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ELECTROPHYSIOLOGY

Impact of high frequency stimulation to confirm a complete box isolation in catheter ablation of non-paroxysmal atrial fibrillation

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Abstract

Introduction: Pulmonary vein (PV) isolation (PVI) including the left atrial posterior wall (LAPW) (Box-PVI) is proposed as an additional strategy for non-paroxysmal atrial fibrillation (NPAF), however, the efficacy remains controversial. The more reliable and durable the Box-PVI we can create, the better the rhythm outcomes might be than with a conventional PVI alone. This study focused on the potential exit conduction of the box lesion and investigated whether the conventional Box-PVI would be sufficient.

Methods and Results: We enrolled 350 consecutive patients with NPAF that underwent a conventional encircling Box-PVI and examined whether latent exit conduction and dormant "exit" conduction independently remained on the LAPW and in the PVs using high frequency stimulation (HFS) and an adenosine triphosphate (ATP) injection. All electrograms inside the box lesion were eliminated in all cases, however, HFS inside the box propagated outward in 23 cases (6.6%) without any exit conduction by conventional burst stimulation, and 24 cases (6.9%) exhibited only dormant "exit" conduction of the LAPW. Additional ablation where positive HFSs were observed created a complete bidirectional Box-PVI in 43 (41.3%) of the cases without a first pass Box-PVI. The recurrence rates depended on the groups classified according to the HFS response.

Conclusion: HFS delivered with an ATP injection on the LAPW and in the PVs following a Box-PVI could not only elucidate true exit block but also identified possible incomplete lesions or connections outside the ablation line, whose elimination could achieve a complete Box-PVI leading to a better rhythm outcome.

KEYWORDS
adenosine triphosphate, box isolation, dormant conduction, exit block, pulmonary vein isolation

Abbreviations:: AF, atrial fibrillation; ATP, adenosine triphosphate; AV, atrio-ventricular; Box-PVI, box pulmonary vein isolation (left atrial posterior wall isolation including pulmonary vein); CBS, conventional burst stimulation; CF, contact force; HFS, high frequency stimulation; LA, left atrium/atrial; LAPW, LA posterior wall; LAPWI, LAPW isolation; LS, long standing; NPAF, nonparoxysmal AF; PV, pulmonary vein; PVI, PV isolation; RF, radiofrequency; SR, sinus rhythm.

1 | INTRODUCTION

A left atrial posterior wall (LAPW) isolation (LAPWI) including a pulmonary vein (PV) isolation (PVI) (Box-PVI) is one of the options for additional atrial fibrillation (AF) ablation,[1] of which the efficacy remains controversial.[2] AF recurrences as well as newly developed arrhythmogenic substrates have been attributed to an incomplete Box-PVI due to not only reconnections of the roof and bottom lesions but also epicardial connections of the LAPW, which may hardly be perceivable.[2,3] We can obtain better outcomes if we do not overlook the above incomplete lesions and superfluous connections.

Bidirectional block, that is, entrance and exit block of the PVs and LAPW is indispensable for a PVI and LAPWI. Recently, a high-resolution mapping system with a microelectrode catheter has allowed the visualization of very tiny potentials that are not distinguishable with conventional electrodes,[4] which would suggest that the criteria for entrance block are obscure, because the local electrograms would depend upon the potential of the hardware and skill of the operator. On the other hand, one of the necessary conditions for these isolations is exit block,[5] so we had better focus on the exit block more strictly using another pacing method beyond conventional pacing, which may give us new insight. Moreover, checking dormant conduction using adenosine triphosphate (ATP) has remained controversial,[6] however, it could become useful for checking for dormant "exit" conduction if we focus on exit block.

In this study, we applied high frequency stimulation (HFS) inside the box lesion and injected ATP followed by HFS in order to investigate whether latent exit conduction remained including dormant "exit" conduction in patients in which a conventional Box-PVI was performed. Moreover, we delivered additional radiofrequency (RF) energy inside the box lesion where positive HFS responses were observed in order to create a complete Box-PVI and examined whether a complete Box-PVI based on our definition would affect the long-term prognosis.

2 | METHODS

2.1 | Study population

Three hundred fifty-one consecutive patients referred to our institution with symptomatic drug-refractory non-paroxysmal AF (NPAF) were enrolled in this retrospective cohort study for an initial catheter ablation between September 2015 and January 2022. We subdivided NPAF into persistent AF, which was that lasting for more than 1 week but less than 1 year, and long standing (LS) persistent AF, which was that lasting for longer than 1 year. Written informed consent was obtained from all patients. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board and Tokushukai Group Ethics Committee, and all patients provided written informed consent for the procedure.

2.2 | Study protocol

2.2.1 | Ablation procedure

The procedures were performed at least 1 month after the withdrawal of all antiarrhythmic drugs. Amiodarone was not prescribed in any patients. Multidetector computed tomography was performed prior to the procedure to evaluate the anatomical variations in the LA and PVs including the coronary artery imaging in each patient. If the patient was suspected to have any coronary artery stenosis, we performed coronary angiography and percutaneous coronary intervention prior to the ablation if necessary. All the procedures were performed under deep sedation with dexmedetomidine, propofol, and buprenorphine, and with esophageal temperature and direct blood pressure monitoring. The activated clotting time was kept at approximately 300 s all through the procedure. After a standard transseptal puncture, an irrigation catheter with a contact force (CF) sensor (THERMOCOOL SMARTTOUCH Catheter or THERMOCOOL SMARTTOUCH SF Catheter, Biosense Webster, Irvine, CA) was inserted through a deflectable sheath and used in combination with a 3D mapping system (CARTO, Biosense Webster, Irvine, CA), and at least one circular catheter or PentaRay catheter was inserted into the LA in all patients. We delivered RF energy with 30–40 Watts on the anterior and roof regions and 25–30 Watts on the posterior region of the PVs while measuring the CF, which was kept between 5 and 20 g for all RF applications whose target ablation index was 500 and 450, respectively. No patients underwent high-power short duration RF deliveries. We applied RF energy to the anterior portion of each PV along with the LA roof and bottom regions for a box shaped single ring encircling all the PVs and LAPW (Box-PVI) in all patients. We also performed cavo-tricuspid isthmus ablation in all patients during the waiting period after the above procedures.

