Original Article

Association between Elevated Left Atrial Pressure and Poor Prognosis after PVI for Atrial Fibrillation

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Objective: Left atrial (LA) stretch attributable to elevated LA pressure is known to play an important role in the perpetuation of atrial fibrillation (AF). However, the relation between LA pressure and the outcome of pulmonary vein isolation (PVI) for AF remains to be elucidated. Therefore, we investigated the relationships between post-PVI recurrence of AF, LA pressure, and pre-ablation variables.

Methods and Results: The study group comprised 60 consecutive patients who were undergoing ablation for AF (46 men, 14 women; mean age, 59.5 ± 11 years; paroxysmal AF [PAF], $n = 35$; persistent AF [Per AF], $n = 25$). The patient characteristics and biomarkers of inflammation, fibrosis and heart failure measured before ablation were compared between patients in whom AF recurred after a 3-month blanking period and those in whom it did not. No significant differences were found in clinical or echocardiographic variables or biomarker concentrations between the patients with and without recurrence. However, the mean LA pressure was elevated in patients in whom AF recurred (12.2 ± 0.99 vs. 7.99 ± 0.62 mmHg, respectively, $P < 0.001$). Body mass index and serum atrial natriuretic peptide (ANP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations were higher; hypertension was more prevalent, and the LA diameter and volume were greater in patients with a mean LA pressure $\geq$ the median value of 10 mmHg compared with those patients with a mean LA pressure < 10 mmHg, despite a similarity in the left ventricular ejection fraction.

Conclusions: Elevated LA pressure is associated with post-PVI AF recurrence. Therefore, measuring LA pressure before PVI might be useful in identifying patients at risk for post-ablation AF recurrence, and an aggressive ablation strategy might be needed for these patients.

Key words: atrial fibrillation, pulmonary vein isolation, left atrial pressure, recurrence

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Introduction

Percutaneous pulmonary vein isolation (PVI) is an effective therapy for maintaining sinus rhythm (SR) in symptomatic drug refractory atrial fibrillation (AF) patients^{1,2)}. The Long-term single procedure success rates for maintaining SR have been reported to vary widely, ranging from 40% to more than 70%^{3–5)}. Various clinical parameters determined before the ablation procedure have been studied as predictors of AF recurrence post-PVI. These include age; type and duration of the AF; left atrial (LA) size; left ventricular ejection fraction (LVEF); and presence of structural heart disease, hypertension, and/or obstructive sleep apnea^{6–11)}. LA pressure is an invasive variable that can be obtained after transseptal puncture. Elevated LA pressure represents atrial and pulmonary vein stretch, which is reported to play an important role in the development and maintenance of AF¹²⁾. We studied the relation between LA pressure and recurrence of AF

after PVI and its relation to previously reported preprocedural variables.

Patients and methods

Patients

Included in the study were 60 patients with drug refractory non-valvular paroxysmal AF (PAF; i.e., AF lasting ≤ 7 days, [$n = 35$]) or persistent AF (PerAF; i.e., AF lasting > 7 days [$n = 25$]) who were scheduled for PVI at Nihon University Itabashi Hospital between January 2013 and December 2014. All provided written informed consent for their inclusion. None had undergone a previous ablation procedure or surgery within the prior 60 days, none had exhibited signs or symptoms of acute coronary syndrome within the prior 60 days, and none had had a recent infection or history of collagen vascular disease. All underwent electrocardiography (ECG) and transthoracic and transesophageal echocardiography before PVI. The study protocol for this retrospective study was approved by the

Human Research Ethics Committees of Nihon University Itabashi Hospital (May 25, 2016; RK-160614-10).

