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Original Article

The significance of pulmonary veins isolation radiofrequency time and the evolution of left atrium volume on a twelve-year observational follow-up of paroxysmal atrial fibrillation patients

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ABSTRACT

Aims: Pulmonary vein isolation (PVI) is the treatment of choice of paroxysmal atrial fibrillation (PAF). However, radiofrequency delivery at extra-PV sites may be additionally required. We compared clinical and procedural characteristics of patients undergoing PVI alone versus adjunctive extra-PV substrate modification, at first procedure and repeat procedures for AF recurrence.

Methods: 587 patients with PAF undergoing radiofrequency (RF) ablation were retrospectively included. Extra-PV ablation was performed in case of sustained AF despite PVI, or at re-do procedures without PV conduction recovery. Demographic, clinical and electrophysiological predictors of survival without re-intervention were analysed in patients' groups having undergone one (G1), two (G2) or three or more procedures (G3).

Results: At baseline procedure, PV RF ablation time was shorter in G1 compared to G2/G3 whereas extra-PV RF ablation time was greater in G3 compared to G1. The proportion of patients requiring PV re-isolation decreased with repeat procedures. Smaller LA before procedure 1 (p1) or p2 was associated with PV reconnection at p2. Conversely larger LA before p1 was associated with extra-PV substrate modification at p2. Late re-do procedure timing (>1yr) was associated with increasing LA volume. Only longer PV and total RF time predicted poorer survival free from AF without re-intervention.

Conclusion: Longer PV RF time predicted requirement for re-ablation during follow-up. Smaller LA size predicted an increased probability of PV reconnection and decreased extra-PV substrate modification at p2. LA size decreased in patients undergoing early re-intervention, whereas it increased in patients undergoing re-intervention later on suggesting ongoing remodelling or progression.

1. Introduction

The need for a second procedure due to a relapse of atrial arrhythmia is not infrequent in patients with atrial fibrillation (AF),[1] hence there is a need to identify predictors of AF recurrence. The electrophysiological findings in paroxysmal atrial fibrillation (PAF) patients with recurrent atrial fibrillation after initial ablation are not uniform. In many patients, there is evidence of pulmonary veins (PV) reconnection which warrants PV re-isolation.[2] However, pulmonary vein isolation (PVI) may not be enough and radiofrequency (RF) delivery at extra-PV sites has been shown to improve outcome[3] although the optimal strategy of extra-PV ablation in these patients is not clear. We sought to compare clinical and procedural characteristics of patients requiring PVI and extra-PV substrate modification, in a cohort of patients with PAF requiring one or several ablation procedures over 12 years.

2. Methods

2.1. Study population

Consecutive patients who underwent catheter ablation of paroxysmal AF at our institution between 02/2002 and 07/2014 were included in this retrospective analysis. Patients with less than one-year follow-up were excluded (n = 30). Three groups were defined: patients who underwent only one procedure (G1), two

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Abbreviations

CS	Coronary sinus
G1	Group with one procedure only
G2	Group with two procedures
G3	Group with three procedures
LA	Left atrium
PAF	Paroxysmal atrial fibrillation
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RF	Radiofrequency
P1	First procedure
P2	Second procedure (re-do)
P3	Third procedure (re-do)

procedures (G2), or three or more procedures (G3). The study was approved by the institutional review board.