2.2.2 | Confirmation of the box lesion

1. Feasibility study of HFS for confirming exit block

First of all, in order to elucidate the feasibility of using HFS for verifying exit block, we examined the response to delivering HFS at 20 Hz with an amplitude of 20 V and pulse width of 10 ms, which was the maximum power of the electrical stimulator (SEC-5104, Nihon Kohden, Tokyo, Japan) on the LAPW or inside the PVs during sinus rhythm (SR) before the ablation while monitoring the CF in 20 patients. The atrial rhythm became irregular during the HFS delivery at all sites in the atrium even with only 1 g of CF (Figure 1A), or AF was provoked after cessation of the HFS with a CF of 5 g or more for more than 5 s (Figure 1B) in all cases, which we defined as an "HFS (+)" response. On the other hand, no cases remained in SR during the HFS delivery, which we defined as an "HFS (-)" response. According to the above findings that the HFS delivery could activate the atrial myocardium in all cases independent of the CF, we thought HFS would be feasible

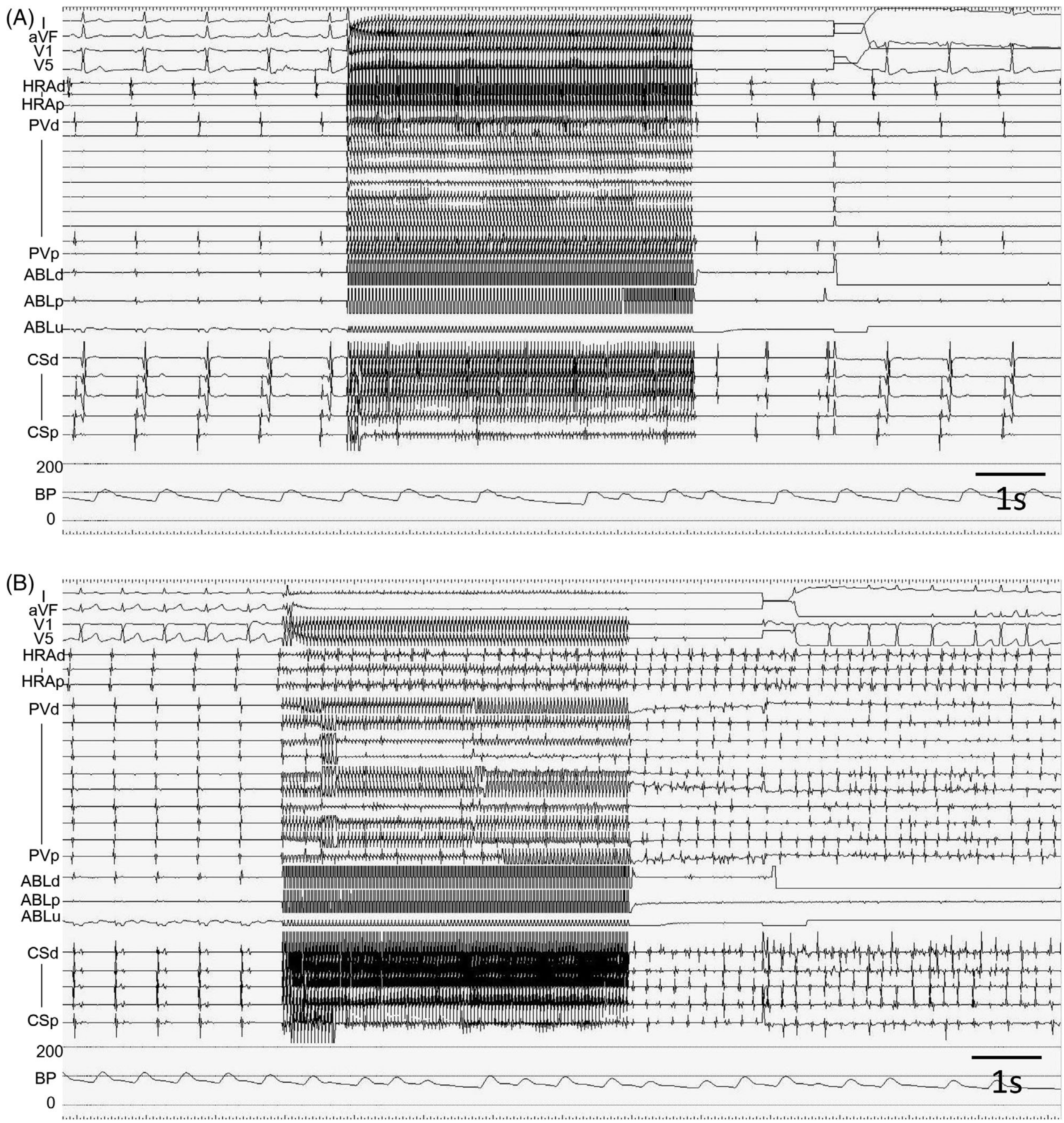


FIGURE 1 Intracardiac tracings recorded during high frequency stimulation (HFS) on the left atrial posterior wall (LAPW) during sinus rhythm (SR) in the cases before the ablation with a contact force of 1–2 g (A) and 9 g (B), respectively. The atrial rhythm became irregular during the HFS (A), and the HFS disrupted the atrial rhythm provoking AF after cessation of the HFS (B). We defined those as an HFS (+) response. The tracings are surface ECG leads I, aVF, V1, V5, and the intracardiac electrograms recorded by the distal to proximal electrodes of the high right atrial (HRAd-p) catheter, distal to proximal electrograms recorded by a circular catheter within the pulmonary vein (PVd-p), distal, proximal, and unipolar electrograms recorded by an ablation catheter (ABLd, ABLp, and ABLu) on the LAPW, distal to proximal coronary sinus catheter (CSd-p) electrograms, and the blood pressure.

for evaluating the local conductivity suggesting whether or not exit block could be created, and we then examined the completion of the bidirectional Box-PVI as follows.

2. Protocol to confirm the bidirectional Box-PVI (Figure S1)

We first confirmed the disappearance of the electrograms from each PV and the LAPW inside the encircling line using a PentaRay catheter or a circular catheter with 20 electrodes, that is, the completion of the entrance block. If any electrograms remained, we created an activation map of the electrograms inside the entire box area using the PentaRay catheter or circular catheter in order to find any gaps in the ablation lesions. Some cases in which the electrograms were not organized and the gaps were hardly identifiable required cardioversion, and then we created an activation map during SR to find any gaps. Then we applied additional RF energy to the gaps of the ablation lesions or inside the box area until they were eliminated. We then restored the rhythm to SR using cardioversion if the rhythm was not yet restored to SR in order to perform the following examination for confirming exit block.

Subsequent to the confirmation of entrance block during SR, we delivered HFS with a CF of more than 5 g for more than 7 s at each of at least three points at the center and on both lateral sides of the LAPW close to the PV carina and inside all PVs (Figure S2A and B). Moreover, we delivered conventional burst stimulation (CBS) at the same sites (100 bpm, 20 V×10 ms, with a CF of more than 5 g) in order to confirm whether the response to the CBS was the same as that to the HFS. We defined the case as a "CBS (+)" response if the CBS propagated outward and as a "CBS (-)" response if the CBS did not. If the atrial rhythm was affected during either type of stimulation due to residual exit conduction, we tried to identify the gaps in the ablation lesions by seeking out residual electrograms along the ablation line or by a pace-capture method,[7] and delivered additional RF energy along the circular ablation line. If the atrial rhythm was still affected by either type of stimulation, we then applied RF energy where HFS (+) responses were observed at a distance of more than 5 mm from the ablation line inside on the LAPW to eliminate the residual exit conduction.

