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Original Article

The feasibility of a Box isolation strategy for non-paroxysmal atrial fibrillation in elderly patients

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ABSTRACT

Background: Catheter ablation of non-paroxysmal atrial fibrillation (non-PAF) is a therapeutic challenge especially in elderly patients. This study describes the feasibility of a posterior left atrium isolation as a substrate modification in addition to pulmonary vein isolation, the so-called Box isolation, for elderly patients with non-PAF.

Methods: Two hundred twenty-nine consecutive patients who underwent Box isolations for drug-refractory non-PAF were divided into two groups according to their age; younger group comprising 175 patients aged <75 years and elderly group comprising 54 patients aged ≥ 75 years.

Results: During 23.7 ± 12.0 months of follow-up, the arrhythmia-free rates after one procedure were 53.1% in younger group versus 48.1% in elderly group ($p=0.50$). Following the second procedure, all patients had electrical conduction recoveries along the initial Box lesion. However, a complete Box re-isolation was highly established in both age groups (87.1% vs. 92.9%, respectively; $p=1.00$). Recurrence of macro-reentrant atrial tachycardia was mainly associated with the gaps through the initial Box lesion in both age groups (25.8% vs. 21.4%, $p=1.00$), but typical cavo-tricuspid isthmus (CTI) dependent atrial flutter was significantly observed in the elderly patients' group only (all events were observed within 6 months after the initial procedure; 3.2% vs. 28.6%, $p=0.009$). After two procedures, the arrhythmia-free rates increased to 73.1% in younger group versus 66.7% in elderly group ($p=0.38$). The occurrence rate of procedural-related complications did not differ between the two age groups, and there were no life-threatening complications even in elderly patients.

Conclusions: Box isolation of non-PAF is effective and safe even in elderly patients. A prophylactic CTI ablation combined with Box isolation might be feasible to improve the long-term outcome.

1. Introduction

The prevalence of atrial fibrillation (AF) increases steadily with age [1]. Since elderly patients have age-related degenerative changes that result in high rates of medical comorbidities, hepatic and kidney dysfunction, and physiologic changes of the atrial substrate, these factors can render the catheter ablation of AF a therapeutic challenge [2–4]. Nonetheless, because of the remarkable progress of catheter ablation of AF over the last decade, the effectiveness and safety of catheter ablation in elderly patients have been reported [4–7]. Moreover, the indications of AF ablation have been broadened in clinical practice. However, catheter ablation of non-paroxysmal AF (PAF) for elderly patients remains a therapeutic challenge since it has a less favorable outcome than that of PAF, and frequently requires additional ablation strategies for substrate modification, in addition to pulmonary vein isolation (PVI) [8,9]. There is still a paucity of data regarding catheter ablation as a therapeutic choice for non-PAF in elderly patients.

Referring to the ablation strategies for substrate modification of non-PAF, there are two most widely used additional ablation strategies that target the roof and mitral isthmus linear lesions [8–10] or complex fractionated electrograms [8,9,11]. However, in the Substrate and Trigger Ablation for Reduction (STAR) of AF II trial, those ablation strategies could not improve the cure rate as compared to PVI alone [8]. There is another method for an extensive substrate modification ablation targeting the isolation of the posterior left atrium (PLA), the so-called Box isolation [12,13]. This strategy arose from the concept that the PLA would play an

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important role in the maintenance of AF [14–16]. In the latest study, the PLA isolation with a PVI demonstrated a significantly high rate of sinus maintenance compared to PVI alone in patients with persistent AF [17]. However, to the best of our knowledge, there have been no reports on the feasibility of the Box isolation strategy regarding the impact of aging. Therefore, the aim of this study was to evaluate the long-term efficacy and safety of this Box isolation strategy for elderly patients with non-PAF.

2. Materials and methods

2.1. Study population

This retrospective study included all the patients who underwent catheter ablation with the Box isolation strategy for drug-refractory non-PAF, at Hayama Heart Center between January 2012 and December 2014. All patients underwent computed tomography (CT) before each procedure for exclusion of any left atrial thrombi and assessment of the morphology of the PVs and left atrium (LA). In the case of an uncertain thrombus, an additional trans-esophageal echocardiogram was performed to confirm it. The exclusion criteria in this study were patients with prior AF ablation attempts (radiofrequency hot balloon-based, surgical-based, or catheter-based), under dialysis, or those who had failed to be followed up for no less than 6 months. The enrolled patients were divided into two groups according to age <75 years and ≥ 75 years. Persistent AF was defined as AF episodes lasting >7 days and/or requiring intervention for termination, and long-standing persistent AF was defined as continuous AF uninterrupted for >1 year [18]. All the patients gave their written informed consent before the procedure.