2.2. Electrophysiology study

All antiarrhythmic drugs were discontinued 5 half-lives before the procedures, except amiodarone, which was discontinued for at least 72 h. A transesophageal echocardiography was systematically performed within 24 h before the electrophysiological study to exclude a left atrial thrombus. A multi-electrode catheter (hexa to deca-polar, 2-5-2 mm electrode spacing) was placed in the distal coronary sinus (CS)/great cardiac vein. In later cases, another multipolar catheter was placed with its base in the high right atrium (RA) and its tip against the anterolateral RA free wall. Left atrial (LA) access was obtained by transseptal puncture. An open irrigated-tip ablation catheter (typically Thermocool, Biosense Webster, Diamond Bar, CA) was used for RF delivery and a 10 or 20-electrode circular mapping catheter (Lasso, Biosense Webster) for PV mapping. PVI was performed in all cases guided by circular catheter mapping and selective PV angiography. LA volume was calculated from still frames recorded during PV angiography. Initially additional extra-PV ablation targeting fractionated LA and CS potentials was performed in case of sustained AF despite stable PVI with the endpoint of AF termination or elimination of target potentials whereas for later patients, extra-PV ablation targeting fractionated CS and LA potentials was performed in step-wise fashion in case of inducible sustained AF after PVI. The ablation catheter was used for target electrogram (EGM) selection by visual analysis. A standardized induction protocol of 8-paced beat sequences delivered from the LA appendage or the distal CS with 1–2 ms stimulus duration, 25 mA bipolar output was decremented from 300 ms down to 200 ms or the effective atrial refractory period in steps of 10 ms. When sustained AF > 5 min (sAF) was induced after PVI, extra-PV ablation targeted fractionated CS potentials first. After eliminating fractionated CS potentials, inducibility was re-evaluated and in case of sAF, LA fragmented potentials were targeted. After ablation, if AF persisted, sinus rhythm was restored by electrical cardioversion. When non-inducibility was confirmed, no further ablations were performed. A minimum 30-min waiting time was used to screen for early PV reconnection and PVI was reconfirmed at procedure end. Adenosine challenge was performed to screen for dormant PV conduction at the end of the waiting time for the last 2 years, with additional ablation being performed to eliminate it.

Continuous endocardial bipolar electrograms were filtered (band-pass 30–500 Hz) and digitally recorded (LabSystem Pro, Boston Scientific, Marlborough, MA) along with surface electrocardiogram (ECG).

2.3. Statistical analysis

The difference in baseline clinical and electrophysiological characteristics between groups were established using linear regression and logistic regression with a Tukey post-hoc test. Linear and logistic mixed effects models were used to describe inter-group difference between each procedure in patients who had a total of two or three procedures, adjusting for intra-individual variability. Survival free from AF curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Cox proportional-hazards regression was used to identify factors associated with higher risk of re-intervention. We defined the survival free from AF as absence of documented re-intervention and event as documented re-intervention. All statistical analyses were performed with R software. R Core Team (2018). R: A language and environment for statistical computing. Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org.

3. Results

3.1. Baseline characteristics (Table 1)

3.1.1. Clinical baseline characteristics

A total of 587 patients were included in the study, of which 421 underwent only a single ablation procedure during the observation period (G1), 138 underwent one redo ablation procedure for AF recurrence (G2) and 28 underwent ≥2 redos (G3).

3.1.2. 2 redos (G3)

Baseline age, gender distribution, CHADS2 score and LA diameter did not differ significantly between G1, G2 and G3. However, LA volume at baseline was larger in G3 patients compared to G1 and G2.

3.1.3. Electrophysiological baseline characteristics

Procedural parameters of the index procedure (p1) in G1, G2 and G3 patients are also summarized in Table 1. Intervention time was similar in the three groups. RF time at PVs was longer in G2 and G3 patients compared to G1. Fluroscopy time was greater in G3 Patients compared to G1.

We tested for inducibility 32% (134/421), 19% (26/138) and 0% (0/28) of the patients in G1, G2, G3 respectively. In those patients we induced AF, Flutter or no arrhythmia in 114, 16 and 4 patients respectively in G1, and 25, 1, and 0 patients in G2.

3.1.4. Evolution of ablation and LA echo parameters

Echocardiographic LA dimension (LA volume as well as AP diameter in parasternal view (not shown)) did not change significantly from de novo ablation to redo in all subgroups (Table 2). PV RF time decreased progressively from p1 to 3 in all subgroups as well as the number of PVs (re-)isolated and the proportion of procedures where the PVs were targeted. On the other hand, there was a progressive increase, from p1 to p3, in the proportion of procedures where extra PV sites (CS and LA) were targeted and in the mean RF time at those sites.

