Conduction recovery following catheter ablation in patients with recurrent atrial fibrillation and heart failure

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Matteo Anselmino, MD PhD*, Mario Matta, MD*, T. Jared Bunch, MD PhDÀ, Martin Fiala, MD PhD§, Marco Scaglione, MD¶, Georg Nölker, MDÿ, Pierre Qian, MD**, Thomas Neumann, MDÀÀ, Federico Ferraris, MD*, Fiorenzo Gaita, MD Prof*.

*Cardiology Division, Department of Medical Sciences, University of Turin, Turin, Italy.

ÀIntermountain Heart Institute, Intermountain Medical Center, Murray, UT, USA.

§ Department of Cardiology, Heart Centre, Hospital Podlesi as, TŚinec, Czech Republic.

¶ Division of Cardiology, Cardinal Massaia Hospital, Asti, Italy.

ÿDepartment of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany.

**Department of Cardiology, Westmead Hospital, University of Sydney, Australia

ÀÀDepartment of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany.

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Corresponding Author:

Fiorenzo Gaita, MD Professor
Cardiology Division, Department of Medical Sciences,
ñCittà della Salute e della Scienzaò University of Turin
Corso Bramante 88, 10126 Turin, Italy
Phone: +39-0116335570 Fax: +39-0116966015
Email: fiorenzo.gaita@unito.it

Abstract

Background. Atrial fibrillation (AF) catheter ablation is increasingly proposed for patients suffering from AF and concomitant heart failure (HF). However, the optimal ablation strategy remains controversial. We performed this study to assess the prevalence of pulmonary vein (PV) or linear lesion reconnection in HF patients undergoing repeated procedures.

Methods and Results. At seven high-volume centres, 165 patients with HF underwent a repeat procedure after a first AF ablation including PV isolation alone (47 patients, group A) or PV isolation plus left atrial lines (118 patients, group B). Group A patients presented more often paroxysmal AF ($p<0.001$), less enlarged left atrium ($p<0.001$) and less left ventricular systolic dysfunction ($p=0.031$) compared to Group B, that more commonly had atypical atrial flutter ($p<0.001$). Forty-one (87%) patients in Group A and 69 (58%) in Group B presented at least one reconnected PV ($p<0.001$). Sixty-one (52%) patients in Group B presented at least one reconnected atrial line (left isthmus or roof). Patients without any reconnected PV (n=54, 33%) more frequently experienced persistent AF ($p<0.001$), had longer AF duration ($p=0.047$) and larger left atrial volume ($p<0.001$). Twenty-five patients (15%) with no PV and/or line reconnection did not significantly differ, concerning baseline characteristics, compared to those with at least one reconnected ablation site.

Conclusion. As in the general AF population undergoing catheter ablation, PV reconnection is frequent in patients with HF and symptomatic recurrence. However, one third of patients presented arrhythmic recurrences even in the absence of PV reconnection, highlighting the importance of the underlying atrial substrate.

Abstract word count: 250

1. Introduction

Atrial fibrillation (AF) catheter ablation is a proven safe and effective therapeutic option for patients suffering from AF and concomitant heart failure (HF) [1-2]. Recent randomized trials [3-5] and a large meta-analysis [6] consistently reported an improvement in systolic HF symptoms and left ventricular ejection function (LVEF) after AF ablation. However, freedom from AF after a single procedure is limited, and when long-term outcomes of 5 years or greater are examined, recurrences occur in the majority of patients [7]. As a consequent, many patients with systolic HF (about one third) require at least two procedures to effectively maintain long-term sinus rhythm (SR) [7].

The optimal first line non pharmacological strategy to address AF in these patients remains controversial: previous studies supported, due to the complexity of the atrial substrate, left atrial linear ablation on top of pulmonary vein isolation (PVI) [8-10]. However, recent studies of AF ablation in general and surgical populations have failed to support the additive benefit of ablation beyond PVI [11-12]. In fact, aiming to investigate the singular role of PVI in AF ablation, a recent study reported, among a general population of patients undergoing repeated procedures for AF recurrence, a high prevalence of PV conduction recovery following the index PVI [13]. In this study, PV re-isolation alone was effective in subsequent SR maintenance, indirectly suggesting a durable role of PV triggers.

AF ablation patients that have concurrent systolic HF may have arrhythmia driven not only by PV triggers, but pathological atrial substrate; the latter reflecting chronic exposure of the atrium to the underlying diastolic and systolic dysfunction [14-15]. Nonetheless, there are no data available concerning sites of recovery or reconduction following a first transcatheter ablation procedure. We therefore conducted the present study aiming to determine the incidence of PV reconnection or failure of other linear lesions in in a population of patients with HF undergoing repeated procedures for recurrent atrial arrhythmia following a first, failed, AF ablation procedure.