3. Protocol to check dormant "entrance" and "exit" conduction using ATP and HFS

After a more than 20 min waiting period after the above procedures and eliminating any spontaneous reconnections, we first delivered HFS with a CF of more than 5 g at the center of the LAPW to confirm there were no acute exit reconnections, and we injected 40 mg of ATP to check whether or not the PV electrograms would appear again, namely, to confirm whether any dormant "entrance" conduction of the PVs could be provoked. Moreover, we then delivered HFS with a CF of more than 5 g at the center of the LAPW for more than 3 s just when atrio-ventricular (AV) block was provoked in order to examine whether the atrial rhythm could be affected by the HFS, namely, to confirm whether dormant "exit" conduction of the box lesion could be provoked independent of any dormant "entrance" reconnections.

If sinus arrest was provoked or AV block could not be provoked, we repeatedly administered an adjusted dose of ATP (20–60 mg) to create sinus beats with complete AV block and then delivered the HFS. If any dormant conduction was provoked, we then applied additional RF energy to any gaps or where positive HFS responses were observed.

4. Endpoint of the procedure and classification depending on the HFS response

We defined our target as a complete bidirectional Box-PVI with no electrograms (defined as a voltage of less than 0.05 mV) inside the block lesion and no exit conduction on applying HFS with no dormant "entrance nor exit" conduction of any PVs or the LAPW. Moreover, in order to investigate whether or not the PVI would be completed independent of the LAPW, we classified cases without a complete bidirectional Box-PVI into subgroups according to the incomplete culprit site. Since we defined complete exit block of the ipsilateral PVs as the absence of carina conduction,[8] we applied ATP injections followed by HFS deliveries for both carinas to examine the dormant "exit" conduction of the PVs in the same manner as that for the LAPW and classified them as a complete bidirectional PVI with an incomplete LAPWI or incomplete bidirectional PVI.

2.3 | Patient follow-up

After the Box-PVI procedure, all patients received clinical follow-up at 2 weeks, 1, 3, 6, and 12 months, and at least once a year, to check their 12-lead ECG and any symptoms. Antiarrhythmic drugs were continued for the first 3 months after the procedure in some patients and then ceased in all patients after the procedures. Twenty-four-hour Holter monitoring was performed at least three times from 3 months to 12 months after the procedure and then at least once every year in all patients. An implantable loop recorder was inserted in patients who consented, and an ambulatory ECG recorder (HCG-901, Omron, Kyoto, Japan) was used if the patients felt any unidentified palpitations in order to check if any tachyarrhythmias could be documented. We defined an arrhythmia recurrence in the patients if any atrial tachyarrhythmias lasting more than 30 s could be documented.

2.4 | Statistical analysis

Continuous variables are expressed as the mean ± SD or median with the first quartile to third quartile (Q1–Q3). We analyzed the parametric data using a Student's t-test and Wilcoxon and Kruskal-Wallis analyses for the nonparametric data. A Chi-squared analysis was used for the categorical variables. The event-free rates were calculated using the Kaplan-Meier survival method, and log-rank statistics were used for comparisons between groups. The data analyses were performed using JMP version 14.2.0 software (SAS Institute, Cary, NC). A $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

One patient out of 351 who had suffered from LS persistent AF could not be restored to SR even after delivering the maximum joules of an external cardioverter during the session. That patient was excluded from the analyses of this study.

TABLE 1 Baseline patient characteristics

	Total (n = 350)	Persistent AF (n = 188)	LS persistent AF (n = 162)	*p* value
Age (years)	67.0 ± 9.4	67.0 ± 9.4	67.0 ± 9.4	.9953
Male, n (%)	272 (77.7)	134 (71.3)	138 (85.2)	.0020
Body weight (kg)	66.0 ± 12.4	64.7 ± 12.4	67.5 ± 12.3	.0332
Height (cm)	165.2 ± 8.6	163.9 ± 8.7	166.7 ± 8.3	.0025
BMI (kg/m2)	24.1 ± 3.7	24.0 ± 3.6	24.3 ± 3.7	.4778
Echocardiography				
Ejection fraction (%)	61.3 ± 11.7	62.9 ± 11.1	59.6 ± 12.1	.0084
Left atrial diameter (mm)	42.2 ± 6.2	40.6 ± 6.0	44.1 ± 6.0	<.0001
Left common PV, n (%)	27 (7.7)	14 (7.45)	13 (8.0)	.8399
Comorbidities, n (%)				
CHADS2 score	1.64 ± 1.18	1.57 ± 1.20	1.71 ± 1.15	.1895
CHA2DS2-Vasc score	2.76 ± 1.72	2.76 ± 1.78	2.74 ± 1.68	.9311
HT	199 (56.9)	105 (55.9)	94 (58.0)	.7456
DM	81 (23.1)	41 (21.8)	40 (24.7)	.5283
CAD	63 (18.0)	31 (16.5)	32 (19.8)	.4860
SHD	40 (11.4)	24 (12.8)	16 (9.9)	.5008
CKD	70 (20.0)	39 (20.7)	31 (19.1)	.7890

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHA2DS2VASc, congestive heart failure/hypertension/2*age ≥ 75 years/diabetes mellitus/2*prior stroke, transient ischemic attack, or thromboembolism/vascular disease/74 > age ≥ 65 years/sex category; CHADS2, congestive heart failure/hypertension/age ≥ 75 years/diabetes mellitus/2*prior stroke, or transient ischemic attack; CKD, chronic kidney disease; DM, diabetes mellitus; HT, hypertension; LS, long-standing; PV, pulmonary vein; SHD, structure heart disease.
The data are presented as the mean ± SD, or n (%).

The baseline characteristics of each subgroup of patients are listed in Table 1. They included 272 men and 78 women with a mean age of 67.0 ± 9.4 years. We defined chronic kidney disease as an estimated glomerular filtration rate of less than 60 and diabetes mellitus as a case treated with any medication or an HbA1C level of 6.5 or more. There were some demographic differences between each subgroup.

3.2 | Procedure results

The procedure related characteristics and flow chart of the procedure and outcomes are shown in Figure 2, Table 2, and the Supplemental Table. The median follow-up period was 775.5 (406.5–1384.8) days.

3.2.1 | Entrance block

All PV and LAPV electrograms were eliminated after creating a single circular line encircling each PV antrum and the LAPW (i.e., the first pass PV and LAPW isolations) in 270 cases (77.1%) and after additional RF deliveries to the residual electrograms inside the box lesion in the remaining 80 cases (22.9%). Thus, we could confirm conventional entrance block of the box lesion in all cases (Figure S2A and B).

3.2.2 | Response to the HFS and CBS delivered in the PVs and on the LAPW

Subsequently, we applied HFS and CBS to each PV and on the LAPW in order to examine the exit conductivity of the block line while comparing the response to each type of stimulation. The atrial rhythm was not affected equally by either of the stimulations anywhere inside the box lesions in 247 cases (70.6%) (Figure 3A). In contrast, the atrial rhythm was affected by both types of stimulation from at least one site inside the box lesions in 80 cases (22.9%) (Figure 3B).

On the other hand, in the remaining 23 cases with an HFS (+) response (6.6%), the response to the CBS did not always correspond with that to the HFS. In those cases, CBS from at least one site inside the box lesion did not conduct outside and thus did not affect the atrial rhythm (Figure 4A). In those cases, some of the atrial rhythms were affected by the HFS while automatic firing was simultaneously observed (Figure 4B), as if exit block had been created. Further additional RF deliveries to the gaps in the box line and inside the box in those cases without such exit block could abolish the exit conduction, but the atrial rhythm was still affected by the HFS, namely, an HFS (+) response remained in 51 cases (14.6%).