3.1.5. Predictors of PV reconnection or RF at extra-PV sites

Predictors of PV ablation - a sign of PV reconnection - or the need of RF targeting extra PV substrates were evaluated with univariate and multivariate logistic regression. For the multivariate model, we used age and body mass index (BMI) and one of the two LA size parameters (LA echo diameter or LA angio calculated

Table 1
Baseline and first procedure characteristics of the 3 groups.

Characteristics	G1	G2	G3	p value
Age	59 ± 11 (n = 421)	58 ± 10 (n = 138)	57 ± 7 (n = 28)	ns
Proportion of male patients	75% (n = 421)	74% (n = 138)	71% (n = 28)	ns
BMI	26.56 ± 4.23 (n = 418)	26.98 ± 4.7 (n = 137)	26.83 ± 3.62 (n = 27)	ns
CHADS2	1.25 ± 1.18 (n = 331)	1.19 ± 1.14 (n = 108)	1.57 ± 1.34 (n = 14)	ns
Duration of intervention	174.31 ± 40.04 (n = 421)"	181.54 ± 43 (n = 138)"	185.71 ± 37.82 (n = 28)	ns
Time of fluoroscopy	49.42 ± 16.73 (n = 137)	49.42 ± 16.73 (n = 137)"	55.5 ± 15.37 (n = 28)	G1-G2: ns G1-G3: 0.005 G2-G3: ns
LA echo diameter (cm)	3.95 ± 0.63 (n = 209)	4.01 ± 0.64 (n = 85)	4.21 ± 0.5 (n = 23)	ns
LA volume (ml)	86 ± 24 (n = 359)	84 ± 23 (n = 113)	103 ± 29 (n = 18)	G1-G2: ns G1-G3: 0.009 G2-G3: 0.006
Mean number of PV isolated/re-isolated due to reconnection	3.88 ± 0.37 (n = 421)	3.85 ± 0.42 (n = 138)	3.96 ± 0.19 (n = 28)	ns
Procedure with RF at CS and/or LA	24% (100/421)	26% (36/138)	14% (4/28)	ns
Cumulated RF time at PVs (min)	30 ± 13 (n = 386)	35 ± 13 (n = 131)	39 ± 10 (n = 19)	G1-G2: <0.001 G1-G3: 0.007 G2-G3: ns
Cumulated RF time at CS or LA (min)	1 ± 3 (n = 388)	2 ± 4 (n = 126)	0 ± 2 (n = 26)	ns
Cumulated total RF time (min) (min)	31 ± 12 (n = 387)	36 ± 13 (n = 131)	39 ± 10 (n = 19)	G1-G2: <0.001 G1-G3: 0.008 G2-G3: ns

Table 2
Ablation parameters and clinical evolution in G2 and G3.