2. Methods

The present multicentre study involved seven high-volume electrophysiological laboratories routinely performing AF transcatheter ablation in patients with a LVEF lower than 50%. All included patients had a history of drug-refractory, symptomatic, paroxysmal or persistent AF and a concomitant structural cardiomyopathy characterized by a LVEF < 50%, received a prior AF ablation procedure at the same Center (including PV isolation and when appropriate additional left or right atrial lesions), and were referred for at least one additional AF catheter ablation procedure, due to the occurrence of documented AF, atypical atrial flutter or atrial tachycardia symptomatic recurrences. Arrhythmic recurrences were defined as any episode of AF, atypical atrial flutter or atrial tachycardia lasting at least 2 minutes and documented through 12-leads ECG, Holter monitoring or implantable loop recorder. Referral for redo ablation was considered in patients experiencing arrhythmia-related symptoms, left ventricular function and/or functional class impairment related to the arrhythmic recurrences. Patients in whom procedural details concerning the index or the repeated procedure (e.g. PVI, linear lines, etc.) were not complete or validated were excluded. All patients provided written informed consent to the catheter ablation procedures.

2.1. Recovery or reconduction assessment

The number and sites of PV conduction recovery were recorded. Additionally, in case left atrial (LA) linear lesions (roof line, mitral isthmus line, posterior line) had been performed at the first procedure, the persistence of block lines tested by pacing manoeuvres, activation and voltage mapping were registered.

The repeated procedures were then performed, according to each Centerôs preference or protocols, using 4-mm tip irrigated radiofrequency catheters or cryoballoon. Based on single patientsô

characteristics and atrial substrate, additional lesions such as PV isolation, LA linear lines, or complex fractionated atrial electrograms (CFAE) were performed [16].

2.2. Statistical analysis

Continuous variables were reported as mean (standard deviation, SD) or median (range), and categorical variables as number (%). Continuous data were compared by one-way ANOVA test after normal distribution was confirmed, and, in a selection of cases, additionally analyzed as tertiles. Categorical variables were compared in cross-tabulation tables by Pearsonôs chi-square test. Due to the potential bias resulting from the inclusion of atypical flutter/tachycardia recurrences, that may rely on different pathophysiological mechanisms than those driving AF, data was also analysed considering only AF recurrences. Aiming to test the independent correlation of the recorded parameters, variables reporting a significant correlation at univariate analysis (p value <0.05) were included in a multiple logistic regression analyses. The best subset models were run applying odds ratio (OR) likelihood scores. All tests of significance were two-tailed, and a p value <0.05 was considered statistical significant. All analyses were performed using SPSS 21.0.

3. Results

At seven high-volume centres, out of 719 patients, over a mean period of 3 years (2012-2015), the 165 AF patients with concomitant HF undergoing a repeated transcatheter AF ablation were included (age 55±17 years; 83% males). Baseline characteristics are listed in Table 1. Sixty-four (39%) patients suffered from paroxysmal AF, with a mean AF history duration of 74±84 months. Echocardiographic parameters included a mean LA volume of 121±68 ml, and a mean LVEF 41±8%. At the time of the index procedure, 47 (28%, Group A) patients underwent PVI alone, while 118 (72%, Group B) underwent additional LA linear lesions or CFAE ablation; in particular, in 104 patients a roof line and mitral isthmus line were performed, and 44 underwent CFAE ablation. Patients in Group A presented higher prevalence of paroxysmal AF ($p<0.001$), less severely enlarged LA volume ($p<0.001$), less LVEF dysfunction ($p=0.031$), shorter time to AF recurrence ($p<0.001$), and a higher prevalence of prior antiarrhythmic Ic class drugs treatment ($p=0.019$). In comparison, patients in Group B reported a higher prevalence of atypical atrial flutter recurrences, compared to Group A ($p<0.001$).

Details concerning the second procedures are reported in Table 1. Briefly, 61 (37%) patients underwent repeated PVI alone, 61 (37%) underwent PVI and additional LA lesions while 43 (26%) underwent linear lesions or CFAE ablation; complication rate was 3.0%, without difference between Groups A and B ($p=0.391$). Forty-one (87%) patients in Group A and 69 (58%) in Group B presented at least one reconnected PV ($p<0.001$); no significant differences were detected among the prevalence of each of the four PVôs recurrence rate (Figure 1 and 2). Among patients in Group B, 61 (52%) and 55 (47%) presented, respectively, left isthmus and roof line reconnection across the line, and these patients underwent repeated linear ablation to achieve conduction block.

Among the two groups, 54 (33%) patients presented without evidence of reconnected PVs (Table 2); these patients were more often affected by persistent AF ($p<0.001$), had a longer AF duration ($p=0.047$), presented with more severely enlarged LA volumes ($p<0.001$), more often were treated

with extensive LA ablation at the initial procedure (p<0.001) including lines and CFAE, and were more commonly affected by atypical flutter (p<0.001). The complication rates did not differ between the two groups (p=0.688).

Aiming to limit potential bias deriving from the inclusion of atypical flutter/tachycardia recurrences, that may rely on different pathophysiological mechanisms than those driving AF, an additional analysis was run stratifying by AF (n=100) or organized tachycardia (n=65) relapses. The presence of persistent vs. paroxysmal AF (p<0.001), of a larger LA volume (p=0.001), a lower LVEF (p=0.027), an ablation scheme including linear lesions (p=0.001) and CFAE ablation (p=0.002) related to arrhythmic recurrence despite the absence of documented PVs reconnection, also when considering AF recurrences only (Table 3 and Figure 3).