2.2. Electrophysiological study

All the procedures were performed under intravenous sedation. A probe (Esophastar, Japan Lifeline) that during the procedure was inserted through a nasogastric tube monitored the intraluminal esophageal temperature (LET) [19]. After the transseptal access, an initial intravenous heparin bolus (100–200 IU/kg) was administered, with an additional bolus to maintain the activated clotting time between 300 and 400 s. Two decapolar circular mapping catheters (Libero, Japan Lifeline, Japan) through two long sheaths (SL-0, St Jude Medical, St. Paul, MN) and a quadripolar open 3.5-mm tip irrigated radiofrequency ablation catheter (Thermocool Navistar, Biosense Webster or CoolPath Duo Sofiable, St. Jude Medical, St. Paul, MN) through a deflectable sheath (Ultimum Agilis, St. Jude Medical, St. Paul, MN) were introduced into the LA by one transseptal puncture. A steerable quadripolar electrode catheter (Inter NOVA, Chiba, Japan) was positioned in the right ventricular apex; a duo-decapolar electrode catheter (Inter NOVA, Chiba, Japan) was positioned within the right atrium; and a duo-decapolar electrode catheter (Inquiry catheter, St. Jude Medical, St Paul, MN) was positioned within the coronary sinus (CS). The mapping and ablation were guided by a 3 dimensional electroanatomic mapping system integrated with multislice CT imaging (CARTO Merge, Biosense Webster, Diamond Bar, CA, or NavX, St. Jude Medical, St. Paul, MN).

2.3. Ablation protocol for the Box isolation in the initial procedure

At the beginning, a contiguous line was created at the roof of the LA between the superior PVs with a radiofrequency (RF) power of 25–30 W. The energy was delivered at each site until local electrograms were no longer obtained (or reduced to <0.05 mV) or the impedance dropped by 20 Ω. In creating a contiguous line, the formation of double potentials was also defined as the local endpoint of the ablation. After completion of the roof line, a left ipsilateral PV isolation was performed by first creating a contiguous line at the anterior portion, while the posterior portion of the ipsilateral PVs was electrically ablated, targeting only the sites of the earliest activation. Thereafter, a contiguous line was created at the floor line connecting both the inferior PVs. The RF energy was reduced to 20 W near the esophageal region. When the LET exceeded 39 °C during the RF delivery, the energy was terminated immediately, and 10–20 mL of cooling solution was repeatedly injected through the gastric tube to prevent the incidence of esophageal thermal injury [19]. Finally, the right antra of the ipsilateral PVs were ablated with the same technique as that for the left PVs. By moving up the anterior-superior contiguous line to join the previous roof line, the Box lesion was created. Further, a mapping catheter was placed on the posterior wall to confirm whether the PLA potentials still existed. If any potential remained within the Box lesion, detailed point-by-point mapping along the roof and floor lines was performed to identify any gaps. If needed, a decapolar ring catheter was placed on the posterior wall in order to determine the activation sequence or identify the earliest breakthrough, and another repetitive mapping and ablation was performed. Thereafter, if AF did not convert to sinus rhythm, electrical cardioversion was administered aiming to restore the sinus rhythm. The endpoint of the Box isolation was (1) all electrical activity dissociated or absent within the Box area during sinus rhythm or under CS pacing, and (2) pacing from the PLA and all four PVs during sinus rhythm was unable to capture the myocardium outside the Box area.

Finally, 20 mg of ATP was rapidly injected to evaluate the dormant conduction. If any sustained typical cavo-tricuspid isthmus (CTI) dependent atrial flutter (AFL) was documented before or during the procedure, a CTI ablation was performed. No aggressive attempt was made to create a mitral isthmus line unless any sustained perimitral AFL appeared during the procedure.

