 [127, 236] 140 [77, 236] <0.001

Echocardiographic parameters
LVDD, mm
49 [46, 52] 50 [45, 53] 49 [46, 52] 0.442
LVDS, mm
30 [28, 34] 32 [27, 36] 30 [28, 34] 0.098
LVF, %
65 [61, 70] 64 [58, 68] 66 [62, 70] 0.072
LA diameter, mm
46 [43, 51] 48 [44, 52] 46 [42, 50] 0.291
Septal E/e
10 [8,12] 10 [8,10] 9 [8,12] 0.001
LAVI, ml/m²
48 [41, 59] 55 [44, 66] 48 [41, 57] 0.023
LAEF, %
34 [27, 40] 34 [28, 38] 35 [27, 40] 0.120
TAPSE, cm
21 [19,23] 18 [15,21] 21 [19,24] <0.001
FAC, %
42 [38, 47] 41 [37, 48] 42 [38, 48] 0.633
PASP, mmHg
29 [26, 35] 35 [31, 45] 28 [25, 31] <0.001
LAAnother V, ms
35 [24, 48] 31 [25, 46] 36 [27, 49] 0.105

Medications
DOAC
183 (90.1) 35 [85.4] 148 (91.4) 0.250
AAD
24 (11.8) 16 (14.6) 18 (11.1) 0.533
ACEI/ARB
83 (40.9) 14 [32.4] 69 (42.6) 0.326
Beta-blocker
91 (44.8) 14 [34.2] 77 (47.5) 0.124
Statin
46 (22.7) 9 [22.0] 27 (22.8) 0.903

Procedural characteristics
Procedure time (min)
165 [125, 202] 160 [120, 218] 165 [125, 200] 0.756
Number of applications
84 [65, 106] 77 [65, 84] 83 [63, 106] 0.985
Total time of the applications (min)
35 [24, 43] 31 [24, 51] 35 [24, 43] 0.976
Fluoroscopy duration (min)
19 [13,31] 20 [14,24] 19 [13,32] 0.756
CTIB
88 [43,33] 13 [31.7] 75 [46.3] 0.092
SVCI
31 (15.3) 6 [19.5] 13 [14.2] 0.598
LAPWI
39 [19.2] 11 [26.8] 28 [17.3] 0.166
Other non-PF foci ablation
18 [8,9] 6 [14.6] 12 [7.4] 0.146

Complications
Cardiac tamponade
0 (0) 0 (0) 0 (0) –
Pneumonia
1 (0.05) 0 (0) 0 (0) 0.614
Phrenic nerve palsy
1 (0.05) 0 (0) 0 (0) 0.614
Bleeding at the puncture site
0 (0) 0 (0) 0 (0) –

Continuous data are presented as the median (interquartile range). Categorical variables are presented as numbers (percentage). P values, the patients with TAPSE/ PASP ≤ 0.57 vs those with TAPSE/ PASP > 0.57. AAD, anti-arrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CRP, C reactive protein; CTIB, cavo tricuspid isocham block; DOAC, direct oral anticoagulant; FAC, fractional area change; LAAV, left atrial appendage flow; LA, left atrium; LAPWI, left atrial posterior wall isolation; LVDD, left ventricular end-diastolic diameter left ventricular diameter; LVDS, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PV, pulmonary vein; SVCI, superior vena cava isolation; TAPSE, tricuspid annular plane systolic excursion.

LRAF in PerAF patients.

4.3. Impact of TAPSE/PASP on LRAF in PerAF patients

TAPSE/PASP is a noninvasively measured index of RV-PA coupling based on its correlation with invasively evaluated RV systolic elastance and pulmonary arterial elastance in patients with HFpEF [21]. In PerAF
patients, LA remodeling is the main pathogenesis and right-sided cardiac dysfunction is also considered to be an important factor for AF maintenance. Severe TR is independently correlated with AF recurrence after ablation [22]. RV dysfunction is associated significantly with the occurrence of post-operative AF in the context of cardiac surgery [23].

