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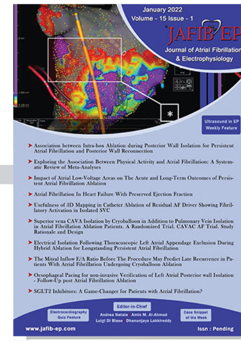


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# Association between Intra-box Ablation during Posterior Wall Isolation for Persistent Atrial Fibrillation and Posterior Wall Reconnection

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**Abstract**

Background: Posterior wall isolation (PWI) combined with pulmonary vein isolation (PVI) has been proven effective for persistent atrial fibrillation (AF). Intra-box ablation, defined as application in the “box” area during PWI in this study, is sometimes necessary when linear ablation of the roof and bottom fails to achieve complete isolation. This study aimed to investigate the factors of patients requiring intra-box ablation and to evaluate the effect of intra-box ablation on clinical outcomes.

Methods: This is an observational study including patients who underwent PVI and PWI for persistent AF in the first procedure from June 2017 and March 2020, at the Tokyo Metropolitan Hiroo Hospital. When linear ablation of the roof and bottom failed to complete PWI, intra-box ablation was added. Six months after the procedure, patients undertook follow-up electrophysiological study and additional ablation as the second procedure. Findings of the left atrium (LA) mapping and ablation in the first procedure and posterior wall (PW) reconnection in the second procedure were evaluated. Patient characteristics and outcomes were compared between patients with and without intra-box ablation.

Results: Of the 93 patients included in this study, successful PWI was achieved in 91 (mean age, 67.5±9.8 years; male, 75.3%), and intra-box ablation was needed in 59 (63.4%). Shorter PW activation time (40.3±10.4 vs 51.3±15.2, p=0.026) and larger upward conduction patterns in the PW were significant association with the necessity of intra-box ablation. More PW reconnection in the second procedure was observed in patients with intra-box ablation than in those without intra-box ablation (21/28,75.0% vs 8/20, 40.0%; p=0.020).

Conclusion: We showed that the requirement of intra-box ablation was related to lower durability of PW. Findings of LA mapping suggested the possibility that PW conduction velocity and patterns was one of the mechanisms of failure of linear PWI.

## Introduction

Pulmonary vein isolation (PVI) is a standard strategy of catheter ablation for atrial fibrillation (AF). However, it is less effective for persistent AF than for paroxysmal AF [1]. The posterior wall (PW), with its complex structure of varied wall thickness and mixed fibers, is known to play an important role in AF [2,3]. Previous meta-analyses showed that less AF recurrence was observed in patients with both of PVI and posterior wall isolation (PWI) than in those with PVI only [4,5].

However, PW reconnection is a problem and the effectiveness of the hybrid of endocardial and epicardial ablation has been reported [6-9]. Epicardial procedure involves some risks, such as cardiac tamponade and pericarditis, and should be limited to refractory AF cases. Improving the PWI technique from the endocardial approach is needed to reduce refractory AF. Linear ablation of roof and bottom is one of the strategies for PWI. After failing to achieve complete PWI by linear ablation, the application in “box” area, which is defined as intra-box ablation in this study, is sometimes required. The characteristics of patients who need intra-box ablation and the impacts of intra-box ablation on clinical outcome remain unknown.

Hence, this study is aimed to investigate the characteristics of patients with intra-box ablation and to evaluate the effect of intra-box ablation on AF recurrence.

## Key Words

Atrial Fibrillation, Box Isolation

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## Material and methods

### Study population

This was a single-center observational study. Patients who underwent PVI and PWI for persistent AF in the first procedure between June