At multiple logistic regression analyses, performed to assess the independent significance of each of the above mentioned parameters in relation to AF recurrences despite absence of PV reconnection, LA volume emerged as the only independently related parameter, as the III tertile of LA volume, above 120 ml, presented an OR of 5.09 (95% CI 1.19-26.19; p=0.048) (Table 4). On the other side, conduction recovery over atrial ablation lines was slightly more common within patients relapsing with an atrial tachycardia/atypical flutter: more in details, while the incidence of roof line reconnection did not differ (31 vs. 23%, p=0.267), the left isthmus line, recovered in 17% vs. 64% (p=0.013), in patients suffering AF or organized arrhythmias, respectively.

Of note, 25 (15%) patients presented no PV and/or atrial line recovery at the time of the repeated procedure, despite the documented arrhythmia recurrences. Baseline characteristics of these patients were not significantly different, except for a trend towards longer AF duration (p=0.078) and lower LVEF (p=0.082) compared to the remaining population; patients without any reconnection site more frequently underwent CFAE ablation at the initial procedure (p=0.044) and presented with atypical flutter (p=0.003) compared to AF in the alternative group (Supplemental Table A).

Fifty (30%) of the 165 patients enrolled underwent a third procedure (Supplemental Table B and C). Among them, 18 (37%) experienced AF, while the majority, 32 (63%), suffered atypical atrial flutter (p=0.028). Fifteen of them had previously been approached by PVI alone, while 35 by extensive LA ablation. In the first group, 6 (40%) patients reported no reconnected PVs, while this percentage was higher (24, 70%) in the second; furthermore, in the latter the prevalence of left isthmus and roof line conduction recovery was 67% and 54%, respectively (supplemental Figure A and B).

4. Discussion

The present work is the first multicentre study aiming to assess the durability of PVI and atrial linear ablation in a population of patients with systolic HF. In light of the latest European guidelines [2] recommending AF ablation in patients with HF (class IIa) to improve functional class and LVEF by breaking the vicious circle between AF and HF, knowledge on conduction recovery patterns is of extreme clinical relevance. Despite the heterogeneity of the population and of the ablation tools and protocols, given that the optimal approach for AF ablation in these patients is controversial, and the lack of clear published data on this population, the present findings are, in our opinion, significant and thought-provoking. In this population, and consistent with other studied populations, the rate of conduction recovery of at least one PV was high in patients that present for a repeated ablation: globally more than half of the previously isolated PVs were found to be reconnected at redo procedure. However, one third of patients undergoing repeated procedures for atrial arrhythmic recurrence had absence of PV reconnection, suggesting the importance of non-PV mechanisms in the AF pathogenesis, in particular within patients with a larger LA volume, lower LVEF that suffered persistent, long-history AF. These parameters, on top of all LA volume, should therefore candidate to identify patients at higher risk of AF recurrences, despite the persistence of PV isolation. In patients with HF, therefore, the PVôs role in AF genesis and maintenance seems less pivotal, highlighting the need to further treat external PV antral and the underlying atrial substrate.

4.1. Reconnection sites and arrhythmic recurrences

Concerning the first procedural approach, less than one third of patients underwent PVI alone, while the majority underwent a more extensive LA ablation. Baseline characteristics of the two groups were different: patients with persistent AF, longer AF history, lower LVEF and larger LA volume underwent more frequently an extensive LA ablation. This is in accordance with previous studies

suggesting, in these conditions, a more aggressive substrate modification strategy may be required in addition to PVI to provide long-term arrhythmia free benefit [9,17-18].

Index procedure approach predicted arrhythmia outcomes in this cohort of systolic HF patients. In those with PVI alone, AF recurrence alone was more common. In contrast, in patients that had extensive substrate modification recurrent atypical flutter rates were higher. Of note, almost half of the latter patients had recovered conduction along one or more of the previously performed lines, confirming the challenge of achieving a durable line of block [19] and the consequent proarrhythmic role of incomplete lesions [11].

One third of all patients presented with no PV conduction recovery, suggesting, in patients with AF and concomitant HF, a relevant role for non-PV mechanisms that trigger and sustain arrhythmic recurrences, not only in case of organized atrial arrhythmias but also of AF recurrences. This prevalence is higher compared to a prior report that examined post-ablation recurrence rates in the general population [13], likely due to the more complex atrial substrate in patients with reduced LVEF. Persistent AF, larger LA volume and more depressed LVEF reflect more advanced atrial disease, in which AF can occur even in the absence or independently of PV triggers.

The latter hypothesis is also supported by the larger prevalence of PV reconnection among the ñPVI alone groupò compared to ñPVI + lines groupò. The ñPVI alone groupò likely represents patients with less extensive atrial disease, in whom PV triggers still play a major role. The ñPVI + lines groupò includes, instead, patients with more advanced atrial disease, in whom PV triggers are less pivotal compared to the role exerted from reconnection of previous ablation lines or progression of the underlying atrial (extra-PV) disease. In fact, previous literature has already reported high PV reconnection rates even in patients free from arrhythmic recurrences [20].