All of the HFS (-) sites also exhibited a CBS (-) response, however, all of the CBS (-) sites did not always exhibit an HFS (-) response. Moreover, all of the cases with a negative response to that stimulation on the

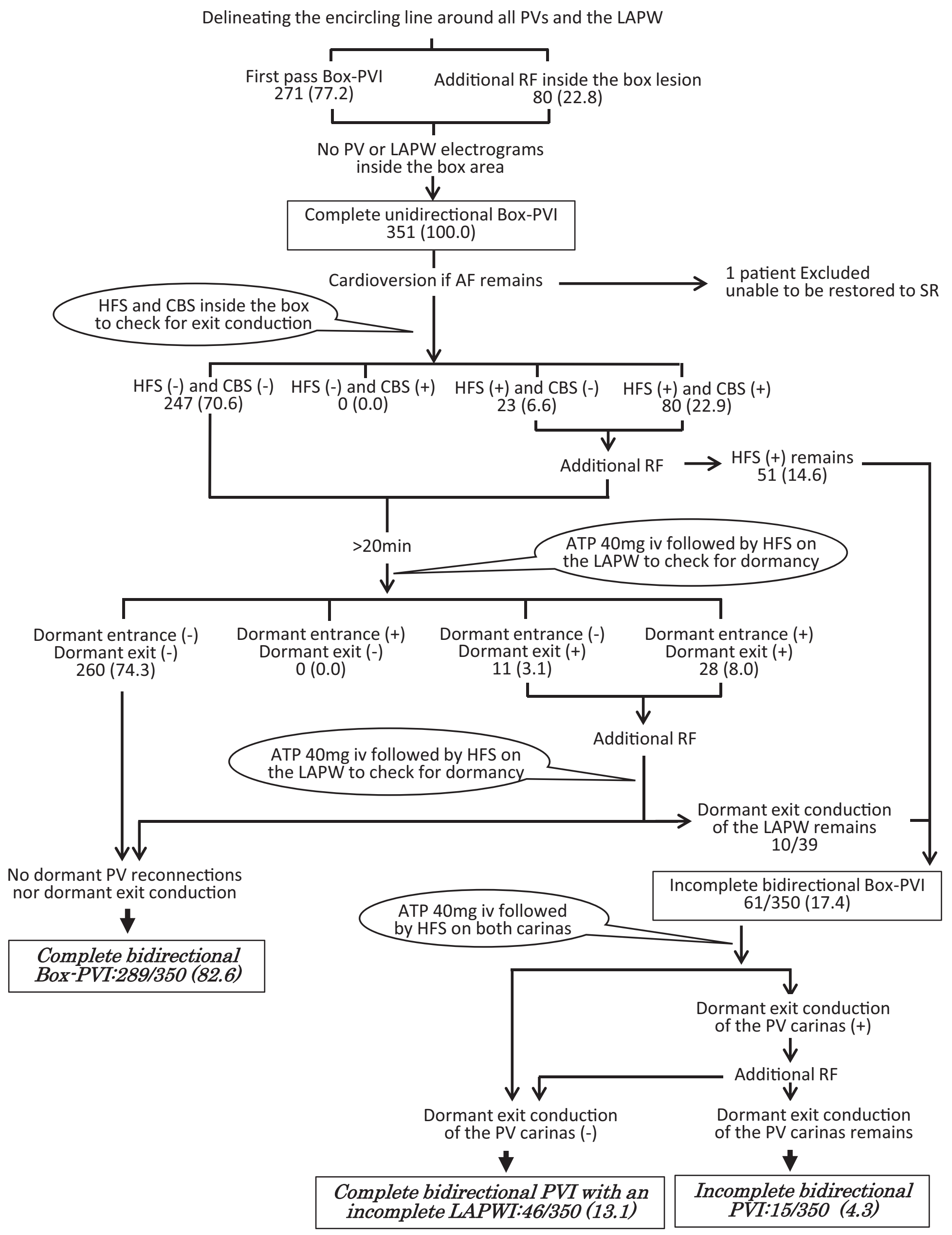


FIGURE 2 Flowchart of the procedure and outcomes. Conventional entrance block of the box lesion was obtained in all study cases, however, the response of the HFS and conventional burst stimulation (CBS) differed among the individuals. Moreover, a concomitant adenosine triphosphate (ATP) injection could elicit dormant "exit" conduction in addition to the dormant "entrance" conduction suggesting incomplete lesions. The data are presented as the n (%). See the text and Table 2 for the details. AF indicates atrial fibrillation; Box-PVI, box pulmonary vein (PV) isolation, LAPWI, LAPW isolation; PVI, PV isolation; RF, radiofrequency energy application. The other abbreviations are the same as in Figure 1.

LAPW also exhibited a negative response in the PVs, however, all of the cases with a negative response to that stimulation in the PVs did not always exhibit a negative response on the LAPW.

3.2.3 | Dormant response and the final classification

More than 20 min after the above examinations, we checked not only the conventional entrance dormancy but also the exit dormancy by means of an ATP injection followed by HFS. According to the above results that the HFS and LAPW would be more specific for examining the box lesion, we applied the HFS on the LAPW in order to check the exit dormancy (Figure 5A and B). All of the cases with a positive dormant "entrance" PV reconnection exhibited positive dormant "exit" responses to the HFS on the LAPW as well, but positive dormant "exit" responses to the HFS on the LAPW did not always exhibit a positive dormant "entrance" PV reconnection. Dormant "entrance" PV reconnections provoked by an ATP injection were seen in 34 cases (9.7%), and we encountered dormant "exit" conduction alone in 24 cases (6.9%). Additional RF deliveries

TABLE 2 Procedure outcome

	Total n = 350 (%)	Persistent AF n = 188	LS persistent AF n = 162	*p* value
Entrance block of the PV and LAPW	350	188	162	–
with one circular line alone	270 (77.1)	147 (78.2)	123 (75.9)	.7019
Exit block of the LAPW				
HFS (-) and CBS (-)	247 (70.6)	132 (70.2)	115 (71.0)	.9067
HFS (-) and CBS (+)	0	0	0	–
HFS (+) and CBS (-)	23 (6.6)	15 (8.0)	8 (4.9)	.2855
HFS (+) and CBS (+)	80 (22.9)	41 (21.8)	39 (24.1)	.7019
Reconnections				
Provoked dormant entrance conduction of the PV	34 (9.7)	19 (10.1)	15 (9.3)	.8574
Provoked dormant exit conduction of the LAPW alone	24 (6.9)	12 (6.4)	12 (7.4)	.8326
Dormant exit conduction of the LAPW remained	10 (2.9)	5 (2.7)	5 (3.1)	1.000
Dormant exit conduction of the PV and LAPW remained	2 (0.6)	0 (0.0)	2 (1.2)	.2135
Final results				
Complete bidirectional Box-PVI	289 (82.6)	156 (83.0)	133 (82.1)	.8879
with one circular line alone	246 (70.3)	131 (69.7)	115 (71.0)	.8153
with additional RF inside the box	43 (12.3)	25 (13.3)	18 (11.1)	.6249
Complete bidirectional PVI with an incomplete LAPWI	46 (13.1)	26 (13.8)	20 (12.4)	.7520
Incomplete bidirectional PVI	15 (4.3)	6 (3.2)	9 (5.6)	.3014
Procedure complications	0	0	0	–