2.4. Study endpoints and follow-up

Follow-up visits were scheduled every 1–3 months after the procedure, including a physical examination and 12-lead electrocardiogram. Twenty-four-hour Holter monitoring was performed every 6 months, and before the discontinuation of anti-arrhythmic drugs (AADs) or when the patients felt an irregular pulse or any symptoms of recurrence. The patients were recommended to have an event recorder and were instructed not only to record all symptomatic events, but also to record at fixed intervals to detect any asymptomatic events. In patients with implanted devices such as a pacemaker, ICD, or CRT, interrogation of the devices was also used to confirm any arrhythmia recurrence. Oral anticoagulation therapy (OAT) was generally discontinued after 3–6 months in patients without AF recurrences, according to the $CHADS_2$ score. The AADs were gradually decreased after 3 months, depending on any AF/atrial tachycardia (AT) recurrence or the referring physician's decision. Recurrence was defined as episodes of AF or AT lasting >30 s that were documented by any monitoring modality. A second procedure was strongly recommended after the 3-month blanking period.

2.5. The second procedure

The electrophysiological study was the same as that in the initial procedure. First, if the patients were in macro-reentrant AT when the procedure was initiated, they underwent activation and entrainment mapping using electroanatomical mapping and ablation. Thereafter, mapping along the entire previous ablation line was systematically performed to identify the gaps under sinus rhythm or during CS pacing after electric cardioversion in the case of an AF rhythm. Gaps were defined as the recovery of electrical potentials with amplitude greater than 0.05 mV along the previous ablation line. These gaps were all ablated until the isolation of the PLA and all the 4 PVs was reestablished by the same method as in the initial procedure. After completion of the Box isolation, induction by rapid atrial pacing was performed, and if any further sustained macro-reentrant AT was induced, the AT was mapped and ablated.

2.6. Statistical analysis

The continuous variables were described as mean ± standard deviation (SD), or median (minimum, maximum). Student's *t*-test, Fisher exact test, and Mann–Whitney *U*-test were used to compare the differences across the two age groups. The long-term freedom from AF was analyzed using the Kaplan–Meier method. All tests were 2-sided, and statistical significance was set at a value of $p < 0.05$. The data were analyzed by SPSS software version 23.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Baseline characteristics

Three hundred and nineteen patients underwent the Box isolation for non-PAF during the entire period. Among those patients, 84 with prior AF ablation attempts (28 patients with radiofrequency hot balloon-based, 16 with surgical-based, and 40 with catheter-based ablation), 5 undergoing dialysis, and 1 that failed to be followed up for no less than 6 months were excluded. Finally, 229 patients were included in this study. Of those patients, 175 were in the younger age group with an average age of 62.8 ± 9.2 years, and 54 were in the elderly group, with an average age of 79.1 ± 3.3 years (Table 1). The elderly patients had a high proportion of female (25.1% vs. 40.7%, respectively; $p = 0.038$) and higher prevalence of comorbidities such as hypertension (45.7% vs. 63.0%, respectively; $p = 0.030$), diabetes (9.1% vs. 25.9%, respectively; $p = 0.004$), congestive heart failure (14.3% vs. 29.6%, respectively; $p = 0.015$), and valvular heart disease (5.1% vs. 14.8%, respectively; $p = 0.033$). The left atrial diameter was significantly large in the elderly patients (48.8 ± 7.7 mm vs. 51.6 ± 8.1 mm, respectively; $p = 0.026$).

The procedural characteristics are summarized in Table 2. The total number of applications, and the total procedural time did not differ between the two age groups. Isolation of all 4 PVs was completed in all the patients. A complete Box isolation was accomplished in 76.0% of the younger patients and 75.9% of the elderly patients ($p = 1.00$). The biggest cause of an incomplete Box isolation was the difficulty in achieving an adequate RF delivery due to frequent LET rises while creating the floor or roof lines adjacent to the esophagus. The proportion of additional ablation (CTI ablation [10.9% vs. 11.1%, respectively; $p = 1.00$] and mitral isthmus linear ablation [2.3% vs. 0%, respectively; $p = 0.58$]) performed was similar between the two age groups.

3.2. Long-term outcome

During an average follow up of 23.7 ± 12.0 months, the arrhythmia free rates with success of AADs after one procedure were 53.1% in younger group versus 48.1% in elderly group. ($p = 0.50$) (Fig. 1A). According to the type of AF, the arrhythmia free rates were 65.5% vs. 61.3%, respectively in patients with persistent AF ($p = 0.67$) and 40.6% vs. 28.0%, respectively in patients with long-standing persistent AF ($p = 0.29$).

Table 1
Baseline characteristics.

