








Impact of left atrial box surface ratio on the recurrence after ablation for persistent atrial fibrillation

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Abstract

Background: The posterior wall of the left atrium (LA) is a well-known substrate for atrial fibrillation (AF) maintenance. Isolation of the posterior wall between the pulmonary veins (box lesion) may improve ablation success. Box lesion surface area size varies depending on the individual anatomy. This retrospective study evaluates the influence of box lesion surface area as a ratio of total LA surface area (box surface ratio) on arrhythmia recurrence.

Methods: Seventy consecutive patients with persistent AF (63 ± 11 years, 53 men) undergoing computed tomography (CT) imaging and ablation procedure consisting of a first box lesion were included in this study. Box lesion surface area was measured on electroanatomical maps and total LA surface area was derived from CT. Patients were followed with 24-h electrocardiography and exercise tests at 3, 6, and 12 months after AF ablation. Arrhythmia recurrence was defined as any AF/atrial tachycardia (AT) beyond 3 months without antiarrhythmic drugs.

Results: During a median follow-up of 13 (interquartile range = 10-17) months, 42 (60%) patients had AF/AT recurrence. Multivariate Cox proportional regression analysis showed that a larger box surface ratio protected against recurrence (hazard ratio [HR] = 0.81; 95% confidence interval [CI] = 0.690-0.955; $P = 0.012$). Left atrial volume index (HR = 1.01 [0.990-1.024, $P = 0.427$]) and a history of mitral valve surgery (HR = 2.90; 95% CI = 0.970-8.693; $P = 0.057$) were not associated with AF recurrence in multivariate analysis.

Conclusion: A larger box lesion surface area as a ratio of total LA surface area is protective for AF/AT recurrence after ablation for persistent AF.

KEYWORDS

catheter ablation, left atrial box lesion, persistent atrial fibrillation ablation, substrate modification

1 | INTRODUCTION

Wide circumferential pulmonary vein isolation (PVI) is the first step in atrial fibrillation (AF) ablation as the pulmonary veins (PVs) and their antrum harbor the majority of triggers and are an important substrate for the maintenance of AF.¹ However, PVI alone in patients

with progressively diseased atria has a poor outcome and additional ablation strategies may be required.²⁻⁵ Both histological and electrophysiological determinants of AF, such as fibrosis, drivers and rotors are frequently found within the (inferior part of the) posterior wall of the left atrium (LA), which may be explained by a common embryologic origin with the PVs.⁶⁻¹⁰ Several studies have demonstrated that

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catheter ablation of the posterior wall, in addition to PVI, improves ablation outcome.^{11,12} Similarly, a surgical approach aiming to isolate the posterior wall resulted in 76% free of AF recurrences in patients with long-standing persistent AF.¹³

The insertion of the PVs in the LA can be highly variable between patients. A larger distance between the insertion of the superior PVs and inferior PVs increases the box lesion surface area. As the potentially arrhythmogenic posterior LA is not only confined to the area between the PVs but also it may extend caudally toward the coronary sinus,^{9,10,14} a variable part of the posterior LA will not be included in the box lesion, depending on the insertion of the inferior veins. In addition, with progressive left atrial dilation, the box lesion surface area as a ratio of total left atrial surface area may decrease further. We, therefore, hypothesized that differences in box lesion surface area normalized to total left atrial surface area may be an important factor influencing ablation outcome.

2 | METHODS

2.1 | Inclusion

Consecutive patients with symptomatic drug-refractory persistent AF who underwent PVI and isolation of the posterior LA between the PVs (box lesion) between 2013 and 2017 at the Leiden University Medical Center (LUMC) were retrospectively analyzed. During this period, all patients in the LUMC with persistent AF referred for ablation were treated with PVI plus box lesion. All consecutive patients with an (attempted) box lesion were included in the study. In all patients, a box lesion was performed in addition to a circumferential PVI referred to/defined as index procedure. Patients were treated according to the institutional clinical protocol and provided informed consent. Approval for the current retrospective analysis was obtained from the Institutional Review Board.