Abbreviations: AF, atrial fibrillation; Box-PVI, box pulmonary vein isolation; CBS, conventional burst stimulation; HFS, high frequency stimulation; LAPW, left atrial posterior wall; LAPWI, LAPW isolation; LS, long-standing; PV, pulmonary vein; PVI, PV isolation.
The answers in each box are the results corresponding to each test including additional interventions. The data are presented as the n (%).

could abolish all of the conventional dormant “entrance” PV reconnections, however, the dormant “exit” LAPW conduction remained in 10 cases (2.9%) including two cases (0.6%) with dormant “exit” PV carina conduction.

We intended to create a complete bidirectional Box-PVI with a single encircling ring, but we could not create that in 104 cases (29.7%). However, additional RF deliveries where the HFS (+) responses were observed inside the box lesion could complete the Box-PVI in 43 out of those cases (41.3%), and finally no dormant PV reconnections nor dormant “exit” conduction, which meant the complete Box-PVI, was provoked in 289 cases (82.6%). There was no significant difference in the procedural result rates between the subgroups classified by the AF severity, and we encountered no procedure related complications.

3.2.4 | Clinical outcome following the Box-PVI confirmed by HFS and ATP

The Kaplan-Meier curves of the arrhythmia free survival differed among the groups classified based upon the HFS response, and the cases with a complete Box-PVI had the best clinical outcome (Figure 6A). We subdivided the subjects according to the AF severity. The aspect of those curves of the persistent and LS persistent AF were comparable, which also depended on the exit block classified by the HFS response (Figure 6B and C). The rhythm outcome in the groups in which a complete Box-PVI was obtained, was comparable irrespective of the additional RF ablation for the box lesion (Figure 6D).

4 | DISCUSSION

4.1 | Main findings

1. Most of the response to the CBS corresponded with that of the HFS. However, 23 cases (6.6%) exhibited no exit conduction with the CBS on the LAPW, but they demonstrated an HFS (+) response, suggesting that the CBS might overlook incomplete exit block.
2. The ATP administration followed by the HFS independently revealed dormant “exit” conduction suggesting an insufficient lesion in 11 cases (3.1%) with an HFS (-) response and no dormant “entrance” conduction, which could have never been unveiled otherwise.
3. An additional RF delivery where an HFS (+) response was observed but with no electrograms could eliminate the above residual exit conduction, that is, to create a complete Box-PVI, suggesting that some HFS (+) response sites might be highly correlated with culprits of an incomplete Box-PVI.

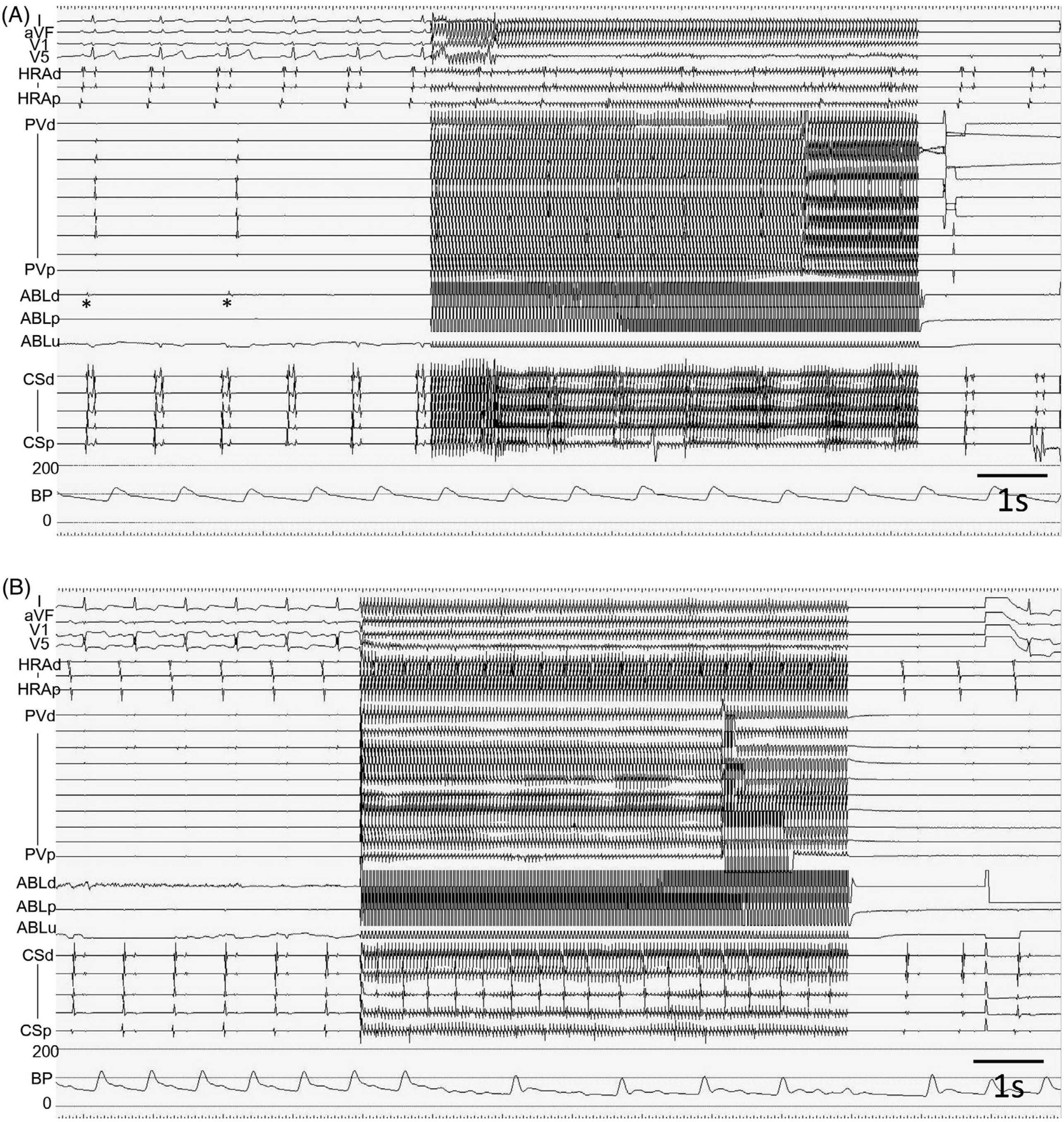


FIGURE 3 Intracardiac tracings recorded during the HFS on the LAPW during SR in the cases after a complete Box-PVI (A) and incomplete Box-PVI (B). A: Bump artifact (asterisks) of the catheter on the LAPW that preceded the PV electrograms did not conduct to the atrium, which certified that the catheter was in contact with the LAPW, and the atrial rhythm was not affected during or after the HFS. We defined this tracing response as an HFS (-) response. B: The atrial rhythm was affected during the HFS, which was an HFS (+) response. The order of the tracings and abbreviations are the same as in Figures 1 and 2.