Variable	Younger group < 75 Years (*N*=175)	Elderly group ≥ 75 Years (*N*=54)	*P*-value
Age (years)	62.8 ± 9.2	79.1 ± 3.3	< 0.001
Female, sex (%)	44 (25.1)	22 (40.7)	0.038
BMI (kg/m²)	24.7 ± 5.7	23.5 ± 4.0	0.08
Time from the first diagnosis of AF (months)	40 (7-300)	40 (8-340)	0.69
Persistent AF	106 (60.6)	29 (53.7)	0.43
Long-standing persistent AF	69 (39.4)	25 (46.3)	0.43
CHADS2 score ≥ 2 (%)	43 (24.6)	43 (79.6)	< 0.001
Hypertension (%)	80 (45.7)	34 (63.0)	0.030
Diabetes (%)	16 (9.1)	14 (25.9)	0.004
Congestive heart failure (%)	25 (14.3)	16 (29.6)	0.015
Prior stroke (%)	18 (10.3)	10 (18.5)	0.15
Structural heart disease (%)	28 (16.0)	14 (25.9)	0.11
Ischemic heart disease (%)	11 (6.3)	4 (7.4)	0.76
Cardiomyopathy (%)	11 (6.3)	2 (3.7)	0.74
Valvular heart disease (%)	9 (5.1)	8 (14.8)	0.033
Prior open heart cardiac surgery (%)	5 (2.9)	2 (3.7)	0.67
Implantable device (%)	6 (3.4)	4 (7.4)	0.25
Medication			
Number of ineffective antiarrhythmic drugs	2.57 ± 1.04	2.50 ± 1.08	0.69
Warfarin (%)	54 (30.9)	21 (38.9)	0.32
Novel oral anticoagulant (%)	121 (69.1)	33 (61.1)	0.32
Antiplatelet agents (%)	18 (10.3)	8 (14.8)	0.34
ARB/ACE inhibitor (%)	64 (36.6)	22 (40.7)	0.63
Transthoracic echocardiography			
LAD (mm)	48.8 ± 7.7	51.6 ± 8.1	0.026
LVEF (%)	63.3 ± 10.3	64.4 ± 9.1	0.46

All data are expressed as the mean ± SD or *n* (%) or median (minimum-maximum). The patients were divided into 2 groups according to the age. BMI = body mass index; AF = atrial fibrillation; ARB = angiotensin receptor antagonist; ACEI = angiotensin-converting enzyme inhibitor; LAD = left atrial diameter; LVEF = left ventricular ejection fraction.

Table 2
Characteristics in the initial procedure.

Variable	Younger group < 75 years (*N*=175)	Elderly group ≥ 75 years (*N*=54)	*P*-value
(A) Procedural characteristics			
Number of applications	86.0 ± 20.9	80.7 ± 27.9	0.20
Total procedural time (min)	142.4 ± 27.7	140.2 ± 40.2	0.71
(B) Details of the catheter ablation content			
Complete Box isolation (%)	133 (76.0)	41 (75.9)	1.00
PVI (%)	175 (100)	54 (100)	1.00
CTI ablation (%)	19 (10.9)	6 (11.1)	1.00
MI ablation (%)	4 (2.3)	0 (0)	0.58

All data are expressed as the mean ± SD or *n* (%). The patients were divided into 2 groups according to the age. PVI = pulmonary vein isolation; CTI = cavo-tricuspid isthmus; MI = mitral isthmus.

In the second procedure, all the patients had an electrical recovery of the initial Box lesion, and there was a high prevalence of recurrence along the roof line (77.4% vs. 78.6%, respectively; $p = 1.00$) and floor line (75.8% vs. 71.4%, respectively; $p = 0.74$) (Table 3). Most of the conduction recoveries in the floor line were observed adjacent to the esophageal area regardless of the age. Moreover, the recurrence ratio of each PV did not differ between