2.2 | Ablation procedure

Prior to the procedure, patients underwent a 320-slice Computer Tomography (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) and image segmentation to visualize the anatomy of the LA and PVs and to guide the ablation.¹⁵ The computed tomography (CT) scan was performed in a phase window between 65%-85% of R-R interval in patients with a heart rate ≥ 60 beats per minute and 75% of R-R interval in patients with a HR below 60 beats per minute.¹⁶ Antiarrhythmic drugs (AADs) were discontinued for five half-lives before ablation, with the exception of amiodarone which was continued until 1 month after ablation. Catheter mapping and ablation were performed under uninterrupted anticoagulation with a double transseptal approach using a 3D electroanatomical mapping system (CARTO3, Biosense Webster, Diamond Bar, CA, USA) or Ensite Velocity System (Model EE3000, St. Jude Medical, MN, USA), an irrigated 3.5-mm ablation catheter (Biosense Thermocool, Biosense Thermocool Smarttouch or St. Jude Medical Coolpath Duo) and a 10-polar circular mapping catheter (Lasso 2515, Biosense Webster). During the

index procedure, a box lesion was applied in all patients, in addition to a circumferential first or redo PVI. A roof line between the superior ostia of the superior PVs and a posterior line between the inferior ostia of the inferior PVs were created to complete the LA box lesion. The posterior line was drawn directly across the posterior wall between the inferior ostia of the inferior PVs. The operators did not extend the box lesion inferiorly below this level. Radiofrequency energy was delivered with a power of 25 W at the roof and the posterior LA wall and with 30 W at the anterior LA (maximum temperature, 43°C; flow rate, 17-20 mL/min, 30 s). If patients were not in sinus rhythm after ablation, an electrical cardioversion was performed. Entrance block in the PVs and the box lesion were confirmed using maximal signal amplification. In addition, exit block from the box lesion was demonstrated by pacing with high output (10 mA/2 ms) at the posterior LA. PVI and box lesion isolation were reconfirmed ≥ 30 min after the last RF application.

2.3 | Follow-up

Follow-up at the outpatient clinic was performed in all patients at 3, 6, and 12 months after the procedure. Follow-up included the clinical history for symptoms suggestive of recurrent AF, 12-lead electrocardiography (ECG), 24-h Holter monitoring, and an exercise test (at 3 and 12 months). AADs were continued until the first outpatient clinic visit at 3 months. After this blanking period of 3 months, the AADs were stopped in all patients. Patients were encouraged to obtain ECG recordings in case of symptoms to determine recurrence. Recurrence was defined as any AF or atrial tachycardia (AT) on a 12-lead ECG or lasting >30 s on Holter monitoring beyond 3 months.

2.4 | Calculation of left atrial and box lesion surface areas

The total LA surface area of all patients was measured on the segmented CT data after importing the original CT data into the CARTO system using the CARTO Merge software. The box lesion surface area, bordered by the posterior circumferential ablation lines adjacent to the PV ostia, the roofline, and the posterior line was measured on the electroanatomical (EA) maps using dedicated software of CARTO and Ensite Velocity systems (Figure 1). In addition, the ratio of the box lesion surface area to the total LA surface area (box surface ratio) was calculated. The distances between the contralateral PVs (box lesion width), between the roof and posterior line (box lesion height), and the distance between the middle of the posterior line to the mitral annulus was measured. Both in patients with and without atypical/mitral isthmus-dependent flutter at follow-up, the distance between the posterior line and the mitral annulus was measured. For outcome comparison, the study subjects were divided into two groups according to the box surface ratio (above and below the median).

2.5 | Statistical analysis

Clinical, echocardiographic, and ablation data were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Centre, Leiden, The Netherlands)