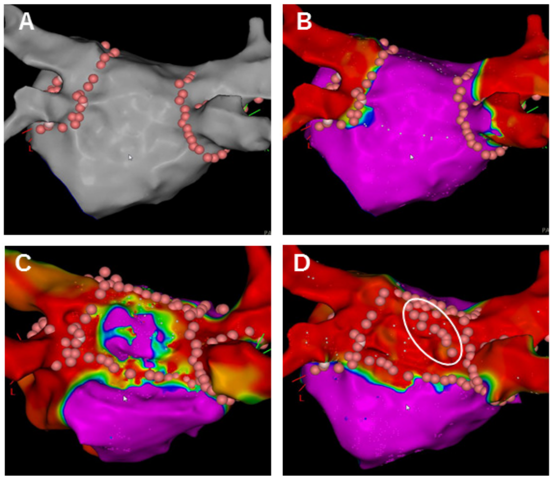


**Figure 1:** **An example of PVI and PWI.**

These figures show the procedure of PVI and PWI. A) First, PVI is performed. B) After PVI, LA mapping during RA pacing is performed to confirm PVI. This map is analyzed after the procedure. C) Linear ablation for PWI is performed. When compete PWI is not achieved, posterior wall mapping is performed. D) In this case, intra-box ablations (in white circle) are required to achieve complete PWI. After PWI, posterior wall mapping is performed again to confirm endpoints.
PVI, pulmonary vein isolation; PWI, posterior wall isolation; LA, left atrium; RA, right atrium.

2017 and March 2020 at the Tokyo Metropolitan Hiroo Hospital were included in this study. Patients who previously experienced catheter ablation for AF, atrial flutter or atrial tachycardia were excluded. Patients who required additional ablation other than PVI and PWI during the first procedure, for example, mitral isthmus ablation and complex atrial fractionated electrograms, were also excluded.

## Protocol for catheter ablation

Anti-arrhythmic drugs (AADs) were discontinued for ≥5 half-lives prior to ablation. Oral anticoagulant therapy was initiated at least 1 month prior to the procedure.

In the first procedure, the protocol was as follows: the first circumferential PVI and ablation of the carina were performed (Fig.1 A); Left atrium (LA) mapping during right atrium (RA) pacing was conducted to confirm PVI (Fig.1 B); roof and bottom linear ablation was performed for PWI (Fig.1 C); and lastly, when linear ablation failed to complete PWI, intra-box ablation was added (Fig.1 D).

The electrophysiological study and ablation were performed under deep sedation, using an intravenous administration of propofol. A 20-polar superior vena cava (SVC)-RA-coronary sinus (CS) electrode catheter (BeeAT, Japan Lifeline, Tokyo, Japan or Inquiry, Abbott, Abbott Park, Illi, USA) was inserted via the right subclavian vein into the coronary sinus. The PVs and LA were mapped using a multielectrode mapping catheter (PentaRay, Biosense Webster, Diamond Bar, CA, USA) and a three-dimensional anatomical mapping system (CARTO, Biosense Webster). A 3.5-mm irrigated-tip catheter (ThermoCool Smart touch SF, Navistar, BiosenseWebster) was used for ablation. PVI was performed using a circular mapping catheter (Lasso, Biosense Webster) placed within the ipsilateral ostia of the superior and inferior PVs. The endpoint of PVI was the achievement of a bidirectional conduction block between the LA and PVs. After PVI, cardioversion was delivered to restore sinus rhythm. LA mapping was conducted by multielectrode catheter (PentaRay, Biosense Webster) during high RA pacing (basic cycle length, 600 msec), and then PWI was conducted.

During PWI, the PentaRay was placed at the PW to record its electrical potential. Roof line and bottom line ablation were conducted to achieve PWI. After linear ablation, LA mapping was conducted to confirm isolation of the PW. The area under 0.05 mV was defined as the scar area. The endpoint of PWI was defined as the absence of electrical activity in PW, and the inability to conduct from posterior wall to LA, which was confirmed by 5 mA output pacing from PentaRay at PW. Automaticity and local capture recorded by the PentaRay in the PW were also supportive findings of complete PWI. When PWI was incomplete after linear ablation, PW mapping was performed to search for the gap. In case the propagation map showed excitement traversing the gap to the PW, the gap was ablated. When the gap ablation failed to complete PWI or the gap was unclear, applications in the "box" area, which were defined as intra-box ablation, were conducted. The intra-box area was defined as the area surrounded by the roof and bottom line with a margin of 4-mm. The area with electrical activity was ablated. In this case, the endpoint was the absence of electrical activity captured by high output pacing with 20 mA; if pacing was captured, ablation was added until pacing was not captured.

Radiofrequency (RF) energy was applied point-by-point, and the setting differed per term as Table 1 shows.