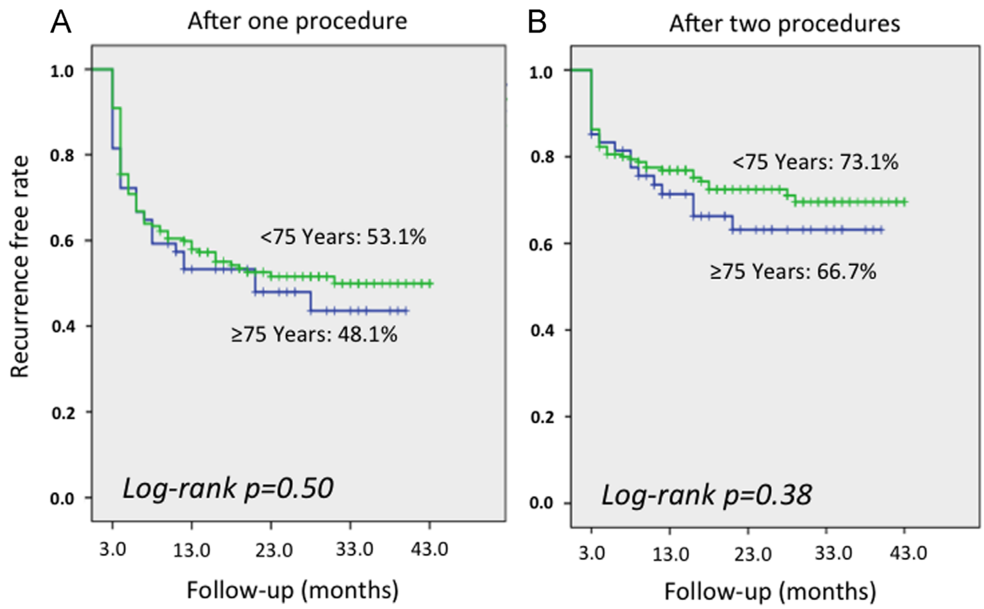

Fig. 1. Kaplan–Meier survival curve of the freedom from AF/AT recurrence after the Box isolation of non-paroxysmal AF according to the different age groups (< 75 years or ≥ 75 years). (A) After 1 procedure. (B) After 2 procedures. This analysis period began after a 3-month blanking period. AF=atrial fibrillation. AT=atrial tachycardia.

Table 3
Characteristics in the second procedure.

Variable	Younger group < 75 years (*N*=62)	Elderly group ≥ 75 years (*N*=14)	*P*-value
(A) Location of the recurrence			
Roof line (%)	48 (77.4)	11 (78.6)	1.00
Floor line (%)	47 (75.8)	10 (71.4)	0.74
LIPV (%)	29 (46.8)	6 (42.9)	1.00
LSPV (%)	31 (50.0)	8 (57.1)	0.77
RIPV (%)	30 (48.4)	7 (50.0)	1.00
RSPV (%)	32 (51.6)	7 (50.0)	1.00
(B) Recurrence type of the atrial arrhythmia			
Gap related left atrial flutter (%)	16 (25.8)	3 (21.4)	1.00
Cavo-tricuspid dependent atrial flutter (%)	2 (3.2)	4 (28.6)	0.009
Perimitral atrial flutter (%)	2 (3.2)	1 (7.1)	0.46
Focal atrial tachycardia (%)	0 (0)	1 (7.1)	0.18
Paroxysmal atrial fibrillation (%)	8 (12.9)	3 (21.4)	0.41
Persistent atrial fibrillation (%)	37 (59.7)	9 (64.3)	1.00
(C) Complete Box re-isolation (%)	54 (87.1)	13 (92.9)	1.00

All data are expressed as the n (%). The patients were divided into 2 groups according to the age. LIPV=left inferior pulmonary vein; LSPV=left superior pulmonary vein; RIPV=right inferior pulmonary vein; RSPV=right superior pulmonary vein.

the two age groups. The mechanism of the macro-reentrant AT was mainly due to the gaps through the initial Box lesion in both age groups (25.8% vs. 21.4%, respectively; $p=1.00$). However, they were all successfully ablated and rendered noninducible. Nevertheless, in the elderly patients, recurrences as typical CTI dependent AFL (typical AFL) were also highly observed compared with the younger group (3.2% vs. 28.6%, respectively; $p=0.009$). All the typical AFL episodes were documented within 6 months, even after the blanking period of the initial procedure. The perimitral AFL was relatively rare in both age groups (3.2% vs. 7.1%, respectively; $p=0.46$). At the end of the session, the complete Box re-isolation was highly achieved in both age groups (87.1% vs. 92.9%, respectively; $p=1.00$). After two procedures, the arrhythmia-free rates with success off AADs increased to 73.1% vs. 66.7%, respectively ($p=0.38$) (Fig. 1B).

Table 4
Adverse events.