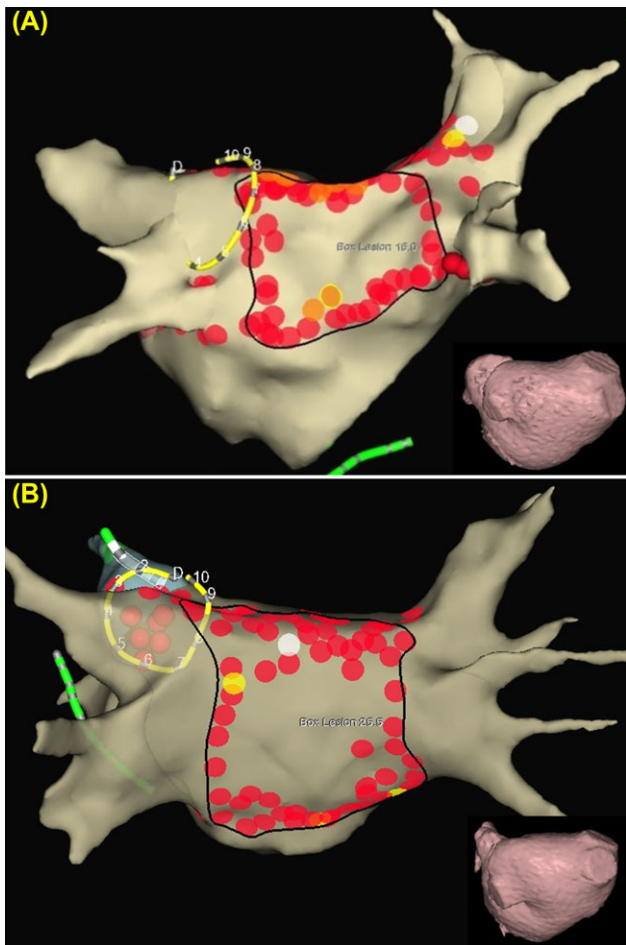


FIGURE 1 Box lesion area surface measurement. Box surface area measurement on electroanatomical maps in Ensite. Panel A: a posteroanterior view of the posterior wall of the left atrium with an example of a small box surface ratio (box surface area = 16.0 cm², total LA surface area on CT = 203.0 cm² measured in CARTO, box surface ratio = 0.08). Panel B: a posteroanterior view of the posterior wall of the left atrium with an example of a large box surface ratio (box surface area = 25.5 cm², total LA surface area on CT = 184.9 cm², box surface ratio = 0.14). CT = computed tomography; LA = left atrial [Color figure can be viewed at wileyonlinelibrary.com]

and were retrospectively analyzed. Continuous variables were expressed as mean \pm standard deviation or median (interquartile range [IQR]) and compared by an unpaired *t*-test or Mann-Whitney U test when indicated. Categorical variables were presented as numbers and percentages, and compared by the χ^2 or Fisher's exact test when appropriate. Kaplan-Meier survival curves were constructed to compare the AF-free survival between the two groups. Multivariable Cox proportional regression analysis was performed to detect any independent significant predictors of AF/AT recurrence reported as hazard ratio (HR) with 95% confidence interval (CI). Previously reported predictors of AF recurrence¹⁷ after catheter ablation were tested in the univariate model. Variables with a *P* < 0.1 in the univariate analyses were included in the multivariate analyses using the "enter" method. *P* < 0.05 was considered as a significant value. All analyses were performed with the SPSS version 23 statistics software package (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Study group

During the study period, 76 patients underwent box lesion isolation, in addition to PVI. From this group, six patients were excluded (EA maps were of insufficient quality to delineate the box lesion surface area [*n* = 4], EA maps were not retrievable [*n* = 1], multislice CT scan was not performed prior to ablation [*n* = 1]). The remaining 70 patients (63 \pm 11 years, 53 men) comprised the study population.

3.2 | Baseline characteristics

Persistent AF was diagnosed in 39 (56%) patients and long-standing persistent AF in 31 (44%) patients. The median duration of AF from the first diagnosis to the index ablation procedure was 70 (IQR = 40-114) months. The LA volume index was 50 \pm 22 mL/m² in the recurrence group and 41 \pm 13 mL/m² in the nonrecurrence group (*P* = 0.050). Thirty-one patients (56%) had undergone prior PVI. This was not significantly different between the recurrence and the nonrecurrence group. In the entire population, the median LA surface area was 196 (IQR = 172-233) cm², the box lesion surface area was 20 (IQR = 18-24) cm², and the median box surface ratio was 0.10 (IQR = 0.09-0.14). Eighty-four percent of the population was on AAD before the ablation. Fifty-one patients (73%) were using beta-receptor blocking drugs (sotalol: *n* = 27, 38%), 11 (16%) patients were using flecainide, 19 patients (27%) were using amiodarone, and two patients (3%) were using disopyramide. Four patients (6%) were on rate control with digoxin. Baseline characteristics are provided in Table 1.

3.3 | Procedural characteristics and complications

Table 2 provides the procedural details of the index ablation including additional ablation lesions beyond PV and box isolation. The box lesion was successfully isolated in 67 patients (96%), while isolation could not be achieved in three patients despite extensive ablation. Thirty-five patients (50% of the cases in which the index procedure was a reablation) underwent a redo PVI. Additional ablation (focal AT ablation, continuous fractionated atrial electrogram ablation, superior vena cava ablation, and mitral isthmus ablation) during the index procedure was performed in 10 (14%) patients. This was equally distributed between the groups and was not significantly different. One patient (1%) had a complication related to the vascular access (femoral pseudoaneurysm). No other complications occurred during the index procedure. During the repeated procedure, a single patient experienced cardiac tamponade that required drainage. No other complications were reported during the repeated procedures.