PVI procedure

Warfarin was administered to all patients for 1 month or more before the ablation procedure, and anticoagulation (international normalized ratio, 2–3) was achieved in all. In addition, LA thrombus was ruled out by means of transesophageal echocardiography performed one day before the procedure. Antiarrhythmic drugs were discontinued for a washout period of at least 5 half-lives before the procedure (no patient was taking amiodarone). PVI was performed under sedation achieved with intravenous infusion of dexmedetomidine, propofol, and fentanyl, as previously described¹³⁾. In brief, after vascular access was obtained, single transseptal puncture was performed, and heparin was administered intravenously to maintain an activated clotting time of > 300 seconds. Immediately after the transseptal puncture, an 8-Fr long SL1 sheath (St. Jude Medical, St. Paul, MN, USA) was introduced into the left atrium, and mean LA pressure was recorded with a hemodynamic monitoring system (RMC-5000, Nihon Kohden Co, Tokyo, Japan) during SR in patients with PAF and during AF in patients with PerAF. After 3 long sheaths (2 SR0 sheaths and 1 SL1 sheath; St. Jude Medical) were inserted into the left atrium via the transseptal puncture, 2 decapolar circular mapping catheters (Lasso; Biosense Webster, Diamond Bar, CA, USA) and an irrigated 3.5-mm-tip mapping and ablation catheter (Thermocool; Biosense Webster) were advanced into the left atrium. Extended encircling ipsilateral PVI was performed, guided by the 2 Lasso catheters and a 3-dimensional electroanatomical mapping system (CARTO 3; Biosense Webster)^{14, 15)}. Targeting ipsilateral PVs in pairs, we placed radiofrequency (RF) lesions at least 1 cm outside the PV ostia. Lesions were placed within 1 cm of the ostium of the left superior PV (LSPV) because of the narrow ridge of tissue between the anterior aspect of the LSPV and the LA appendage. RF energy was delivered at power setting of 20–35 W and an irrigation flow rate of 17–30 mL/min. The upper temperature limit was set to 41°C. On the posterior wall, the RF power was reduced to 25 W, and the irrigation flow rate was set to 17 mL/min. AF remaining in any patient at the end of the procedure was electrically cardioverted to SR, after which all PVs were remapped to confirm PVI. The procedure was considered complete when spontaneous associated PV potentials were no longer recorded by the circular mapping catheter (entrance block) and disassociation of PV potentials from LA activity was noted either spontaneously or with PV pacing (exit block). A waiting time of ≥ 20 minutes after the index isolation was used to monitor for early PV reconnection, and if spontaneous conduction or adenosine triphosphate (ATP; 30 mg, bolus injection)-induced PV conduction occurred, reconnected PVs were reisolated. No induction testing (via burst pacing or isoproterenol infusion), prophylactic linear ablation, or complex fractionated atrial electrogram ablation was performed.

Laboratory tests

Blood samples were collected from the femoral vein before the ablation procedure for baseline measurement of biomarkers of inflammation, heart failure, and fibrosis; high-sensitivity C-reactive protein (hs-CRP) in serum (by immunonephelometry with a BNII analyzer [Dade Behring, Deerfield, IL, USA] according to the manufacturer's recommended protocol and at a detection limit of 0.175 mg/L); atrial natriuretic peptide (ANP) in serum (with a chemiluminescent enzyme immunoassay kit [Shionogi Co., Ltd., Tokyo, Japan]); N-terminal pro-brain natriuretic peptide (NT-proBNP) in serum (with a electrochemiluminescence immunoassay kit [Roche Diagnostics, Inc., Mannheim, Germany]); and interleukin-6 (IL-6) in serum (with a commercially available ELISA kit [Fujirebio Inc., Tokyo, Japan]). Also measured were transforming growth factor (TGF)- β 1 in plasma (with an enzyme-linked immunoassay kit [R&D systems, Inc., Minneapolis, MN, USA]); and matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of MMP-1 (TIMP-1) in serum (with a commercially available one-step sandwich enzyme immunoassay kit [Kyowa Pharma Medical Co, Ltd., Toyama, Japan]).

Echocardiographic evaluation

Comprehensive transthoracic echocardiography was performed 1 day before the ablation procedure with an ACUSON Sequoia C256 echocardiography system (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). Left atrial dimension (LAD) was measured in the parasternal long axis view at end systole, LA volume was measured from apical 4 chamber view by area-length method, and left ventricular ejection fraction (LVEF) was assessed by means of M-mode echocardiography (Teichholtz method). Measurements from 3 consecutive beats were averaged. An apical 4-chamber view was used for Doppler tissue imaging of the mitral annulus, and the ratio of mitral inflow early filling velocity (E) to velocity of the early medial mitral annular ascent (e') was determined.