Given the lack of clinical trials clearly testing the active role of PV reconnection in AF recurrences, and/or data deriving from positive controls, especially in the setting of patients with underlying structural disease and reduced LVEF, current practice should be based on the only available

observations. Based on the present findings, a severely dilated LA volume is, in our opinion, the strongest predictor of arrhythmia recurrences despite persistent PV isolation, suggesting that patients with severe LA enlargement (i.e. above 120-150 ml) should be treated by an alternative ablation approach at their index ablation procedure. Although among the general population, indirect support to this thesis derives from the recent GAP-AF trial [21]. This study demonstrated that complete is superior to incomplete circumferential PV isolation concerning 3-months AF ablation efficacy; however, this was not due to higher rates of persistent PV isolation. This finding surely suggests that more ablation is more effective than less ablation, but also highlights that the mechanisms of AF recurrences are not strictly linked to PV reconnection and that there, indeed, is a potential relevant role of non-PV mechanisms in AF recurrences also in the general population.

Additionally, a recent report suggested that the altered substrate in HF patients may provide a role for non-PV mechanisms even in patients with paroxysmal AF [22]. This finding is consistent with the lower incidence of reconnected PVs among patients treated with PVI + lines compared to those treated with PVI alone: the first group, characterized by more advanced disease, most likely presents a higher burden of atrial fibrosis, that limits the role of PV triggers in supporting arrhythmic recurrences, and may, even more, result in a sort of fibrosis-induced ñablationò of the PVs trigger due to the progressive reduction of muscular sleeves.

In further support of non-PV mechanisms in systolic HF patients, those who underwent a third ablation procedure, PV reconnection rates were even lower (44%) compared to that reported in the general population [13]. This subgroup was selected by failure of two prior ablations that targeted the PVs, and is likely a population with a more advanced atrial disease [23], in which PV ectopies are not pivotal, while the atrial substrate plays a dominant role in causing AF recurrence. However, 44% of patients still experienced PV reconnection, which also highlights the challenges of obtaining durable PVI even with repeated attempts.

4.2. *Absence of reconnection sites and arrhythmic recurrences*

About 15% of the patients referred for repeated procedures suffered arrhythmic recurrences without any reconnected PV and/or line. Unfortunately, none of the baseline characteristics permitted differentiation between these ñnon-responderò patients and the others, though there was a trend towards longer AF duration and lower LVEF. During the repeated procedure, these patients and those with passive residual PV reconnections were, in case of recurrent AF, frequently approached with additional CFAE ablation, felt to be involved in areas of micro-reentry and focal triggers resulting in atrial arrhythmia relapses [24-25]. Following AF conversion into atypical flutter or in case of primary recurrent atrial tachycardia, these extra-PV mechanisms or localized sources could be directly identified to underlie the recurrent arrhythmia mechanism and ablated with more selective approach. Indeed, this subgroup of patients (arrhythmia relapses despite isolated PVs and validated atrial linear blocks) may receive the greatest benefit from an atrial substrate modification approach, failed among unselected general populations [26-29].

Indeed, in our opinion, by widening available knowledge, the present findings further support the usefulness of an extensive substrate modification for patients with advanced atrial disease, a frequent feature among patients with HF and severely reduced LVEF.

5. Limitations

First, the retrospective non-randomized design does not permit to perform a standardized evaluation of the parameters analysed. Second, the inclusion of patients from different centres, along with different procedural tools and protocols, although being representative of the real-life picture of current clinical practice, may increase heterogeneity among the population studied. Third, the high prevalence of atypical flutter/tachycardia recurrences suggest that many patients suffered arrhythmic recurrences mainly due to the difficulties in achieving durable conduction block across ablation lines. However, even after considering AF recurrences alone, severe LA enlargement emerged as an independent predictor of AF recurrences despite durable PV isolation, identifying therefore a subgroup of HF patients that warrants extensive substrate modification for rhythm control already at index procedure. Indeed, the active role of PVs in arrhythmic recurrences cannot be confirmed, as the recording of focal activity from PV was not reported. Furthermore, studies that examine the role of durable PVI isolation on arrhythmia recurrence remain significantly limited by the finding that durable PVI is often no achieved. As such, until PVI are completely eliminated through durable electrical isolation, there role in arrhythmia genesis and maintenance cannot be excluded. Last, the relatively limited sample of patients included in the study may limit the statistical relevance.

6. Conclusion

Based on the present findings, atrial substrate in HF patients appears more important than in the general AF population, and substrate modification may be required to reduce atrial arrhythmia recurrences. Severe LA enlargement, severely reduced LVEF and persistent/long standing AF are associated with reduced success of AF control with PVI alone.