3.4 | Follow-up

After a median follow-up of 13 (IQR = 10-17) months, 42 patients (60%) experienced AF/AT recurrence after a median duration of 10 months (IQR = 5-14). Of these patients, 28 (67%) had recurrence of AF, 12 (29%) had recurrence of atypical flutter/AT, and two (5%) of both. In 16 (24%) patients, there was an improvement of their

TABLE 1 Demographic and baseline characteristics between patients with and without AT/AF recurrence

	All (n = 70)	AF/AT recurrence (n = 42)	No AF/AT recurrence (n = 28)	P value
Age, years	63 ± 11	63 ± 11	63 ± 10	0.950
Male gender, n (%)	53 (76)	33 (79)	20 (71)	0.495
Body mass index (kg/m ²)	27 ± 4	27 ± 4	27 ± 4	0.529
Comorbidity				
Hypertension, n (%)	37 (53)	22 (52)	15 (53)	0.922
Hyperlipidemia, n (%)	27 (39)	20 (47)	7 (25)	0.057
Diabetes mellitus, n (%)	6 (9)	5 (12)	1 (4)	0.390
Structural heart disease, n (%)	21 (30)	15 (36)	6 (21)	0.201
OSAS, n (%)	6 (9)	4 (10)	2 (7)	1.000
eGFR < 30, n (%)	1 (1)	1 (2)	0 (0)	1.000
Duration of AF, months	59 (41-116)	59 (36-112)	57 (43-115)	0.405
Type of AF				
Persistent, n (%)	39 (56)	25 (60)	14 (50)	0.432
Long standing persistent, n (%)	31 (44)	17 (41)	14 (50)	0.432
Prior PVI, n (%)	39 (56)	26 (62)	13 (46)	0.202
Prior mitral valve surgery, n (%)	8 (11)	6 (14)	2 (7)	0.462
LV ejection fraction < 35	1 (1)	1 (2)	0 (0)	1.000
LA volume index (mL/m ²)	46 ± 19	50 ± 22	41 ± 13	0.050
CHA ₂ DS ₂ -VASc	2 ± 1	2 ± 1	2 ± 1	0.697
AAD, n (%)	59 (84)	36 (85)	23 (82)	0.745

Values are reported as the mean ± standard deviation, median (interquartile range), or n (%).

AAD = antiarrhythmic drug; AF = atrial fibrillation; AT = atrial tachycardia; eGFR = estimated glomerular filtration rate; LA = left atrium; LV = left ventricle; NOAC = novel oral anticoagulant; OSAS = obstructive sleep apnea; PVI = pulmonary vein isolation.

TABLE 2 Procedural details of the index procedure between patients with and without AT/AF recurrence

	All (n = 70)	AT/AF recurrence (n = 42)	No AT/AF recurrence (n = 28)	P value
Successful box isolation, n (%)	67 (96)	40 (95)	27 (96)	0.810
CARTO, n (%)	48 (69)	29 (69)	19 (68)	0.916
Force sensing catheter, n (%)	20 (29)	11 (26)	9 (32)	0.589
Additional ablation, n (%)	10 (14)	6 (14)	4 (14)	1.000
CFAE, n (%)	3 (4)	1 (2)	2 (7)	0.335
SVC isolation, n (%)	3 (4)	2 (5)	1 (4)	0.810
Mitral isthmus, n (%)	4 (6)	2 (5)	2 (7)	0.674
Focal AT, n (%)	3 (5)	2 (6)	1 (5)	0.810

Values are reported as the mean ± standard deviation, median (interquartile range), or n (%).

AF = atrial fibrillation; AT = atrial tachycardia; CFAE = continuous fractionated atrial electrogram; LA = left atrium; SVC = superior vena cava.

symptoms and the tachycardia improved from persistent to paroxysmal. AF-free survival off ADD was 40%. AF-free survival on/off AAD was higher (59%). There was no significant difference in recurrence between patients undergoing ablation with and without contact force sensing (62% vs 55% $P = 0.589$). Before the ablation, AADs usage (84% in the total group) was not significantly different between the groups. In the no-recurrence group after the blanking period of 3 months, 38 patients (90%) stopped all AADs and four patients (10%) continued with sotalol in a lower dosage at the discretion of the treating physician as beta-blockade therapy was indicated for concomitant coronary artery disease.