Characteristics compared	Groups	1st procedure	2nd procedure	3rd procedure	p value
LA calculated Volume (ml)	G2	84.41 ± 23.11 (n = 113)	86.54 ± 27.77 (n = 83)	–	ns
	G3	103.09 ± 28.99 (n = 18)	103.15 ± 26.16 (n = 17)	93.76 ± 26.61 (n = 9)	ns
	G2 & G3	86.97 ± 24.73 (n = 131)	89.36 ± 28.08 (n = 100)	–	ns
RF time in all PV (min)	G2	34.87 ± 13.42 (n = 131)	8.4 ± 6.98 (n = 122)	–	<0.001
	G3	39.17 ± 10.34 (n = 19)	7.78 ± 5.87 (n = 22)	2.57 ± 4.88 (n = 27)	p1-p2: <0.001 p1-p3: <0.001 p2-p3: 0.019
	G2 & G3	35.41 ± 13.12 (n = 150)	8.31 ± 6.81 (n = 144)	–	<0.001
RF time at CS and LA	G2	1.72 ± 4.21 (n = 126)	3.05 ± 5.2 (n = 94)	–	0.016
	G3	0.5 ± 1.76 (n = 26)	3.3 ± 5.31 (n = 20)	3.08 ± 5.51 (n = 18)	p1-p2: 0.047 p1-p3: ns p2-p3: ns
	G2 & G3	1.51 ± 3.93 (n = 152)	3.1 ± 5.2 (n = 114)	–	0.002
Total RF time (min)	G2	36.23 ± 12.73 (n = 131)	11.07 ± 7.65 (n = 115)	–	<0.001
	G3	39.85 ± 10.73 (n = 19)	13.17 ± 6.49 (n = 18)	8.33 ± 8.5 (n = 15)	p1-p2: <0.001 p1-p3: <0.001 p2-p3: ns
	G2 & G3	36.69 ± 12.52 (n = 150)	11.36 ± 7.52 (n = 133)	–	<0.001
Mean number of PV isolated	G2	3.85 ± 0.42 (n = 138)	2.6 ± 0.89 (n = 118)	–	<0.001
	G3	3.96 ± 0.19 (n = 28)	2.33 ± 1.13 (n = 24)	1.5 ± 0.85 (n = 10)	p1-p2: <0.001 p1-p3: <0.001 p2-p3: 0.009
	G2 & G3	3.87 ± 0.39 (n = 166)	2.56 ± 0.93 (n = 142)	–	<0.001
RF at PVs	G2	100% (n = 138)	94% (n = 138)	–	<0.001
	G3	100% (n = 28)	86% (n = 28)	48% (n = 28)	p1-p2: ns p1-p3: <0.001 p2-p3: 0.013
	G2 & G3	100% (n = 166)	92% (n = 166)	–	<0.001
RF at CS or LA	G2	26% (n = 138)	56% (n = 138)	–	<0.001
	G3	14% (n = 28)	54% (n = 28)	59% (n = 28)	p1-p2 0.009 p1-p3 0.005 p2-p3 ns
	G2 & G3	24% (n = 166)	55% (n = 166)	–	<0.001

volume). Larger LA dimensions were associated with PV reconnection as well as RF at extra-PV sites. A smaller LA echo diameter at p1 was associated with a higher prevalence of PV reconnection at

p2. Conversely, a larger LA volume at p1 was associated with the need for extra-PV substrate modification at p2 (Table 3).

3.1.6. Time to p2 and change in volume

Time from p1 to p2 did not differ significantly between G2 and G3 (584 ± 664 days (n = 131) vs 707 ± 998 days (n = 25), respectively, $p = 0.56$). We observed 2 different populations: LA dimensions increased from p1 to p2 in patients with late recurrence (≥1 year after p1) while they decreased or did not change significantly in patients with early recurrence <1 year (Table 4). In Table 2, those 2 populations with opposite LA size are pooled together, hence explaining the absence of change. Both linear and logarithmic relationships were significant, with the logarithmic relationship being the stronger (Fig. 1A). There was a positive correlation between PV RF time at p1 and the time elapsed between p1 and p2 (Fig. 1B).

3.1.7. Outcome of the procedures

In a total of 781 procedures, normal sinus rhythm was achieved in 757 procedures (96.9%), 3 of them necessitating drugs. The outcomes of the remaining procedures were as follows: sinus bradycardia,[1] type II atrio-venticular block,[1] high grade atrio-ventricular block necessitating pacemaker implantation,[1] atrial fibrillation,[3] and atrial flutter,[2] Data regarding this parameter was missing for 16 procedures.

3.1.8. Predictors of survival free from AF reintervention

Table 5 summarizes the univariate and multivariate effect of baseline characteristics on survival free from reintervention for AF. The LA echo diameter was not included as it is pathophysiologically correlated with the LA angiographically calculated volume.[4] RF time at PVs (Fig. 1D) RF time in CS/LA (Fig. 1E) and total RF time (Fig. 1F) were the only predictors of poorer survival free from AF reintervention in a univariate Cox proportional hazards model. RF time at PVs and total RF time were the only predictors of poorer survival free from AF reintervention in a multivariate Cox proportional hazards model (*Table 5*. Note: due to collinearity of the variables RF time at PVs and RF time at CS/LA with the variable total RF time, 2 different multivariate models were generated). Moreover, in the subgroup of patients who underwent RF at PVs only at baseline (n = 447) total RF time remained a significant predictor of poorer survival free from AF reintervention in a univariate Cox proportional model (HR: 1.02 (1.00–1.03), p = 0.03). In the subgroup of patients who underwent RF both at PV and CS/LA (n = 140), RF time at CS/LA remained a significant predictor of poorer survival free from AF reintervention in a univariate Cox proportional model (HR: 1.02 (1.02–1.18), p = 0.02).