Post-ablation follow-up

Patients' previously prescribed antiarrhythmic drugs were resumed after the ablation procedure but stopped 3 months later. Other prescribed drugs were not changed during the follow-up period. All patients underwent routine follow-up at our outpatient clinic, where clinical evaluation and 12-lead ECG were performed at 2 weeks,

1 month, and then every 1–3 months thereafter for up to 2 years. Twenty-four-hour Holter ECG recordings were obtained 3–6 months after ablation. When symptoms suggestive of tachycardia developed after ablation, 24-hour Holter monitoring and/or cardiac event recording over a full week was performed to identify the cause of the clinical symptoms. AF recurrence was defined as an electrocardiographically confirmed atrial arrhythmia lasting > 30 seconds after a blanking period of 3 months. The study endpoint was clinically documented AF recurrence or a repeat ablation procedure during the follow-up period.

Statistical analysis

Patients were divided between those in whom AF recurred and those in whom AF did not recur, and differences in clinical variables between these 2 groups were analyzed by Mann-Whitney test. Patients were then divided between those in whom LA pressure was < 10 mmHg and those in whom LA pressure was $\geq$ 10 mmHg, and differences in clinical characteristics, echocardiographic parameters, and biomarkers between these 2 groups were analyzed by Mann-Whitney U test or chi-square test, as appropriate. Data are presented as the number (and percentage) of patients or mean $\pm$ SD values. All statistical analyses were performed with JMP 8 software (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered statistically significant.

Results

Post-PVI AF recurrence

AF recurred in 18 (30%) of the 60 patients within 13 $\pm$ 5 months after PVI. Patients in whom AF recurred did not differ significantly from those in whom AF did not recur

with respect to age, sex, AF duration, body mass index, AF type (Table 1). LAD, LA volume, LVEF, and E/e' also did not differ significantly (39.8 ± 8.4 mm vs. 38.3 ± 6.0 mm, $P = 0.4325$; 53.4 ± 29.2 ml vs. 43.1 ± 17.1 ml, $P = 0.0918$; $61.6 \pm 9.9\%$ vs. $66.2 \pm 9.5\%$, $P = 0.1001$; 10.4 ± 4.5 vs. 14.4 ± 13.3 , $P = 0.081$) between patients in whom AF recurred those in whom AF did not recur.

LA pressure and AF recurrence

LA pressure was significantly higher in patients in whom AF recurred than in patients in whom AF did not recur (12.2 ± 0.99 vs. 7.99 ± 0.62 mmHg, $P < 0.001$).

Biomarkers of inflammation, heart failure, and fibrosis and AF recurrence

hs-CRP, IL-6, ANP, NT-proBNP, TGF- β 1, and MMP-9 concentrations did not differ between patients in whom AF recurred and those in whom AF did not recur (Table 2).

LA Pressure $\geq$ 10 mmHg vs. LA pressure < 10 mmHg: clinical and echocardiographic variables and biomarker concentrations

Clinical and echocardiographic variables and biomarker concentrations were analyzed in relation to LA pressure, which was classified as below or above the median value of 10 mmHg. Body mass index was significantly higher, the prevalence of hypertension was significantly higher, and the prevalence of paroxysmal AF was significantly lower in patients with a mean LA pressure of $\geq$ 10 mmHg than in those with a mean LA pressure of < 10 mmHg (Table 3). LAD, LA volume, and E/e' were significantly greater in patients with a mean LA pressure $\geq$ 10 mmHg (Table 3), and ANP and NT-proBNP concentrations were

Table 1 Patients' pre-ablation clinical characteristics and echocardiographic variables per non-recurrence and recurrence of AF

	Non-recurrence (n = 42)	Recurrence (n = 18)	P value*
Age (years)	59.5 $\pm$ 10.7	60.1 $\pm$ 12.3	0.859
Sex M/F	34/8	12/6	0.168
AF duration (months)	48.7 (23.8–109.5)	97.3 (23.8–109.5)	0.118
BMI (kg/m ²)	23.2 $\pm$ 2.80	23.7 $\pm$ 3.67	0.850
Paroxysmal AF	18 (42)	7 (39)	0.775
Hypertension	20 (47)	11 (65)	0.204
Diabetes mellitus	5 (12)	1 (6)	0.504
Ischemic heart disease)	1 (2)	1 (6)	0.489
Heart failure	16 (37)	6 (35)	0.899
Stroke or TIA	5 (12)	1 (6)	0.504
LAD (mm)	38.3 $\pm$ 6.0	39.8 $\pm$ 8.4	0.433
LAV (mL)	43.1 $\pm$ 17.1	53.4 $\pm$ 29.2	0.092
LVEF (%)	66.2 $\pm$ 9.5	61.6 $\pm$ 9.9	0.100
E/e'	10.4 $\pm$ 4.5	14.4 $\pm$ 13.3	0.081

*obtained by Mann-Whitney test or chi-square test.