4.2 | Incomplete Box-PVI unveiled by the HFS

As we hypothesized, the HFS could occasionally reveal possible incomplete exit block that had been diagnosed as a complete isolated lesion by the CBS. The pace-capture method has been proposed to elicit an incomplete ablation line to fill up the gaps,[7,9] however, HFS, which is well known to penetrate the epicardium,[10,11] might work to provoke not only an insufficient lesion formation but also epicardial connections to the LAPW. Recently, several investigators have reported that epicardial connections between the PVs and remote atrial structures are frequently observed,[12] which contributes to difficulties and recurrence of AF. Furthermore, these epicardial

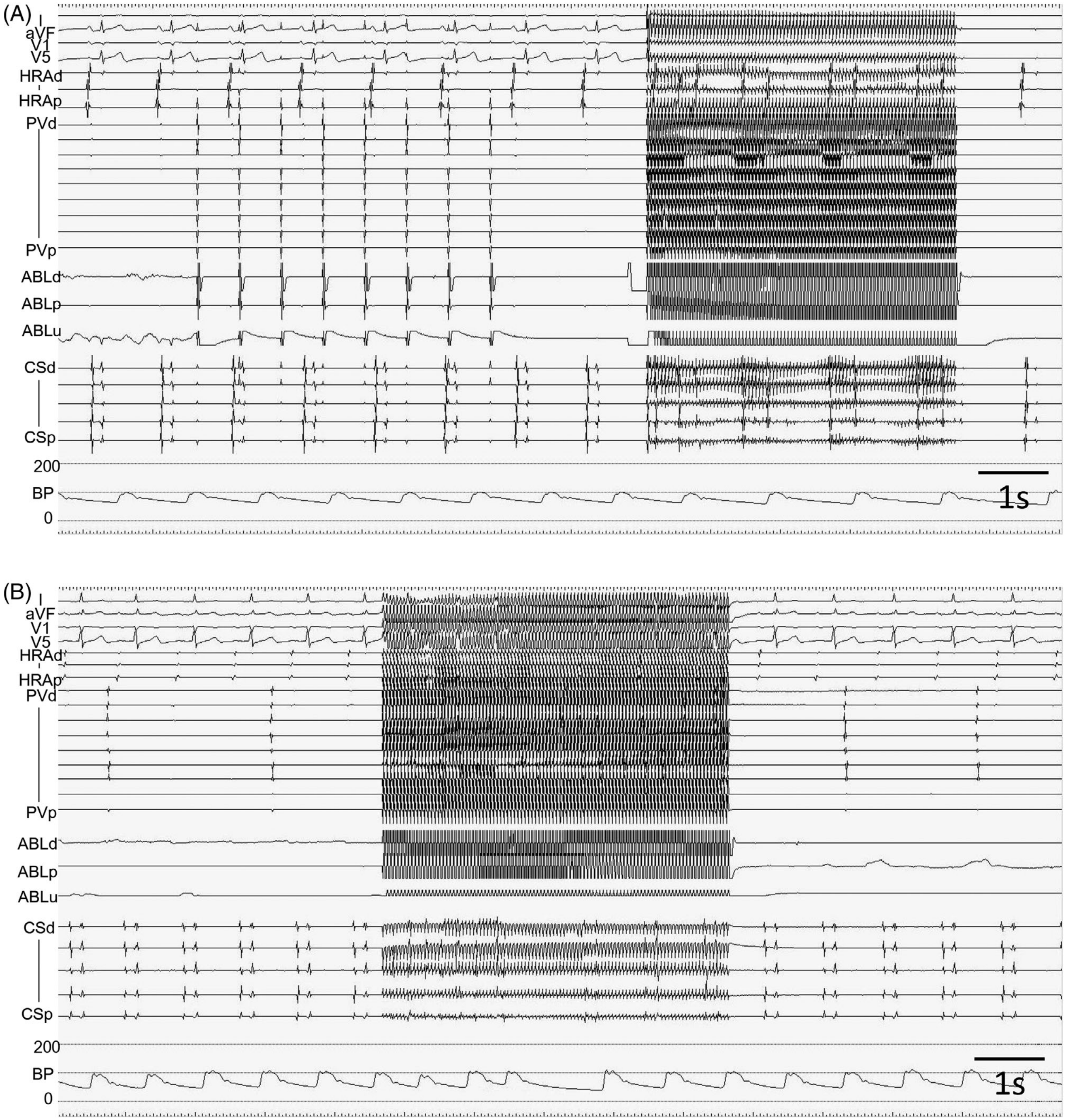
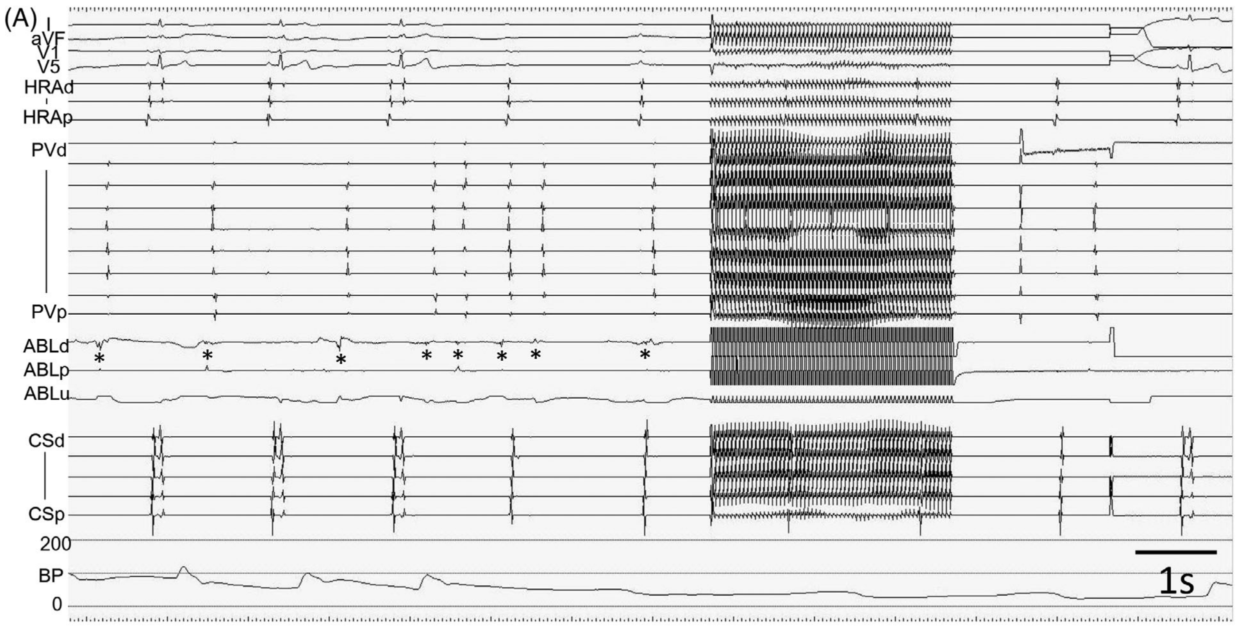