The esophageal temperature was monitored using CIRC-S-CATH (CIRCA Scientific, Englewood, CO, USA), and application was abandoned when the temperature was over 41$^{O}$C.

After confirming the achievement of endpoints, we administered a bolus injection of 20 mg of adenosine triphosphate (ATP) to exclude ATP-provoked dormant conduction of PVs and PW. Catheter ablation was performed to eliminate the presence of reconnection and/or dormant conduction.

## LA mapping analysis

LA mapping was performed after PVI and before PWI during RA pacing by a SVC-RA-CS electrode catheter in most patients, and LA mapping data were analyzed after the procedure. LA mapping was abandoned in cases of ongoing AF after cardioversion and the inability to stabilize RA pacing. Box area was defined as the area surrounded by PVI, roof, and bottom lines. Voltage was measured in the para-line area, which was defined as the area of the roof and bottom line with a

**Table 1:** **Radiofrequency energy settings**

| | PVI except for posterior PVs | posterior PVs | PWI roof line | PWI bottom line |
|---|---|---|---|---|
| from Jun 2017 to Mar 2018 | 30 W, 30 sec | 25 W, 30 sec | 30 W, 30 sec | 25 W, 30 sec |
| From Mar 2018 to Jan 2020 | 40 W, AI 500 | 30W, AI 450 | 40 W, AI 500 | 30W, AI 450 |
| From Feb 2020 to Mar 2020 | 50 W, AI 500 | 50 W, AI 400 | 40 W, AI 500 | 30W, AI 450 |

AI, ablation index; PVs, pulmonary veins; PVI, pulmonary vein isolation; PWI, posterior wall isolation; sec, seconds.

**Table 2: Comparison of patient characteristics between intra-box ablation and non-intra-box ablation groups**

| | Intra-box n=57 | non-Intra-box n=34 | p value |
|---|---|---|---|
| Age [year] | 65.8±10.2 | 68.9±9.1 | 0.13 |
| Sex (male) | 40 (75.4%) | 25 (73.5%) | 0.83 |
| AF duration [months] | 35.6±42.6 | 26.6±29.0 | 0.30 |
| Heart failure | 14 (24.6%) | 7 (20.6%) | 0.19 |
| Hypertension | 35 (61.4%) | 19 (55.9%) | 0.27 |
| Diabetes mellitus | 5 (8.8%) | 3 (8.8%) | 0.99 |
| Stroke | 5 (8.8%) | 4 (11.8%) | 0.64 |
| BNP [pg/] | 295.0±360.1 | 263.7±239.3 | 0.82 |
| Ejection fraction [%] | 55.6±10.6 | 57.4±11.1 | 0.60 |
| Left atrial diameter* [mm] | 42.0±7.3 | 42.8±6.8 | 0.59 |
| Left atrial volume** [ml] | 144.0±47.0 | 156.7±44.3 | 0.22 |

AF, atrial fibrillation; BNP, brain natrium peptide; PW, posterior wall; PV, pulmonary vein.
* Left atrial diameter was measured by transthoracic echocardiography.
** Left atrial volume was measured by computed tomography scan.

margin of 4-mm above and below, and the intra-box area was defined as the "box" area excluding the para-line area. Total activation time of the box area were measured. Activation time reflects how much time the excitement takes to propagate to the whole PW.

CARTO version 7's propagation map and vector map were used to observe the conduction pattern of the PW. The cycle length of the vector map was set to the LA activation time in the propagation map. The excitatory wave front is highlighted in the propagation map; the vector map follows the propagation path of an excitatory wave front.

## Follow-up

After undergoing PVI and posterior isolation, patients were discharged from the hospital with a prescription for oral anticoagulants. The use of AADs could be discontinued three months after ablation, at the physician's discretion. The rhythm and presence of arrhythmias were evaluated based on the patient's symptoms and a resting 12-lead electrocardiogram, which was recorded during regular visits to our outpatient clinic. To detect AF recurrence and atrial tachyarrhythmia, we performed a 24-h Holter monitoring at 1, 3, and 6 months after the first procedure. AF recurrence was defined as AF and other atrial tachyarrhythmias documented lasting longer than 30 seconds regardless of AADs usage. The blanking period was three months, and AF recurrence was evaluated until 6 months after the first procedure.