Different etiology and diseases substrates for right ventricular dysfunction were demonstrated such as pulmonary artery hypertension (Group 1 PH), left-sided heart disease (Group 2 PH), lung disease/hypoxia (Group 3 PH), pulmonary thromboembolic disease (Group 4 PH) and others (Group 5 PH) as previously reported [24–25]. The TAPSE/PASP cutoff value of 0.57 was a useful marker as a predictor of LRAF in PerAF patient who were mainly classified as Group 2 PH, but the TAPSE/PASP has been proven to reflect combined precapillary and postcapillary PH [26]. Postcapillary PH was thought to be the major reason for PH in HFpEF, but precapillary PH has also been shown to be important in the pathophysiology [27]. Activation of neurohumoral factors and production of cytokines cause abnormalities in the endothelium-dependent vasoactive responses and induce impaired pulmonary capillary vascular contraction [28]. In PerAF patients, neurohumoral factors and cytokines are elevated due to low cardiac output and inflammatory status [29]. A previous report showed that AF is strongly related to reduced RV and right atrial function in HFpEF independent of pulmonary pressures [30]. The negative inotropic effect of rhythm irregularity is a possible contributing factor to RV-PA uncoupling [31]. Generally, the elevation in the LA diameter or LA volume is known to be a strong prognostic marker for LRAF after ablation [32]. However, our results showed the no significant relationship between LAVI and LRAF after ablation. The reason for this result is that the patients with LA dysfunction might be included more than previous studies because we enrolled only PerAF patients and those without noticeable TR signal were excluded in the present study. TAPSE/PASP was not significantly correlated with LAVI (p = 0.916, r = 0.007) and multicollinearity among these factors was not confirmed in the present study. TAPSE/PASP < 0.57 was independently and significantly associated with LRAF independent of LA function.

4.4. Improvement in the RV function after ablation in PerAF patients

In the present study, the LVEF, LAEF, FAC, TAPSE and TAPSE/PASP significantly more increased and LA diameter, LAVI significantly more decreased one-year after the ablation than before (Table 3). The maintenance of sinus rhythm after ablation is associated with reverse remodeling of the LA size [33]. Improvement in LA function due to maintenance of sinus rhythm causes an increase in cardiac output and decrease in pulmonary arterial wedge pressure and reduction of TR. The amelioration of postcapillary PH was considered to be the main reason for these changes after ablation, but the reduction in the neurohumoral factors and inflammatory cytokines may bring about an improvement in the abnormal pulmonary capillary vascular contraction.

4.5. Clinical implications

The elevation in the LA diameter or LA volume is known to be a strong prognostic marker for LRAF after ablation [32]. Although the Cox regression analysis revealed that LAVI was not a strong prognostic marker again in our registry, impaired TAPSE/PASP was also proven to be a predictive factor of LRAF. The present finding indicated that RV-PA uncoupling is worth focusing on to improve poor outcomes in PerAF patients after ablation.

4.6. Study limitations

Several limitations of the study need to be acknowledged. First, the present study was a single center, non-randomized registry-based study. Second, continuous monitoring with implantable devices to evaluate arrhythmia recurrence was not used in the present study. However, patients were encouraged to have smartphones or tablet applications and check their pulse rate and rhythm every day and to visit our hospital if they experienced palpitation or other symptoms. Third, in our investigation, the neurohumoral factors and inflammatory cytokines were not measured. Fourth, the previous report showed that prognostic value of TAPSE/PASP were hemodynamically validated with right heart catheterization [26]. The invasive hemodynamic evaluation was not performed in our study. Further investigations are required to confirm the results of this study and to support the understanding of the pathophysiological meaning of RV-PA uncoupling in PerAF after ablation.

5. Conclusion

TAPSE/PASP was proven to be a predictive factor of LRAF independent of LA function after catheter ablation in PerAF patients.

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Disclosure

None.

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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