Data are shown as number (percentage) of patients or mean $\pm$ SD values.

AF: atrial fibrillation; BMI: body mass index; TIA: transient ischemic attack; LAD: left atrial diameter; LAV: left atrial volume; LVEF: left ventricular ejection fraction; E/e': ratio of mitral inflow early filling velocity (E) to velocity of the medial early mitral annular ascent (e').

Table 2 Patients' pre-ablation biomarker concentrations per non-recurrence and recurrence of AF

	Non-recurrence n = 42	Recurrence n = 18	P value*
hs-CRP (ng/mL)	1038.5 ± 1583.9	2117.6 ± 4747.2	0.191
IL-6 (pg/mL)	4.0 ± 5.9	3.6 ± 5.2	0.804
ANP (pg/mL)	107.0 ± 81.3	148.0 ± 113.1	0.118
NT-proBNP (pg/mL)	201.2 ± 383.0	372.1 ± 395.4	0.122
TGF-β1 (ng/mL)	12.0 ± 7.5	13.5 ± 10.0	0.524
MMP-9 (ng/mL)	26.4 ± 14.7	33.0 ± 20.1	0.160

*obtained by Mann-Whitney test.

hs-CRP: high sensitivity C reactive protein; IL-6: interleukin 6; ANP: NT-proBNP: N-terminal pro-brain natriuretic peptide; TGF-β1: transforming growth factor-β1; MMP-9: matrix metalloproteinase 9.

Table 3 Baseline, Echocardiographic and Biomarker Parameters between LA pressure ≥ 10mm Hg and < 10 mmHg

	LA pressure ≥ 10 mmHg (n = 30)	LA pressure < 10 mmHg (n = 30)	P Value
Age (years)	60.4 ± 11.0	58.9 ± 11.3	0.5871
Sex (female)	9 (30)	5 (17)	0.2196
AF duration (months)	54.0 ± 76.8	67.3 ± 63.3	0.467
Body mass index (kg/m ²)	25.0 ± 3.1	23.1 ± 3.0	0.019
Paroxysmal AF (%)	9 (30)	16 (53)	0.0654
Hypertension (%)	21 (70)	10 (33)	0.004
Diabetes Mellitus	4 (13)	2 (7)	0.385
Ischemic Heart Disease	1 (3)	1 (3)	1
Heart Failure	12 (40)	10 (33)	0.592
Stroke or TIA	2 (7)	4 (13)	0.385
LAD (mm)	43.0 ± 7.0	38.0 ± 8.0	0.0113
LAV (mL)	53.1 ± 23.8	38.9 ± 16.3	0.0089
LVEF (%)	63.8 ± 10.3	65.9 ± 9.2	0.4192
E/e'	13.9 ± 10.4	9.20 ± 3.7	0.0243
hs-CRP	1026.9 ± 1430.9	2104.1 ± 3530.1	0.127
IL-6	4.1 ± 4.9	3.6 ± 2.1	0.609
ANP	149.4 ± 76.7	106.6 ± 53.5	0.0015
NT-proBNP	369 ± 373.1	109 ± 393.0	0.011
TGF-β1	14.8 ± 7.9	11.8 ± 10.0	0.202
MMP-9	28.7 ± 17.2	27.1 ± 14.3	0.697

AF = atrial fibrillation; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; hs-CRP = high sensitivity C reactive protein; IL-6 = interleukin-6; ANP = atrial natriuretic peptide; N Terminal -proBNP = N-t pro-brain natriuretic peptide; TGF-β1 = Transforming Growth Factor-β1; MMP-9 = matrix metalloproteinase 9

significantly higher in these patients (Table 3). Systolic and diastolic blood pressure in patients with LA pressure ≥ 10 mmHg and LA pressure < 10 mmHg were 148 ± 8 mmHg, 86 ± 6 mmHg and 132 ± 10 mmHg and 75 ± 8 mmHg.

Discussion

Main findings

We found that clinical characteristics, echocardiographic variables, and biomarker concentrations did not differ significantly between patients in whom AF recurred after PVI and those in whom it did not. Mean LA pressure, however, was significantly higher in patients in whom AF

recurred. Body mass index, prevalence of hypertension and non-paroxysmal AF, LAD, LA volume, E/e', and ANP and NT-proBNP concentrations were significantly greater in patients with elevated LA pressure (mean: ≥ 10 mmHg) than in those without elevated LA pressure. Therefore, diastolic dysfunction of the left ventricle through metabolic syndrome like condition and/or long-lasting irregular rhythm by PerAF might contribute to high LA pressure and AF recurrence after PVI.