In this scenario, an alternative LA ablation approach is most probably needed to achieve effective rhythm control, especially among patients with severely enlarged LA. However, if additional ablation is incomplete or allows substrate for re-entry, then such ablation may be proarrhythmic. Nonetheless, the evidence of arrhythmic recurrences in absence of evident reconnection sites in this study, strongly highlights, at least within patients with AF and HF, the importance of substrate modification. In case future research will succeed in increasing knowledge concerning the role of alternative non-PV mechanisms and the interpretation of atrial substrate (e.g. drivers and/or rotors), this will surely improve the outcome of AF catheter ablation in patients at an advanced stage of the disease, as those with HF who most probably require a distinct, targeted ablation approach.

Conflicts of interest

None.

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Table 1. Baseline characteristics of the study population according to index procedure.

	Overall (n=165)	Group A: PVI alone (n=47)	Group B: PVI + lines (n=118)	p-value
Age, years (SD)	55 (17)	53 (22)	56 (15)	0.401
Male sex, n (%)	137 (83%)	38 (81%)	99 (84%)	0.137
Paroxysmal AF, n (%)	64 (39%)	33 (70%)	32 (27%)	<0.001
Persistent AF, n (%)	43 (26%)	9 (19%)	33 (28%)	
Long-standing persistent AF, n (%)	59 (36%)	5 (10%)	53 (45%)	
AF duration, months (SD)	74 (84)	69 (68)	76 (91)	0.679
Hypertension, n (%)	106 (64%)	33 (70%)	72 (61%)	0.343
Diabetes mellitus, n (%)	26 (16%)	8 (18%)	16 (14%)	0.730
Previous stroke/TIA, n (%)	18 (11%)	5 (11%)	13 (11%)	0.782
CAD, n (%)	20 (12%)	6 (13%)	14 (12%)	0.989
Hyperthyroidism, n (%)	12 (7%)	2 (4%)	11 (9%)	0.093
Amiodarone use, n (%)	56 (34%)	14 (30%)	41 (35%)	0.499
Ic class drug use, n (%)	35 (21%)	16 (34%)	20 (17%)	0.019
Beta-blockers, n (%)	104 (63%)	33 (70%)	72 (61%)	0.296

OAC, n (%)	145 (88%)	38 (81%)	106 (90%)	<0.001
LVEF, % (SD)	41 (8)	44 (7)	41 (8)	0.031
LA volume, ml (SD)	121 (68)	56 (28)	152 (57)	<0.001
PVI alone, n (%)	47 (28%)	47 (100%)	0	-
PVI + lines, n (%)	118 (72%)	0	118 (100%)	-
Left isthmus line, n (%)	104 (62%)	0	104 (88%)	-
Roof line, n (%)	104 (62%)	0	104 (88%)	-
Posterior line, n (%)	21 (13%)	0	21 (18%)	-
CFAE, n (%)	44 (26%)	0	44 (42%)	-
Right isthmus ablation, n (%)	97 (58)	9 (19%)	88 (76%)	<0.001
Complications, n (%)	3 (2%)	1 (2%)	2 (3%)	0.541
Time to recurrence, months (SD)	12 (14)	8 (14)	9 (8)	<0.001
Paroxysmal AF recurrence, n (%)	44 (27%)	30 (63%)	14 (12%)	<0.001
Persistent AF recurrence, n (%)	56 (34%)	14 (30%)	42 (36%)	
Atypical flutter recurrence, n (%)	65 (39%)	3 (7%)	62 (52%)	
Number of reconnected PVs, n (SD)	1.9 (1.6)	3.1 (1.2)	1.5 (1.5)	<0.001

Reconnected PVs - 0 - 1 - 2 - 3 -4	 54 (32) 16 (9) 30 (18) 24 (14) 46 (27)	 4 (8) 1 (2) 6 (13) 11 (23) 25 (54)	 49 (42) 15 (13) 19 (16) 13 (11) 21 (18)	<0.001
Repeated procedure characteristics				
PVI alone, n (%)	61 (37%)	31 (65%)	43 (36%)	<0.001
PVI + lines, n (%)	61 (37%)	14 (30%)	27 (23%)	
Lines/CAFE alone, n (%)	43 (26%)	2 (5%)	48 (41%)	
Left isthmus line, n (%)	74 (44%)	7 (15%)	67 (56%)	<0.001
De novo left isthmus line, n (%)	7 (4%)	7 (15%)	-	-
Roof line, n (%)	70 (42%)	14 (30%)	56 (47%)	0.042
De novo roof line, n (%)	14 (8%)	14 (30%)	-	-
Posterior line, n (%)	23 (14%)	2 (4%)	21 (18%)	0.042
CFAE ablation, n (%)	33 (20%)	7 (15%)	26 (22%)	0.333
Right isthmus ablation, n (%)	42 (25%)	4 (9%)	38 (32%)	0.002
Complications, n (%)	5 (3.0%)	1 (2.1%)	4 (3.4%)	0.391

PVI: pulmonary vein isolation; AF: atrial fibrillation; TIA: transient ischaemic attack; CAD: coronary artery disease; OAC: oral anticoagulant; LVEF: left ventricular ejection fraction; LA: left atrium. CFAE: complex fractioned atrial electrograms.