A pathophysiological explanation for this finding might be the significant positive correlation between the volume of the LA and the RF time (Fig. 1C). To test this hypothesis, we performed a sensitivity analysis: there was no difference in the rate of PV re-isolation between redo patients with the longest (more than the mean) total RF time at PVs (namely more than the mean RF time in that group) during the first intervention compared to those with the shorter (less than the mean) total RF times (91.5% (65/71), vs. 87.4% (83/95), p = 0.39). Neither was a difference present in the rate of RF delivery at CS/LA sites between redo patients with the longest total RF time at PVs during the first intervention (namely more than the mean RF time in that group), compared to the redo patients with the shorter total RF time (56.3% (40/71) vs. 45.3% (43/95), p = 0.16). However, the total RF time at PVs during the second procedure was significantly longer in those in whom the total RF time at PVs during first intervention was the longest when compared to patients with shorter total RF times at the PVs during the first procedure (8.97 ± 7.41 vs 5.88 ± 6.29 [min] p = 0.004). There was no difference in RF time at CS/LA during second procedures between the first procedure longer and shorter PV RF time groups (2.21 ± 4.17 vs 2.07 ± 4.81 [min] p = 0.847).

4. Discussion

The electrophysiological sources of AF can be classified into 2 categories: triggers which initiate AF and the substrate which perpetuates it.[5] While it is well known that pulmonary veins (PV) typically harbour the predominant “triggers”, an increased proportion of extra PV-triggers have been found at re-ablation.[6] Non-PV structures (such as the left atrium (LA), the coronary sinus (CS)[7] or even the right atrium (RA)[8] likely are critical contributors in subsets of patients. In this single-center retrospective analysis, we described the changes in clinical and electrophysiological characteristics in patients needing 1, 2 or 3 procedure(s) for paroxysmal atrial-fibrillation ablation. In our large cohort of longitudinally in-hospital followed PAF patients, we observed a decrease in the importance of the PVs as a target as well as the parallel increasing importance of extra PV-targets with time. We also confirmed that there is a decrease in the size of the LA early after an ablation, as described previously after a relatively short follow-up (a maximum of 2 years).[9] However, in our patients with a late recurrence, after a follow up of more than 12 years, this effect vanishes with an increase in the size of the LA over time being observed instead. We also found that the directional change in LA size seems to be an indicator of where the RF ablation should be targeted during re-ablation since when the LA size decreased, PVs were more frequently targeted, whereas when the LA size increased, extra PV sites became more important targets. To the best of our knowledge, this observation has not been previously described. Overall however, only a minority of paroxysmal atrial fibrillation (PAF) ablation patients underwent extra-PV ablation and only to a limited extent, thus confirming the primary role of stable pulmonary vein isolation (PVI) in PAF patients at least.

Clinical and echocardiographic parameters such as hypertension, left atrial (LA) diameter and valvular AF have been identified that predict recurrence within 30 days after ablation.[10] Scores combining several clinical parameters have also been developed to

Table 3
LA size parameters in G2 & G3 at p1 or p2 as predictors of PV reconnection or RF at CS or LA in p2.

	Site of RF	Groups	Type of logistic regression	LA echo diameter (OR)	LA Volume (OR)
Predictors of p2 at p1	PV reconnection	G2 G2 & G3	Multivariate	0.72, CI = [0.19–2.7], p = 0.61	0.96, CI = [0.92–0.99], p = 0.01
			Univariate Multivariate	0.89, CI = [0.24–3.25], p = 0.85	0.96, CI = [0.93–0.99], p = 0.02
			Univariate	0.76, CI = [0.24–2.46], p = 0.64	0.97, CI = [0.94–0.99], p = 0.01
				0.98, CI = [0.32–2.98], p = 0.97	0.98, CI = [0.95–1], p = 0.05
	RF at CS or LA	G2 G2 & G3	Multivariate	3, CI = [1.35–7.45], p = 0.01	1.02, CI = [1–1.04], p = 0.12
			Univariate Multivariate	2.66, CI = [1.28–6.07], p = 0.01	1.01, CI = [0.99–1.03], p = 0.18
			Univariate	2.3, CI = [1.13–5.06], p = 0.03	1.02, CI = [1–1.04], p = 0.07
				2.26, CI = [1.17–4.71], p = 0.02	1.01, CI = [1–1.03], p = 0.1