LA pressure and recurrence of AF

In a study conducted by Machino-Ohtsuka et al. association was found between , dyslipidemia, and elevated

peak LA pressure (LA pressure at v-wave) and AF recurrence after PVI, but mean LA pressure was not found to be a predictor of such recurrence¹⁶. Linhart et al. showed mean LA pressure but not AF type to be predictive of AF recurrence after PVI in patients with a normal or mildly enlarged left atrium¹⁷. In a study conducted by Moon et al., high mean LA pressure and a large left atrium (LA volume ≥ 125 mL) were independently associated with AF recurrence after PVI in patients treated for persistent AF; however, mean LA pressure was not shown to be a prognostic factor in patients treated for paroxysmal AF¹⁸. Park et al. showed elevated peak LA pressure to be closely associated with electroanatomic remodeling of the left atrium and to be an independent predictor for AF recurrence after PVI¹⁹. In addition, Kishima et al. calculated the difference between mean LA pressure during SR and mean LA pressure during AF (LAPSR-AF) and showed association between a great difference (LAPSR-AF ≥ 0 mmHg) and a poor outcome after PVI²⁰.

LA pressure associated with LA remodeling in patients with AF

Persistent AF results in electrical, structural, and autonomic neural remodeling of the left atrium. The structural remodeling can include such permanent changes such as fibrosis, thickening of the interstitial matrix, and the appearance of potentially arrhythmogenic myofibroblasts²¹. Structural remodeling of the atria accompanies LA enlargement, reduction in LA voltage, and clustering of complex fractionated atrial electrograms²². Hemodynamic stress, such as ventricular systolic or diastolic dysfunction, may be more likely than atrial enlargement to lead to fibrosis because the thin-walled left atrium responds to pressure overload by dilatation rather than wall thickening²³. LA pressure may lead directly to the maintenance of AF by mechano-electrical feedback²⁴ or by a stretch-induced profibrotic reaction that creates a substrate for AF²⁵. LA pressure independent atrial enlargement may also increase the critical mass that begets AF²⁶. We found, in the study described herein, association between LA pressure and patients' clinical and echocardiographic variables and biomarker concentrations. Increased LA pressure was associated with increased body mass index; hypertension; elevated E/e', ANP, and NT-proBNP; and increased LAD and LA volume. However, we found no association between LA pressure and LVEF LA. The increases we found in patients with elevated LA pressure may reflect the presence of left ventricular diastolic dysfunction. The LA stiffness index (difference between the LA peak v-wave pressure and LA x-wave pressure nadir/peak strain during ventricular systole) has been shown to be related to left ventricular diastolic dysfunction, LA dilatation, and collagen synthesis as measured by amino-terminal procollagen type III propeptide and to predict AF

recurrence after PVI¹⁶. High LA pressure in patients with persistent AF has been shown to correlate with dominant frequency in the LA appendage, suggesting that atrial stretch contributes to the maintenance of clinical AF by stabilizing high-frequency sources²⁷. High LA pressure has been shown to be closely associated with low LA voltage¹⁸.

Study limitations

Our study was limited by the small number of patients. In addition, mean LA pressure was measured during SR or during AF, and a significant difference between peak LA pressure obtained in SR and that obtained in AF has been reported (although no such difference in nadir or mean LA pressure has been reported)¹⁹. Also, because AF episodes were identified by intermittent ECG and Holter ECG monitoring, episodes of asymptomatic AF could have been missed. LA pressure was measured invasively just before ablation procedure. Ideally, LA remodeling parameter(s) could be obtained noninvasively to determine treatment strategy, i.e., rhythm control or rate control. We reported non-invasive parameters for left atrial remodeling by transthoracic echocardiographic measurement before ablation procedure^{28, 29}. However, LA pressure information might be useful to determine ablation strategy, i.e., PVI only or PVI + LA ablation.

Conclusion

Elevated LA pressure is associated with post-PVI AF recurrence. Therefore, measuring LA pressure before PVI might be useful for identifying patients at risk for post-ablation AF recurrence, and an aggressive ablation strategy might be needed for these patients.

No conflict of interest on this study

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