Table 2. Baseline population and procedural characteristics stratified according to the presence or absence of at least one PV conduction recovery detected at repeated procedure

	PVs reconnection (n=111)	Absence of PVs reconnection (n=54)	p-value
Age, years (SD)	54.9 (18)	55.8 (16)	0.767
Male sex, n (%)	93 (84%)	44 (82%)	0.457
Paroxysmal AF, n (%)	55 (50%)	8 (15%)	<0.001
Persistent AF, n (%)	28 (25%)	15 (28%)	
Long-standing persistent AF, n (%)	28 (25%)	32 (59%)	
AF duration, months (SD)	62 (59)	95 (114)	0.047
Hypertension, n (%)	62 (56%)	37 (69%)	0.357
Diabetes mellitus, n (%)	16 (14%)	9 (17%)	0.960
Previous stroke/TIA, n (%)	12 (11%)	6 (11%)	0.686
CAD, n (%)	13 (12%)	7 (13%)	0.879
Amiodarone use, n (%)	38 (34%)	18 (33%)	0.968
Ic class drug use, n (%)	31 (28%)	4 (7%)	0.004
Beta-blockers, n (%)	69 (62%)	35 (65%)	0.837
OAC, n (%)	82 (74%)	52 (96%)	0.001
LVEF, % (SD)	42.8 (8)	39.8 (7)	0.052
LA volume, ml (SD)	95 (62)	159 (58)	<0.001
PVI alone, n (%)	41 (37%)	6 (11%)	<0.001
PVI + lines, n (%)	70 (63%)	48 (89%)	
Left isthmus line, n (%)	65 (59%)	39 (72%)	0.079

Roof line, n (%)	65 (59%)	40 (74%)	0.036
Posterior line, n (%)	14 (13%)	20 (37%)	0.003
CFAE ablation, n (%)	20 (18%)	32 (59%)	<0.001
Right isthmus ablation, n (%)	57 (51%)	41 (76%)	0.002
Complications, n (%)	2 (1.8%)	1 (1.8%)	0.688
Time to recurrence, months (SD)	13 (14)	10 (14)	0.218
Paroxysmal AF recurrence, n (%)	40 (36%)	4 (7%)	<0.001
Persistent AF recurrence, n (%)	40 (36%)	16 (30%)	
Atypical flutter recurrence, n (%)	31 (28%)	34 (63%)	

PVI: pulmonary vein isolation; AF: atrial fibrillation; TIA: transient ischaemic attack; CAD: coronary artery disease; OAC: oral anticoagulant; LVEF: left ventricular ejection fraction; LA: left atrium. CFAE: complex fractioned atrial electrograms.

Table 3. Characteristics of patients experiencing paroxysmal/persistent AF recurrences stratified according to the presence or absence of at least one PV conduction recovery detected at repeated procedure.

	Overall AF recurrences (n=100)	PVs reconnection (n=80)	Absence of PVs reconnection (n=20)	p-value
Paroxysmal AF, n (%)	52 (52)	51 (64%)	1 (5%)	<0.001
Persistent AF, n (%)	18 (18)	9 (11%)	9 (45%)	
Long-standing persistent AF, n (%)	30 (30)	20 (25%)	10 (50%)	
AF duration, months (SD)	79 (85)	72 (63)	103 (134)	0.228
LVEF, % (SD)	43.0 (8)	43.6 (8.1)	41.0 (6.4)	0.049
LA volume, ml (SD)	93 (66)	75 (57)	146 (65)	0.001
PVI alone, n (%)	49 (49)	47 (59%)	2 (10%)	0.001
PVI + lines, n (%)	51 (51)	33 (41%)	18 (90%)	
Right isthmus ablation, n (%)	38 (38)	26 (32%)	12 (60%)	0.065
Complications, n (%)	1 (1)	1 (1.3%)	0 (0%)	0.657
Time to recurrence, months (SD)	13 (15)	16 (15)	9 (10)	0.016

PV: pulmonary veins; PVI: pulmonary vein isolation; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LA: left atrium. CFAE: complex fractioned atrial electrograms.

Table 4. Multivariate analysis on patients relapsing with AF only (n=100) assessing the independent correlation to recurrences despite absence of PV reconnection of those parameters significant at univariate analysis ($p<0.05$).

	OR	95% CI	p-value
AF type, paroxysmal vs. persistent	0.772	0.171-3.494	0.737
LA volume, III tertile	5.090	1.192-26.188	0.048
LVEF, III tertile	1.078	0.351-3.307	0.896
PVI alone vs. lines/CFAE	8.127	0.119-35,212	0.499

OR: odds ratio. CI: confidence interval. PV: pulmonary veins; PVI: pulmonary vein isolation; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LA: left atrium. CFAE: complex fractioned atrial electrograms.

Figure legends

Figure 1. Pattern of PVs conduction recovery detected at repeated procedure (n=165 patients), stratified according to first ablation protocol. PV: pulmonary vein. LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein.