3.5 | Predictors of AF/AT recurrence

In univariate analysis, a larger LA volume, a history of prior mitral valve surgery, and a smaller box surface ratio were associated with AF/AT recurrence ($P \leq 0.1$). Male gender; type and duration of AF; body mass index; CHA₂DS₂-VASc score; and previous PVI box lesion width, height, and surface area were not associated with AF recurrence (Table 3). On multivariate Cox proportional regression analysis, only a smaller box surface ratio (HR = 0.81; 95% CI [0.690-0.955]; $P = 0.012$) was independently associated with AF/AT recurrence (Table 3). The box lesion width and height were not significantly different between

TABLE 3 Univariate and multivariate Cox proportional regression analyses for predictors of AF/AT recurrence

Variables	Univariate		Multivariate	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Age	0.990 (0.961-1.021)	0.536		
Female sex	0.716 (0.342-1.502)	0.377		
BMI	1.012 (0.936-1.094)	0.759		
SR at admission	1.493 (0.703-3.169)	0.297		
Previous PVI	1.631 (0.859-3.096)	0.134		
Additional Ablation	1.584 (0.719-3.490)	0.253		
AF duration	1.003 (0.998-1.009)	0.245		
CHA ₂ DS ₂ -VASc	0.961 (0.744-1.240)	0.758		
Distance posterior line to mitral annulus	0.992 (0.953-1.033)	0.705		
Box lesion width	1.038 (0.978-1.101)	0.217		
Box lesion height	0.999 (0.950-1.050)	0.968		
Box lesion surface area	1.004 (0.938-1.074)	0.916		
LA volume index	1.015 (1.000-1.031)	0.046	1.007 (0.990-1.024)	0.427
Prior mitral valve surgery	2.263 (0.936-5.476)	0.070	2.903 (0.970-8.693)	0.057
Box surface ratio	0.850 (0.729-0.991)	0.038	0.812 (0.690-0.955)	0.012

AF = atrial fibrillation; AT = atrial tachycardia; BMI = body mass index; LA = left atrium; EF = ejection fraction; PVI = pulmonary vein isolation; SR = sinus rhythm.

the recurrence and nonrecurrence groups (38 ± 5 and 38 ± 8 mm and 45 ± 8 and 44 ± 9 mm, respectively). The distance between the posterior line to the mitral annulus was 53 ± 8 mm in the recurrence group and 54 ± 8 mm in the nonrecurrence group ($P = 0.639$). In addition, no correlation between the box surface ratio and the distance from the posterior line to the mitral annulus was observed ($P = 0.266$). The distance between the posterior line to the mitral annulus was also not significantly different in patients with and without documented atypical/mitral isthmus-dependent flutter (51 ± 9 vs 54 ± 8 mm; $P = 0.236$). Kaplan-Meier survival curves showed that patients with a larger box surface ratio had a lower incidence of AF/AT recurrence. The median survival (free from AT/AF) after the index LA box lesion was 8 months in the large box surface ratio group and 14 months in the small box surface ratio group ($P = 0.0324$ by logrank test; HR = 0.57 [CI = 0.3086-1.058]) (Figure 2).

3.6 | Repeat procedures

In 15 patients, a reablation was performed after the index box lesion isolation. In all patients, isolation of the PVs and of the box lesion was checked and/or an additional ablation was performed. Two patients underwent a His-ablation after a permanent pacemaker insertion. In the remaining 13, re-PV isolation ($n = 9$), re-isolation of box lesion ($n = 9$), superior vena cava isolation ($n = 1$), mitral isthmus ablation ($n = 4$), anterior box lesion isolation ($n = 1$), and other LA AT ablation ($n = 4$) were performed. Out of 13 patients, follow-up data were available in 10 patients (two lost to follow-up). In one patient, the procedure was aborted because of a cardiac tamponade and AF was accepted. During a median follow-up of 9 (IQR = 5-18) months after the repeat procedure, four (40%) patients maintained sinus rhythm without AADs and six (60%) patients had recurrent AF after a period of 5 (IQR = 4-8)