FIGURE 4 Intracardiac tracings recorded in the cases with an incomplete Box-PVI. (A) The CBS on the LAPW did not propagate outward resulting in maintaining SR, that is, a CBS (-) response, however, the following HFS disrupted the SR, that is, an HFS (+) response. (B) The atrial rhythm was affected during the HFS, which was an HFS (+) response, however, automatic firing was frequently observed. The order of the tracings and abbreviations are the same as in Figures 1 and 2.

connections involving the LA endocardium have been visualized using a high-resolution mapping system.[13,14] In the series in our study, we did not use the high-resolution mapping system with the microelectrode catheter, and therefore, we could not confirm any electrograms related to such connections outside the box lesion. However, an RF delivery to a site with no electrograms and an HFS (+) response, but remote from the ablation line, completed the bidirectional Box-PVI resulting in a better outcome, which suggested that the HFS (+) response might be a surrogate not only of an insufficient lesion but also a possible undetected indispensable connecting pathway across the ablation line.

A scattered approach[15,16] has been reported to reduce the risk of reconnections and to eliminate direct epicardial connections. However, an increased number of RF deliveries to the LAPW could increase the risk of esophageal injury. Other than such an approach, fewer RF deliveries to sites with an HFS (+) response on the LAPW might create a



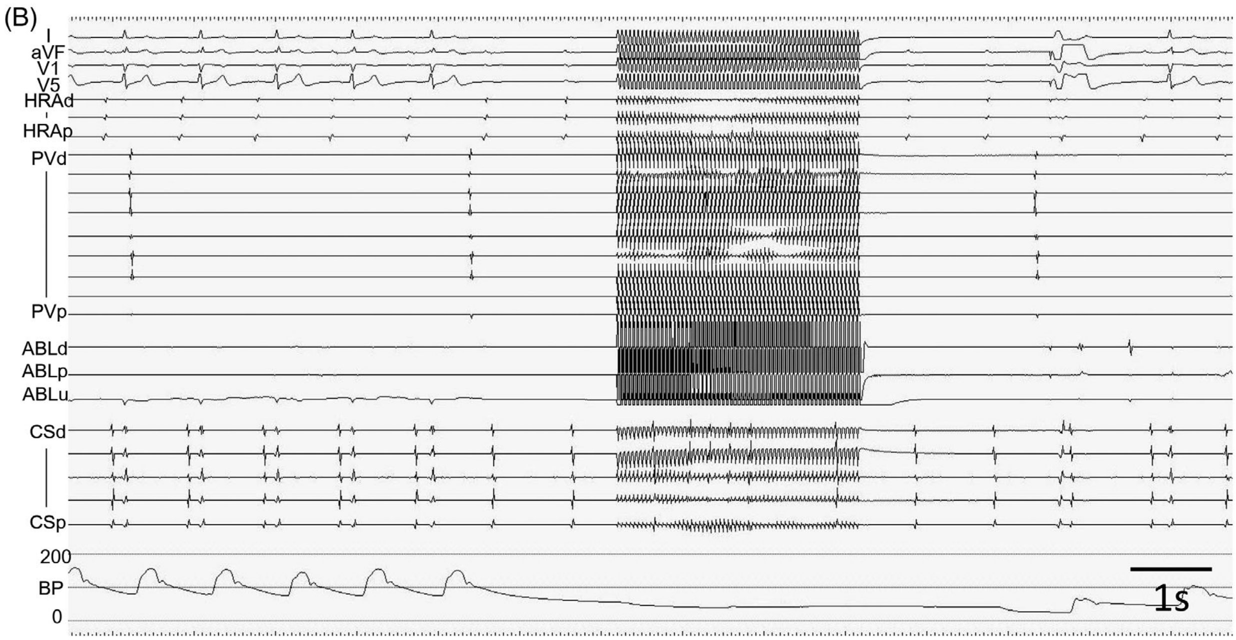


FIGURE 5 Intracardiac tracings recorded during the HFS on the LAPW during SR while provoking atrio-ventricular block by an ATP administration after a Box-PVI in the cases that underwent a complete Box-PVI (A) and incomplete Box-PVI (B). A: The atrial rhythm was not affected by the HFS, which represented an HFS (-) response. Note that the bump artifact (asterisks) of the catheter on the LAPW was similar to that in Figure 3A, which certified that the catheter was in contact with the LAPW. B: The atrial rhythm was affected by the HFS, which was an HFS (+) response, that is, dormant "exit" conduction, however, non-conducted automatic firing before and after the HFS was observed. The order of the tracings and abbreviations are the same as in Figures 1 and 2.

complete LAPW isolation in patients who would require a scattered approach for a complete box-PVI

4.3 | Dormant "exit" conduction

An ATP administration followed by HFS could bring out dormant "exit" conduction on the LAPW, which to the best of our knowledge had never previously been discussed. The injection of ATP had been reported to be an option for examining the durability of lesions by provoking dormant conduction leading to reconnections on isolation lines, however, its efficacy has recently been doubted.[6] Conventional dormant conduction has drawn attention to the entrance conduction based on the reappearance of PV electrograms, that is., dormant "entrance" conduction of the PVs. Thus, it might be difficult to evaluate the dormant conduction of the LAPW in patients undergoing a Box-PVI, since most