Figure 2. Number of reconnected pulmonary veins or incomplete linear lesions documented at repeated procedure, according to index procedure. PVI: pulmonary vein isolation. CFAE: complex fractioned atrial electrograms.

Figure 3. Different patterns of LVEF, stratified by tertiles (A), LA volume, stratified by tertiles (B), atrial fibrillation subtype (C) and catheter ablation protocol performed at index procedure (D) among patients respectively experiencing PVs reconnection or without PVs reconnection at redo procedure. LVEF: left ventricular ejectionfraction. LA: left atrial. AF: atrial fibrillation.

Figure 1.

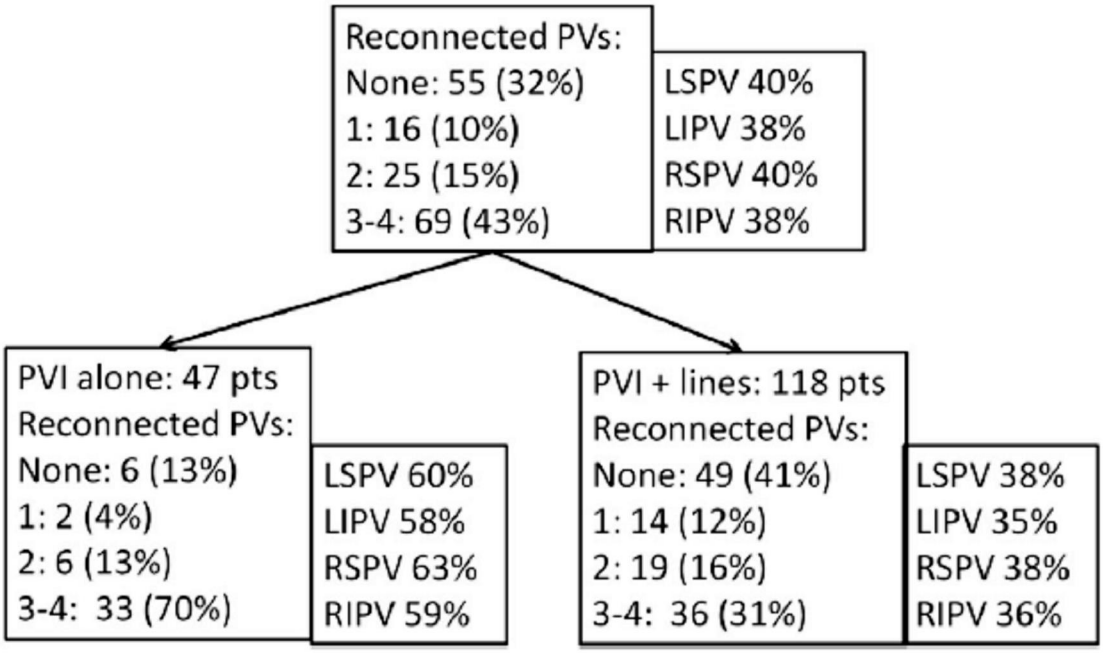

Reconnected PVs:
None: 55 (32%)
1: 16 (10%)
2: 25 (15%)
3-4: 69 (43%)
LSPV 40%
LIPV 38%
RSPV 40%
RIPV 38%
PVI alone: 47 pts
Reconnected PVs:
None: 6 (13%)
1: 2 (4%)
2: 6 (13%)
3-4: 33 (70%)
LSPV 60%
LIPV 58%
RSPV 63%
RIPV 59%
PVI + lines: 118 pts
Reconnected PVs:
None: 49 (41%)
1: 14 (12%)
2: 19 (16%)
3-4: 36 (31%)
LSPV 38%
LIPV 35%
RSPV 38%
RIPV 36%