Variable	Younger group < 75 years	Elderly group ≥ 75 years	*P*-value
(A) Perioperative term	*N*=247 procedures	*N*=71 procedures	
Cardiac tamponade (%)	1 (0.4)	0 (0)	1.00
Atrium-esophageal fistulae (%)	0 (0)	0 (0)	1.00
Vagal esophageal disorder (%)	0 (0)	0 (0)	1.00
Stroke/TIA (%)	0 (0)	0 (0)	1.00
Major bleedings (%)	0 (0)	1 (1.4)	0.22
Arterio-venous fistula (%)	1 (0.4)	1 (1.4)	0.40
Congestive heart failure (%)	2 (0.8)	2 (2.8)	0.22
(B) Long-term	N=175	N=54	
Stroke/TIA (%)	1 (0.6)	1 (1.9)	0.42
Major bleedings (%)	0 (0)	1 (1.9)	0.24
PMI due to sinus bradycardia (%)	4 (2.3)	3 (5.6)	0.36
Congestive heart failure (%)	2 (1.1)	1 (1.9)	0.56
Any cause death (%)	0 (0)	0 (0)	1.00

All data are expressed as the *n* (%). The patients were divided into 2 groups according to the age. TIA=Transient Ischemic Attack. PMI=Pacemaker implantation.

3.3. Adverse events

One cardiac tamponade occurred in a younger patient who needed cardiac drainage, while no event occurred in elderly patients (0.4% vs. 0%, respectively; $p=1.00$) (Table 4). There were no esophageal injuries including any atrio-esophageal fistulae or vagal esophageal disorders in either age group. Furthermore, no stroke/TIA events occurred during the procedures in either group.

One serious bleeding event of a gastrointestinal hemorrhage occurred in an elderly patient (0% vs. 1.4%, respectively; $p=0.22$).

In the long-term after the procedure, one thrombo-embolic event occurred in a younger patient 4 months after the second session despite OAT administration, while one cerebral hemorrhage occurred despite the discontinuation of the OAT (0.6% vs. 1.9%, respectively; $p=0.42$). One gastrointestinal hemorrhage event occurred in an elderly patient receiving both OAT and anti-platelet drugs (0% vs. 1.9%, respectively; $p=0.24$). The prevalence rates of the patients who required pacemaker implantations due to sinus bradycardia did not significantly differ between the two age groups (2.3% vs. 5.6%, respectively; $p=0.36$). All the elderly patients who required pacemaker implantations had more than 3 years of sustained long-standing persistent AF. None of the patients died during the follow-up in either age group.

4. Discussion

4.1. Main findings

The 3 major findings concerning the Box isolation of non-PAF in elderly patients were as follows:

(1) Long-term efficacy of the Box isolation: Elderly patients could achieve similar effectiveness as younger patients with respect to the sinus maintenance rates after Box isolation. Though elderly patients had high electrical conduction recoveries along the initial Box lesion in the second procedure, the complete Box re-isolation was highly achieved, and the sinus maintenance rates greatly increased after 2 ablation procedures.

(2) Safety of the Box isolation: Aging did not have an affect on the adverse effects in either the perioperative term or long-term. No life-threatening procedural-related complications occurred even in the elderly patients.

(3) Macro-rentrant AT after the Box isolation: Recurrence as a gap-related AFL was the major mechanism after the Box isolation regardless of the age, but all recurrences were successfully ablated and rendered noninducible. However, recurrence as a typical AFL was highly observed in the elderly patients only, with all the events documented in the mid-term after the procedure.

4.2. Long-term efficacy of the Box isolation in elderly patients

Previous animal and human reports demonstrated that the PLA plays an important role in the maintenance of AF [14–16]. These results suggest that electrically isolating the PLA in addition to a PVI might result in a much better cure rate than a PVI alone in patients with non-PAF. In the latest study, Bai et al. reported that in persistent AF, proven PLA isolation with PVI could provide a significantly better clinical outcome than PVI alone [17].