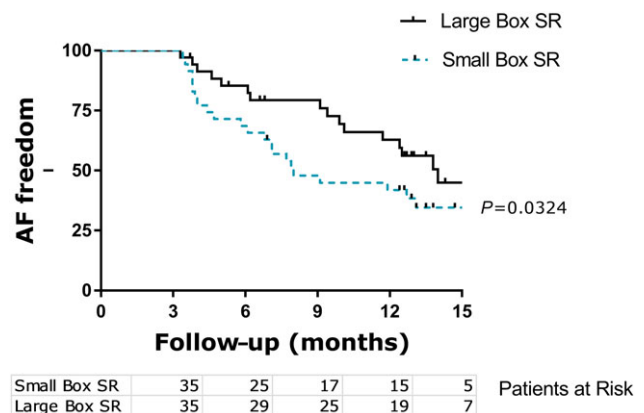


FIGURE 2 Atrial fibrillation-free survival off AAD according to box surface ratio (Box SR). AAD = antiarrhythmic drug; AF = atrial fibrillation; SR = surface ratio [Color figure can be viewed at wileyonlinelibrary.com]

months. In summary, AF-free survival after the index procedure was 40% and after the repeated procedures was 51% off AADs. AF-free survival on/off AAD in the entire group after the repeated procedures was 64%.

4 | DISCUSSION

4.1 | Main findings

The major finding of this study is that a larger box lesion surface area as a ratio of total left atrial surface area is protective for AF/AT recurrence after ablation for persistent AF. To the best of our knowledge, this is the

first study that investigated box lesion surface area ratio in relation to ablation outcome.

4.2 | Benefit of substrate modification beyond PVI

The necessity of extending the ablation beyond PVI by performing substrate modification in patients with persistent AF is currently controversial due to the STAR-AF II trial, in which no benefit of additional ablation beyond PVI was demonstrated.¹⁸ Studies reporting on favorable outcomes after isolation of the posterior wall are not in direct contradiction with the STAR AF II trial as this trial did not include a group undergoing isolation of a part of the LA, in addition to PVI. Isolation of a part of the posterior LA may be a promising strategy, as there is evidence that the LA posterior wall harbors triggers and it is the substrate for AF; animal studies have demonstrated that 80% of the AF triggers are located in the posterior wall, including the PV region, based on electrophysiological and molecular findings.¹⁹⁻²¹ In addition, imaging studies could demonstrate that fibrotic areas (atrial delayed enhancement) are mainly located in the posterior wall.⁶⁻⁸ More specific, the preferential distribution of drivers and atrial fibrosis, beside the PV-antrum, is located in the inferior part of the posterior wall.^{9,10} The importance of targeting the posterior wall in patients with persistent AF is also demonstrated by the encouraging results (62% overall freedom of AF) of surgical ablation²² of the posterior wall. In line with these results, we recently published a 76% success rate with a standalone surgical box lesion in persistent AF.¹³ A meta-analysis comparing catheter ablation of PVI versus PVI with box lesion also showed a benefit of adding a box lesion to PVI in patients with persistent AF.¹¹ In the current study, 1-year success was 40% after a single procedure off AADs and 64% after repeated procedures on/off AAD. Bai et al recently reported an AAD-free survival of 65%, 50%, and 40% after 1, 2, and 3 years of follow-up, respectively, in persistent AF after catheter ablation of the posterior wall.²³ Lim et al reported a 2-year AT/AF drug-free survival of 53% in patients with persistent AF.²⁴ The difference in outcome between surgical and catheter-based isolation of a box lesion can be explained by the higher durability of surgical ablation compared to catheter-based ablation lesions.²⁵ It is unknown if the area of the box lesion in patients undergoing a surgical box lesion is larger than patient undergoing catheter ablation.

As ablation lines have to be connected to anatomical barriers to prevent scar-related reentry, the roof line of a box lesion is connected to the superior ostia of the superior veins and the posterior line of a box lesion is connected to the inferior ostia of the inferior PVs. However, the anatomical posterior LA is not limited to the area between the veins but extends more caudally toward the coronary sinus.^{14,26} In the current study, patients with a small box surface ratio had a decreased arrhythmia-free survival compared to patients with a large box surface ratio, while box lesion width, height, and surface area; total LA surface area; and LA volume were not predictive. A possible explanation is the extent of isolation of the posterior wall, which shares the same embryologic origin with that of the PVs, containing the substrate for AF maintenance. Although the ratio of the isolated box lesion surface area and the total LA surface was calculated, box lesion surface area as a ratio of total left atrial posterior wall surface area could be superior

to sustain our hypothesis. However, as the borders of the posterior wall of the LA are not well-defined in the literature, we did not adopt this parameter.