Table 4
Relation between LA volume and interval from first to second ablation.

	<1 year	≥ 1 year	p-value
Mean change in LA Echo diameter (cm)	−0.07 ± 0.54 (n = 27)	0.32 ± 0.54 (n = 14)	0.037
Mean change in calculated LA volume (ml)	−2.1 ± 21.34 (n = 48)	8.83 ± 21.34 (n = 34)	0.030

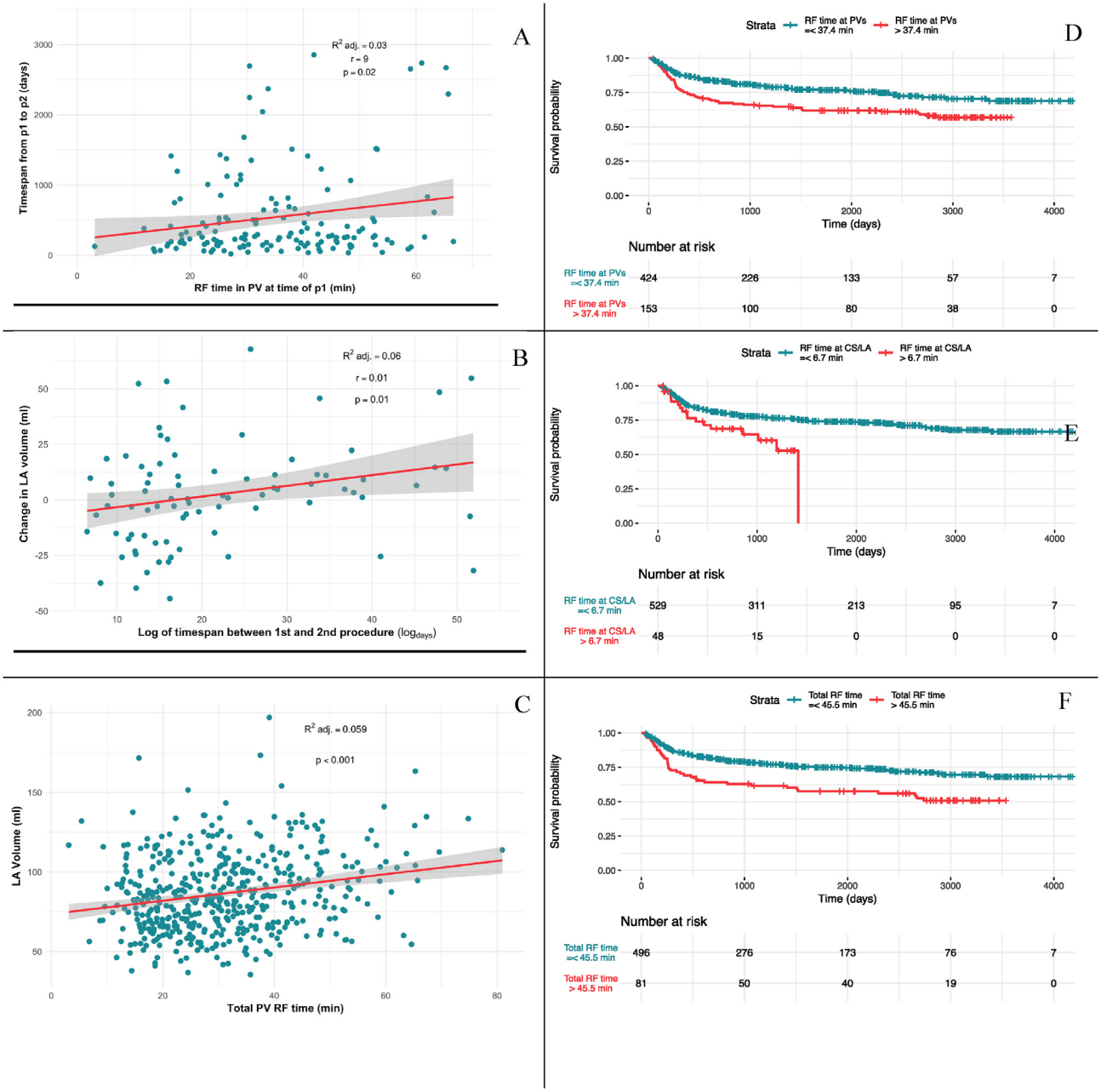

Fig. 1. **A**. Linear regression between timespan from 1st to 2nd procedure and change in LA volume – **B**. Linear regression between logarithm of timespan and change in LA volume in G2 & G3 between p1 and p2 – **C**. Linear regression between RF time in PV at time of p1 and timespan from p1 to p2 – **D**. Linear regression between total RF time and LA Volume – **E**. RF time at baseline at PVs as risk factor for re-intervention – **F**. RF time at baseline at CS/LA as risk factor for re-intervention - **G**. Total RF time at baseline as risk factor for re-intervention.

predict recurrence after catheter ablation.[11] Among those parameters LA enlargement was a strong independent predictor for new-onset AF as well as for AF recurrence after repeat ablation.[12] On the other hand, there is a significant decrease in LA size at post-ablation follow-up,[13] especially when sinus rhythm was maintained.[14] This positive effect on LA size is also present after a second procedure.[15] Other studies have failed to identify reliable predictors of recurrence of AF.[16]

Table 5
Cox Regression predicting a re-intervention.

Predictors	Univariate		Multivariate Model 1		Multivariate Model 2	
	HR (95% CI for HR)	p value	HR (95% CI for HR)	p value	HR (95% CI for HR)	p value
Age	1 (0.98–1.01)	0.60	0.99 (0.97–1.01)	0.44	0.99 (0.97–1.02)	0.60
Sex	1.07 (0.75–1.52)	0.72	1.04 (0.59–1.82)	0.89	1.03 (0.62–1.71)	0.91