Patients underwent a follow-up electrophysiological study and additional ablation for PV reconnection, PW reconnection, and/or non-pulmonary vein foci, if present as the second procedure, 6 months after the first procedure, regardless of AF recurrence. All patients were eligible for the second procedure except for those who rejected it. PV and PW reconnection were evaluated by LA mapping and catheters positioned in the PW and PVs, respectively. When there was PV and/or PW reconnection, applications for gaps were conducted after sites of gaps were searched by using propagation map. After applications for gaps failed to achieve PW re-isolation, intra-box ablation was added. Procedural endpoints were same as the first procedure.

## Outcomes

Primary outcomes were findings of LA mapping after PVI before PWI in the first procedure, such as PW voltage, activation time, and propagation/vector map pattern, abundant applications because of esophageal temperature rise, and reconnection of PW in the second procedure. Secondary outcomes were reconnection of PVs in the second procedure and AF recurrence at six months after the first procedure.

Outcomes and patient characteristics were compared between patients with intra-box ablation and without intra-box ablation (intra-box group vs non-intra-box group).

## Statistical analysis

Normal continuous and categorical data are presented as the mean ± standard deviation and numbers and percentages, respectively. Non-normally distributed data are summarized as median and interquartile ranges. For statistical test, categorical variables were analyzed using the chi-squared test, where appropriate, with Fisher's exact test and trend test otherwise used. Continuous variables were compared using Student's t-test and Mann-Whitney's U test, as appropriate for the data distribution. The level of significance was set at $p<0.05$.

All analyses were performed using Stata/IC 16.1 (StataCorp LCC, Texas, USA).

## Ethics

The study design and procedures were approved by the institutional review board of Tokyo Metropolitan Hiroo Hospital. All patients provided written informed consent before undergoing both the first and the second procedures. The ethical problems with performing the second procedure for all patients were discussed and overcome based on previous reports [10-12] including our data [13,14].

# Results

## Patient characteristics

Altogether, 93 patients underwent PVI and PWI for persistent AF. Figure 2 shows the procedure for patient selection.

Ninety-one patients remained (mean age, 67.5±9.8 years; male, 75.3%) for statistical analysis after two patients were excluded because of unsuccessful PWI. Intra-box ablation was needed in 57 of the 91

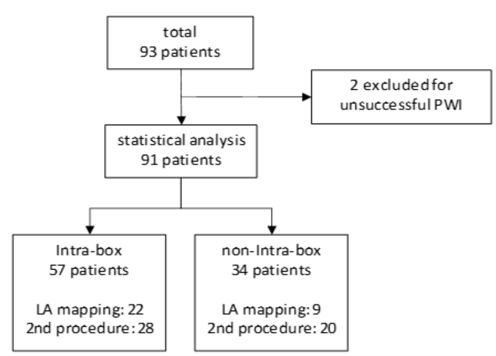


**Figure 2: Flow chart of patient selection**

LA, left atrium; PVI, pulmonary vein isolation; PWI, posterior wall isolation.

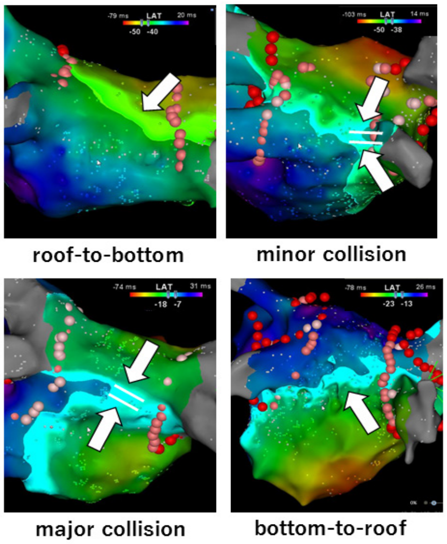


**Figure 3: The posterior wall conduction patterns.**

These figures show activation maps of four posterior wall conduction patterns. Roof-to-bottom pattern, the excitement wave front enters the posterior wall (PW) from the right of the roof line and proceeds to the bottom; minor collision pattern, the excitement wave front enters the PW from the right of the roof line and proceeds to the bottom, and another excitement wave front enters from the right of the bottom and collides at the lower right of the PW; major collision pattern, the excitement wave front enters from the roof and from the bottom colliding in the middle of the PW; and bottom-to-roof pattern, the excitement wave front enters the PW from the bottom and proceeds to the roof, often with low voltage in the anterior wall.

patients (62.6%) to achieve complete PWI. Patient characteristics with and without intra-box ablation are compared in Table 2. There was no difference in patient characteristics between the two groups.