A second explanation of our findings may be that an increase in left atrial size outside the area between the PVs will also decrease the box surface ratio. It may be hypothesized that enlargement of the LA will be more distinct outside the box lesion while the box lesion itself may be more resistant to dilation, as this area is bounded by the PVs. Therefore, the combination of anatomical variation and left atrial dilation outside the box lesion may explain why box surface ratio was predictive of outcome, while box lesion length, width, and surface area were not.

It remains to be proven that the positive influence of a large box lesion is dependent on the substrate modification of the LA posterior wall and not on the extensive atrial debulking per se. Preprocedural visualization of a small posterior LA box as a ratio of left atrial surface could be an important factor in predicting failure in patients in whom a box lesion is considered.

4.3 | Clinical implications

The box lesion surface area and total left atrial surface area can be measured during the procedure irrespective from prior imaging. In concordance with the fact that the AF substrate in the LA posterior wall is not confined to the area between the PVs, it may be hypothesized that ablation of a relatively larger box lesion is beneficial. This may support a decision to increase the size of the box lesion; for example, extending it inferiorly below the level of the PVs toward the coronary sinus, especially in patients with a relatively small anatomical box lesion. However, this hypothesis needs to be proven in further studies. Concordantly, Di Biase et al described PVI together with an extensive box lesion extended down to the coronary sinus and to the left-sided atrial septum in patients with persistent AF and heart failure.²⁷ Two-year follow-up demonstrated 70% freedom from AF/AT off AADs. This is a very respectable outcome considering that heart failure patients with persistent AF are at high risk for recurrence of AF.²⁸ It may be reasoned that the extensive box lesion performed in this study explains the high success rate in these patients with heart failure and persistent AF.

4.4 | Limitations

The present study is a single-center, retrospective study in a small group of patients. Due to the small group of patients, this study may have been underpowered to detect other parameters influencing arrhythmia recurrence. Therefore, this study should be considered as “hypothesis generating.” Several prior studies already have presented data on the value of isolating the posterior wall; however, the aim of this study was not to evaluate the value of posterior wall isolation, but the influence of the size of the ablated anatomical box lesion surface area as a ratio of total left atrial surface area on the outcome of this procedure. Our study did not show that extending the inferior line between the inferior poles of the inferior PVs improved the outcome. Further larger and randomized studies need to confirm

that a relatively larger box lesion or extension of the box lesion inferior from the inferior ostia of the PVs protects against arrhythmia recurrence. In the study population, 56% had undergone a prior PVI, which can have influenced the results. However, this was not significantly different between the groups. During the index procedure in 10 patients (14%), an additional ablation was performed; this was, however, not significantly different between the groups. Moreover, when these 10 patients were excluded from the analysis, the study results remained unchanged. Only repeated 24-h Holter monitoring was used during follow-up. Therefore, asymptomatic AF episodes may have been missed. The recurrence group had more often LA enlargement compared to the nonrecurrence group. However, this number was not significant in multivariate analysis. During the procedure, durable isolation of the PVs and box lesion was not enhanced using maneuvers, such as the pace/ablate method²⁹ or adenosine infusion, which could have improved the outcomes in both groups. No atrial substrate analysis was performed in this study. Distinguishing the presence of fibrotic areas based on magnetic resonance imaging findings and/or high-resolution voltage mapping and comparing the posterior LA with other LA regions could be helpful. Despite the limitations, we believe that this study is an important scientific contribution with potentially valuable suggestions for further research. Box lesion surface ratio is a new parameter to predict outcome in persistent AF ablation and we think that our hypothesis-generating study will trigger new research on extending the box lesion in patients with a small box lesion surface ratio to improve the outcomes.

5 | CONCLUSION

When applying a box lesion in persistent AF ablation, a larger box lesion surface area as a ratio of total LA surface area is protective for AF/AT recurrence.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest. The Heart Lung Center of the Leiden University Medical Center received unrestricted research grants from Medtronic, Biotronik, Boston Scientific, Lantheus medical imaging, St. Jude Medical, Edwards Life sciences & GE Healthcare and unrestricted educational grants from Medtronic, Edwards Life sciences and St. Jude Medical.

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