However, our study demonstrated that it was difficult to achieve a durable isolated Box lesion by a single procedure only, regardless of the age. Thomas et al. reported that the roof line was the major problem area for creating a PLA isolation, and that it might result from deeper muscle bundles on the roof [20]. In addition, our study demonstrated that the floor line was also the major limitation in achieving the PLA isolation. The major recurrence sites at the floor line were adjacent to the esophagus, and were the biggest cause of ending with an incomplete Box isolation due to frequent LET rises. This is the reason why the area that was in direct contact with the esophagus at the floor line might have also affected the achievement of a durable linear lesion. A previous report demonstrated that atrio-esophageal fistulae secondary to catheter ablation are a rare but potentially life-threatening complication and overlapping lines in the PLA might be responsible for it [21]. Further studies are required to determine to what extent we could supply the RF delivery in those areas when creating linear lesions on the floor.

However, after 2 procedures, the sinus maintenance rates increased to 66.7% during 2 years of follow-up in elderly patients. Chao et al. reported that the recurrence free rate of the stepwise ablation strategy for non-PAF was 47.7% after 2 procedures during 3 years of follow-up [9]. In the STAR AF II trial, the atrial arrhythmia free rates of PVI alone or PVI plus a linear or CFAE ablation including drug-on patients were 48–61% after 2 procedures during 18 months of follow up [8]. Our relatively high sinus maintenance rates might result from the effect of an additional PLA isolation requiring 2 procedures to be performed. Therefore, in considering a substrate modification such as the Box isolation strategy for the elderly patients, targeting Box isolation from the initial session, and not a stepwise strategy, might lead to a satisfactory long-term outcome with reducing the number of ablation procedures.

4.3. High prevalence of recurrences as typical AFL in elderly patients

The typical AFL is a frequently coexisting arrhythmia in patients with AF. Previous studies demonstrated that PVs also play an important role in the initiation of AFL and recurrences as symptomatic typical AFL after PVI are only common in patients with either a history of AFL or an episode of typical AFL during an electrophysiologic study [22,23]. Therefore, in patients without documented typical AFL, PVI alone might be sufficient to prevent the recurrence of both AF and AFL. Furthermore, Wazni et al. reported that though typical AFL was more common within the first 8 weeks in patients who did not undergo CTI ablation, the late incidence of typical AFL does not differ whether or not they undergo a CTI ablation [24].

However, in our study, elderly patients without typical AFL documents had higher recurrence rates even after the blanking period of the initial Box isolation. A previous study suggested that patients who had more marked remodeling of the right atrium including slowed conduction, a lower voltage, and a greater proportion of complex signals are more likely to develop sustained typical AFL [25]. There are several possible factors for the advanced remodeling in the right atrium in elderly patients. First, Kistler et al. reported that aging represents a structural remodeling resulting in a generalized conduction slowing of the right atrium and a regional functional conduction delay of the crista terminalis [2]. Second, in our study, the elderly patients had a higher prevalence of congestive heart failure and valvular heart disease than the younger patients. Among the 4 elderly patients who had recurrences of typical AFL after the Box isolation, 2 had moderate mitral regurgitation. A previous report demonstrated that chronic atrial stretch due to a hemodynamic overload leads to a regional conduction slowing and increased atrial refractoriness [26]. Chronic atrial stretch resulted from this valvular heart disease or heart failure in elderly patients might also affect advanced remodeling. The impact of this remodeling might be facilitated in patients with prolonged AF who have substantial electrical remodeling than those with PAF. Therefore, since it is difficult to achieve a durable isolated Box lesion including a PVI to eliminate the triggers of a typical AFL, a prophylactic CTI ablation combined with a Box isolation may be considered for the elderly patients with non-PAF.

4.4. Limitations

Some limitations must be taken into account in interpreting this study. First, the subclinical recurrences of AF/AT could not be completely detected, even though we tried to reduce this error by strongly instructing all the patients to assess their daily pulse. However, since this bias might be equally distributed in both age groups, it did not strongly affect our results. Second, since our study had a retrospective single-arm design and did not compare the efficacy between the Box isolation and PVI alone, it was difficult to discuss the pure efficacy of the PLA isolation without the influence of the PVI. Further clinical research with a randomized trial comparing these 2 ablation strategies is required in the future.

5. Conclusions

A Box isolation of non-PAF is effective and safe even in elderly patients. Though it is difficult to achieve a durable isolated Box lesion with only 1 procedure, 2 procedures can lead to a satisfactory long-term outcome. Recurrence as a typical AFL is high only in the elderly patients. Therefore, in considering the Box isolation strategy for elderly patients with non-PAF, targeting a Box isolation from the initial session with a combined prophylactic CTI ablation might be a feasible strategy.

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Conflicts of interest

All authors declare no conflict of interest related to this study.

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