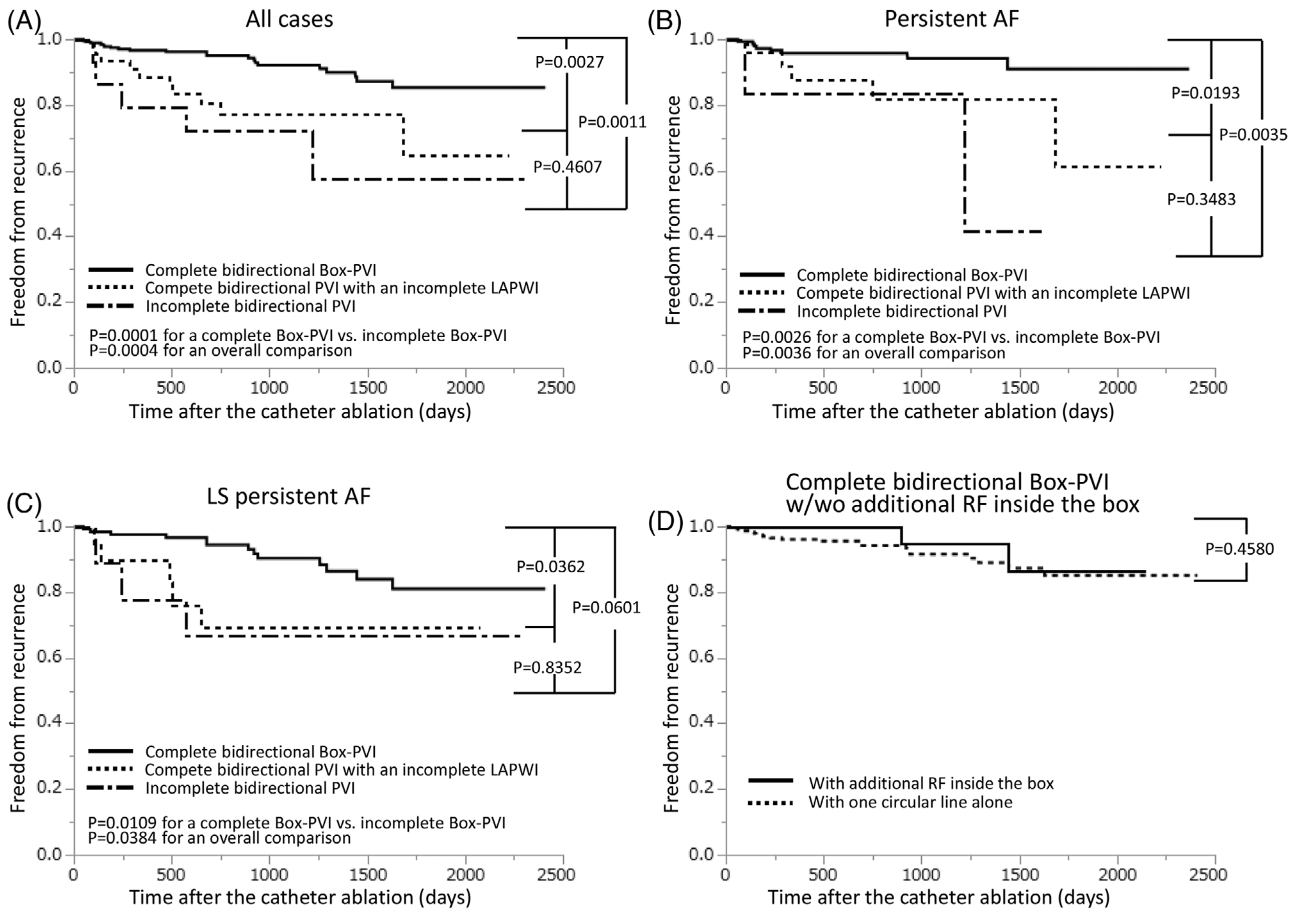


FIGURE 6 Kaplan-Meier curves of the comparison of the freedom from atrial tachyarrhythmias after a Box-PVI among the different isolated levels classified by the HFS response in all patients (A), that in patients with persistent AF (B), that in patients with long-standing (LS) persistent AF (C), and that in all patients in which a complete bidirectional Box-PVI was performed between that with or without additional RF inside the box lesion (D). See the text for the details. The abbreviations are the same as in Figures 1 through 2.

of the local electrograms on the LAPW could be tinier and hardly recordable in a large LA as compared to the PV electrograms. Furthermore, the transient reappearance of the local electrograms could hardly be noticed even with the recently available microelectrode catheter. Since part of the background of the PVI has been based upon the blockade of abnormal PV firing to the LA,[5] it would be important to confirm not only the entrance block but also the exit block as well with an ATP administration. In this study, an ATP administration followed by HFS independently revealed dormant “exit” conduction, which was provoked within 2 s in all after delivering the HFS but disappeared after a while in a manner similar to that of dormant “entrance” conduction. Most of the responses could be eliminated by additional RF deliveries, and their manner was also similar that of dormant “entrance” conduction. Conventional provocation of dormant “entrance” conduction works only for visible PV potentials, however, dormant “exit” conduction could unveil incomplete lesions even with tiny electrograms, such as on the LAPW of a large LA and of PV potentials in LS persistent AF, which we might overlook.

4.4 | Clinical implications

Some of the Box-PVIs may not have been actually completed in the patients whose LAPW had been diagnosed as being completely isolated by the conventional methods. The HFS and ATP would offer the opportunity to reveal any incomplete box lesions and the culprits in patients with an incomplete LAPWI. Additional RF deliveries to the culprit sites could create a complete Box-PVI leading to an improved prognosis.

4.5 | Limitations

There were some limitations. First, we evaluated the exit block and dormant “exit” conduction by delivering HFS inside the ablation line on the basis of confirming the regularity of the rhythm, so the rhythm should have been regular during those examinations. Thus, we could not evaluate the complete Box-PVI in patients who could not be restored to the SR by the ablation or cardioversion. Second, we delivered HFS and then elicited the exit conduction of the LAPW, which could hardly be provoked by the CBS. That might have suggested that we may have overestimated the exit conduction by the HFS. However, some sole additional RF applications at one of the HFS (+) response sites could abolish all of the positive HFS sites remote from the application site. Thus, we believe the HFS (+) response site may have highly been correlated with the culprit site of the incomplete Box-PVI. On the other hand, the HFS was delivered at a distance of more than 5 mm from the ablation line inside on the LAPW to prevent far-field capture outside the line. Moreover, to avoid phrenic nerve, right atrial, and ventricular far-field capture and to prevent pseudo-exit conduction,[17,18] we delivered the HFS on the posterior side of the PVs and their carinas rather than on the anterior side to evaluate the exit block. Therefore, we could have underestimated the complete exit block especially on the anterior side of the Box-PVI. Third, we mainly used a PentaRay catheter with 20 electrodes, which are 1 mm in size and each electrode distance is 2 mm, to check the LAPW electrograms. It might have been insufficient to identify very tiny residual potentials in a diseased or large LA. If we would have evaluated the local electrograms at the HFS (+) response sites using a high-resolution mapping system with a microelectrode catheter, we could have confirmed the electrograms from the undetected tissue connecting to outside the box lesion. Finally, it would have been better to determine the clinical significance of an HFS (+) response as compared to a CBS response and dormant "exit" conduction regarding the freedom from AF recurrence. However, we intended to abolish both of them, therefore, the cases with those received further RF applications. From an ethical point of view, we could not evaluate the prognosis of the cases with exit block diagnosed by the CBS but without our definition of complete exit block. Furthermore, it would not be adequate for a strict evaluation of the recurrence rate to use 24-hour Holter ECG and ambulatory ECG monitoring. However, we finally classified the cases into three groups based upon our results and obtained a reasonable outcome. We thought our methods were appropriate.

5 | CONCLUSION

HFS delivered on the LAPW and PV carina following a Box-PVI could clearly elucidate true exit block, and a concomitant ATP injection could define any dormant "exit" conduction, suggesting incomplete lesions that had been missed. An HFS response may not only provide new insight for confirming exit block but also identify possible incomplete lesions or connections outside the box lesion, whose elimination could achieve a complete Box-PVI. A Box-PVI with complete bidirectional block created and confirmed by HFS and ATP could be one of the efficacious strategies for NPAF.

AUTHOR CONTRIBUTIONS

Kazuo Kato performed the conception, design, and data collection. Shin Hasegawa, Shun Kikuchi, Yukihiro Uehara, Nobuo Ishiguro, Shimpei Tominaga, Akimitsu Tanaka, Hiroko Goto, Norihisa Shibata, and Ryosuke Kametani performed the data collection.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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