There was no major complication, such as cardiac tamponade and esophageal fistula, although minor complications were reported in 3 patients (hematoma at puncture site in 2 and asymptomatic PV stenosis in 1).

## Findings of LA mapping and ablation in the first procedure

LA mapping after PVI and before PWI during high RA pacing was performed in 31 patients. In the LA map, 879±308 points were collected. The comparison between the intra-box group and non-intra-box group is shown in Table 3. PW activation time was significantly shorter in the intra-box group than in the non-intra-box group (40.3±10.4 ms vs 51.3±15.2, p=0.026), although there was no significant difference in two groups.

The propagation maps of posterior wall revealed that there are four patterns (Figure 3, Supplemental videos): the roof-to-bottom pattern, the minor collision pattern, the major collision pattern, and the bottom-to-roof pattern.

The proportion of the upward (from bottom to roof) conduction to that of downward (from roof to bottom) were large in the following order: bottom-to-roof, major collision, minor collision, and roof-to-bottom. More patients with a larger proportion of upward conduction needed intra-box ablation and this trend was statistically significant (4/4, 100% with the bottom-to-roof pattern; 4/4, 100% with the major collision pattern; 9/14, 64.2% with the minor collision pattern; 5/9, 55.6% in the roof-to-bottom pattern; p for trend =0.049).

During the procedure, more patients in intra-box ablation group abandoned applications because of esophageal temperature rise, however there was no significant difference (31/57, 68.9% vs 14/34, 31.1%; p=0.19).

## Findings of the second procedure

Forty-eight of 91 patients (56.5%) underwent the second procedure. Among them, 28 patients were in the intra-box group and 20 patients were in the non-intra-box group. More PW reconnection was observed in patients with intra-box ablation than those without intra-box ablation (21/28,75.0% vs 8/20, 40.0%; p=0.020). There was no significant difference in PV reconnection (10/28, 35.7% vs 4/20, 20.0%; p=0.31).

Among patients with PW reconnection, gap of roof line was observed in 16 patients (55.2%) and gaps of bottom line was in 13 (44.8%). Gap ablation was success in 14 patients (48.3%) and the rest of them needed intra-box ablation. There was no significant difference between intra-box group and non-intra-box group.

## Follow-up

AF recurrence at six months after the procedure was observed more frequently in patients with intra-box ablation (9/57, 15.7% vs 3/31, 9.7%; p=0.14), although there was no significant difference. AADs were continued until 6 months after the procedure in 14 of 91 patients (15.4%).

# Discussion

## Main findings

This observational study is novel for evaluating the characteristics and clinical effect of intra-box ablation during PWI for persistent AF. It showed that short PW activation time and conduction patterns were related to the necessity of intra-box ablation and that intra-box ablation was related to more reconnection of PW.

## Achievement of complete PWI and lesion transmurality

PWI is reportedly effective for persistent AF when combined with PVI [4,5]. The one of the major strategies of PWI is linear ablation, although various strategies have been used [15]. The successful rate of PWI varies between reports, ranging from 36.8% to 96% [7,16-18]. It can be difficult to achieve PWI, especially by linear ablation only. Here, 63.4% of patients required intra-box ablation to complete PWI.