BMI	1.02 (0.99–1.06)	0.25	1.03 (0.98–1.08)	0.24	1.02 (0.97–1.06)	0.49
CHADS2	1 (0.86–1.16)	0.96	1.01 (0.8–1.29)	0.92	1.03 (0.82–1.28)	0.82
LA Vol (ml)	1 (0.99–1.01)	0.92	1 (0.99–1.01)	0.50	1 (0.99–1.01)	0.90
Mean number of PV isolated	0.89 (0.6–1.31)	0.55	0.69 (0.43–1.12)	0.14	0.81 (0.51–1.27)	0.35
Procedure with RF at CS and/or LA	1.33 (0.92–1.91)	0.13	0.97 (0.42–2.22)	0.94	1.22 (0.8–1.86)	0.35
RF time PV	1.01 (1–1.02)	0.05	1.02 (1–1.04)	0.02	–	–
RF time CS/LA	1.06 (1.01–1.1)	0.01	1.07 (0.99–1.16)	0.09	–	–
total RF time	1.01 (1–1.03)	0.02	–	–	1.02 (1–1.03)	0.03

We included electrophysiological parameters in our analysis as well and could show that the RF time (especially in the PVs but also at extra PV sites) was the only *independent* predictor of re-ablation for recurrent atrial fibrillation in a multivariate analytic model; again not previously reported. In previous studies, additional linear ablation, ablation of complex fractionated atrial electrogram or right atrial ablation after PVI in patients with persistent atrial fibrillation was not associated with improved clinical outcomes.[17] An increased incidence of left atrial flutter was however observed after circumferential PV ablation plus left atrial linear ablation with segmental PVI in patients with PAF[18] with the volume of extra-PV tissue ablated linked to the occurrence of atrial tachycardia.[19] We included only patients with paroxysmal atrial fibrillation at the first procedure, and our findings support our individually tailored strategy of reducing the overall RF dose to this particular atrial fibrillation population by limiting extra-PV ablation to only those patients with residual AF despite PVI.