**Table 3: Findings of LA mapping after PVI before PWI**

| | Intra-box n=22 | Non-intra-box n=9 | p value |
|---|---|---|---|
| Max voltage, intra-box [mV] | 5.1±2.0 | 5.0±2.0 | 0.96 |
| Median voltage, intra-box [mV] | 1.4±0.70 | 1.7±1.5 | 0.51 |
| Max voltage, para-line [mV] | 4.6±2.1 | 5.7±2.3 | 0.24 |
| Median voltage, para-line [mV] | 1.1±0.60 | 1.3±0.73 | 0.39 |
| PW area [$cm^2$] | 12.5±2.7 | 13.5±2.0 | 0.35 |
| PW activation time [ms] | 40.3±10.4 | 51.3±15.2 | 0.026 |

LA, left atrium; PVI, pulmonary vein isolation; PW, posterior wall; PWI, posterior wall isolation.

The main reason may be the inability to create a transmural lesion by linear ablation. Some studies evaluating the combination of endocardial and epicardial mapping provide direct evidence of a nonuniform lesion [8, 9, 19]. A previous study showed that 38% of lines, including the roof line and bottom line, required epicardial ablation to create a transmural lesion and that the existence of conduction abnormalities in the epicardium was suggested [8]. Another study of endocardial and epicardial mapping reported end-epi dissociation not only in voltage, but also in propagation [9].

One of the possible causes of non-transmural lesions is the position of the esophagus; hence, ablation should be abandoned because of esophageal temperature rise, thereby avoiding esophageal injury, particularly for the bottom line. Ablation was abandoned in 49.5% of patients in this population.

The endocardial and epicardial ablation hybrid may be effective for creating a transmural lesion; however, it is unclear whether this hybrid is more effective than endocardial ablation only [7]. Although hybrid ablation is reportedly effective and feasible [6-8], it should not be the standard strategy for the first procedure for safety reasons. Thus, improving endocardial ablation strategy is crucial.

Intra-box ablation appeared to be a risk factor for PW reconnection in this study. The necessity of intra-box ablation may reflect the inability of the transmural linear lesion or the connection between the endocardium and epicardium. Clinicians should confirm that PWI is achieved by the pacing maneuver and mapping especially in patients with intra-box ablation, given the higher rate of PW reconnection.

### The relationship between conduction pattern in the PW and intra-box ablation

The PW has a complex structure with varied thickness of the septopulmonary bundle (SPB), and the right side of the SPB has abrupt changes in muscle thickness and fiber direction [20-22]. The conduction abnormality on the left and right boundaries of SBP was reported to provide a substrate for AF [20].

According to the observation of propagation and vector maps, we classified the PW conduction pattern into four patterns: roof-to-bottom, minor collision, major collision, and bottom-to-roof. The main difference among these patterns was the proportion of upward to downward conduction in the PW. The proportion of upward conduction is larger in the order of bottom-to-roof, major collision, minor collision, and roof-to-bottom and the former two patterns were observed in the intra-box ablation group, which means it may be more difficult to achieve PWI by linear ablation only in cases with a larger proportion of upward conduction in the PW. Although this study evaluated the posterior voltage in the first procedure and PW gaps in the second procedure, the mechanism remained unclear.

## Limitations

This was an observational study with a small number of patients. In particular, LA mapping analysis was performed only under RA pacing in a limited number of patients; LA mapping data should be evaluated in a larger number of patients during pacing from several sites to confirm its relationship with intra-box ablation. The half of the patients rejected the second procedures, and it may have caused selection bias that more patients with palpitation and/or AF recurrence tended to undertake the procedure. Under the situation, actual PW durability may be higher. Moreover, this study is underpowered for AF recurrence and its design failed to evaluate long-term AF recurrence because second procedure was conducted 6 months after the first procedure.

This study could not provide solutions to increase the success rate of linear ablation and reduce intra-box ablation. Further study to compare endocardial PWI strategies is needed to improve PWI.

Besides these limitations, this study is novel as it showed the clinical impact of intra-box ablation and new insight on the PW conduction pattern.

## Conclusion

In summary, this observational study firstly evaluated the intra-box ablation during PWI and showed that intra-box ablation during PWI was associated with lower durability of PW. PW activation time and conduction patterns were related to the necessity of intra-box ablation.

## Supplemental videos

Videos show activation maps with vector maps of four posterior wall conduction patterns: roof-to-bottom, major collision, minor collision, and roof-to-bottom.

**Video 1**, roof-to-bottom pattern; **Video 2**, minor collision pattern; **Video 3**, major collision patten; **Video 4**, bottom-to-roof pattern.

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