Our study suggests a that long PV RF time may be a marker for a future relapse. An increased RF time may be related to the severity or extent of the disease at baseline. An increased LA size has been associated with more recurrence after repeat ablation[12] and increased PV RF time may result from an increased LA volume (because of larger PV ostia-antrum circumference) or alternatively from the necessity to ablate repetitively or extensively to achieve PVI due to difficult anatomy, catheter instability and/or increased PV antral wall thickness. Incomplete PVI or suboptimal PVI lesion quality likely results in recurrence after PVI.[20] This study also showed that a smaller LA size at redo ablation predicted an increased risk of PV reconnection and a concomitant decreased need for extra-PV substrate modification. The parallel tendency for increasing extra-PV ablation requirement supports the hypothesis that increased PV RF time at index ablation may simply be a marker for a more advanced AF substrate, possibly in the form of a larger LA with larger PV ostia (requiring more ablation time for PVI) or greater wall thickness.

The temporal evolution of LA volumes after the first ablation procedure was emphasised by our findings that patients undergoing a re-intervention early exhibited a decrease in LA size, whereas patients with later re-intervention exhibited an increasing LA size. Early reduction in LA volumes despite recurrent arrhythmia supports the predominant early role of scarring in LA remodelling whereas late dilatation may represent underlying disease progression.

Our findings affirm the already well-known importance of stable PVI in PAF patients, but also describe a previously undescribed correlation of residual AF and its progression during longitudinal follow-up despite PVI with large or larger LA even in paroxysmal AF patients. Contemporary strategies of contact force guided and standardised ablation dose regimens (e.g. with 'ablation/lesion indexes') may address the former issue by more consistent and more effective achievement of stable PVI whereas the residual extra-PV substrate requires to be addressed by better detection and ablation at the first procedure as well as therapeutic measures to prevent progression of the AF substrate.

5. Limitations

We included patients with paroxysmal atrial fibrillation as baseline and therefore our findings cannot be extended to patients with other types of atrial fibrillation at time of first intervention. Since only patients with a clinical recurrence underwent repeat electrophysiological study, the underlying correlation of stable PVI with the lack of progression or recurrence of AF remains unproven. As such, we did not perform an active search - with the performance of Holter - of recurrence of subclinical atrial fibrillation after ablation. Only patients having had a repeat procedure at our center were counted as recurrence. Patients having had repeat procedures in other centers, and recurrences documented outside or institution for which re-do ablation was not performed could not be counted as recurrence as these data were not available to us. Our data may therefore underestimate the true atrial fibrillation recurrence rate. We did not report peri/postinterventional complications as we did not collect them in the database. Moreover, the change in our ablation protocol during the last two years of the follow-up adds a relative component of inhomogeneity to our data but reflects the real-life an electrophysiology department of a university hospital. This is a monocentric retrospective study with last follow-up in 2014, hence it does not compare with the newest technology and recent strategies. As in many retrospective studies, missing data constitutes a limitation. and as such our conclusions should be considered hypothesis generating requiring confirmation by a prospective study.

6. Summary

In summary, we have shown for the first time that in a large cohort of in-hospital longitudinally followed patients over 12 years, that RF ablation targets for paroxysmal atrial fibrillation evolve and change with decreasing importance of the PVs as targets versus extra-PV substrate over long term follow up. However, an increased RF time for PV isolation and total RF time were the only independent predictors of re-ablation for AF recurrence. This underlines the importance of the PVs as primary targets in patients with paroxysmal AF and therefore of optimal RF ablation in order to achieve stable PVI and favourably affect long term progression. The evolution of the LA size seems to be an important indicator of extra-PV ablation. Further prospective research should be targeted to compare the underlying electrophysiological parameters in

patients with and without progression and to understand the mechanism(s) linking LA size and extra-PV substrate progression.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2022.01.004.

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