Figure 2

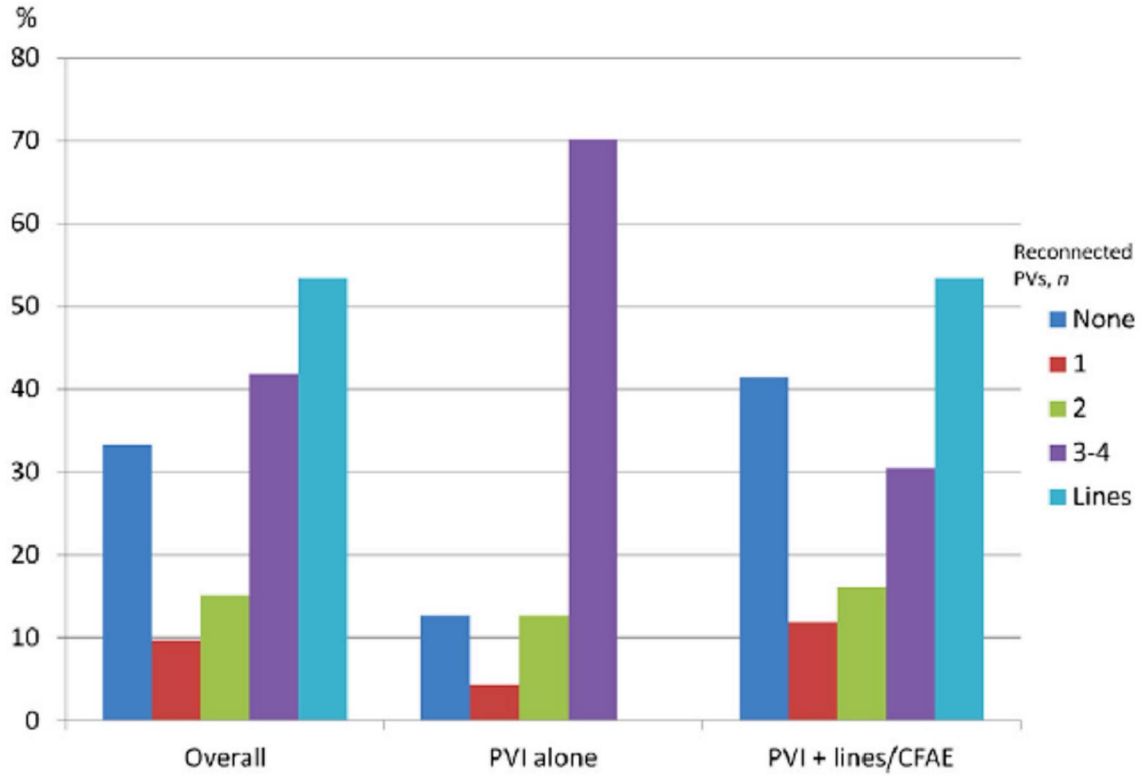
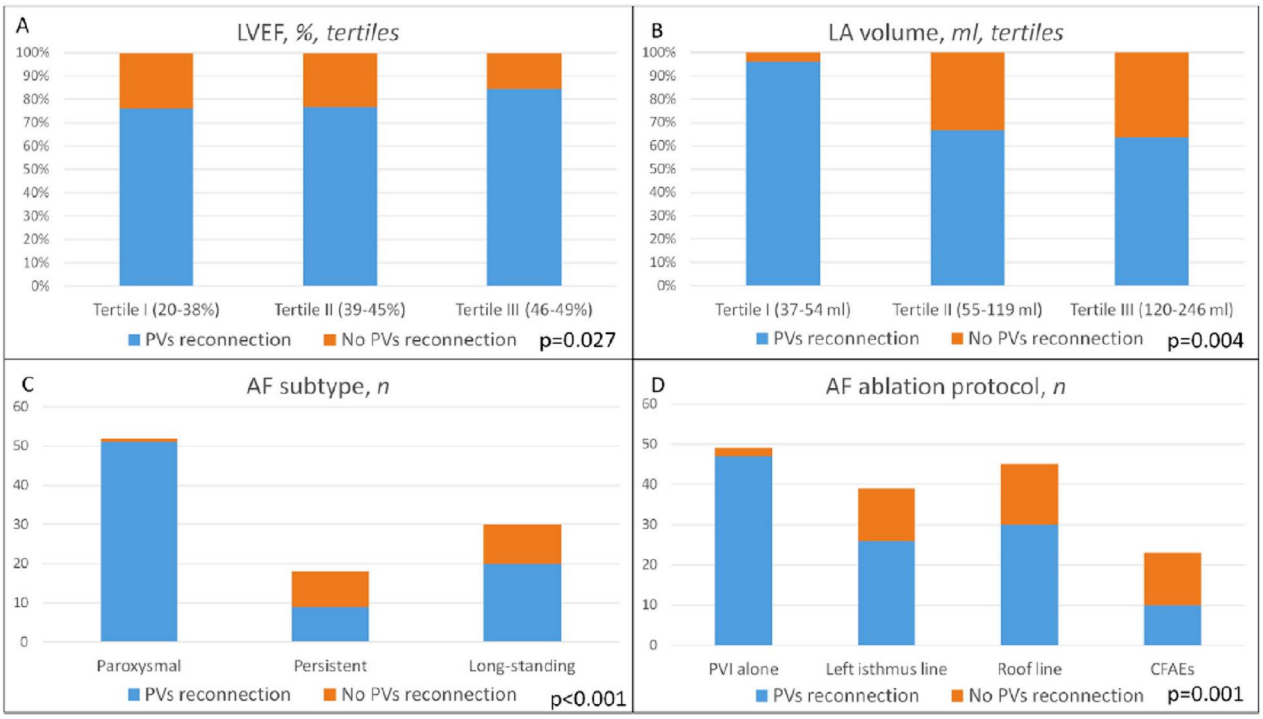

%
80
70
60
50
40
30
20
10
0
Overall
PVI alone
PVI + lines/CFAE
Reconnected PVs, n
None
1
2
3-4
Lines

Figure 3.


A
LVEF, %, tertiles
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Tertile I (20-38%)
Tertile II (39-45%)
Tertile III (46-49%)
PVs reconnection
No PVs reconnection
p=0.027
B
LA volume, ml, tertiles
Tertile I (37-54 ml)
Tertile II (55-119 ml)
Tertile III (120-246 ml)
PVs reconnection
No PVs reconnection
p=0.004
C
AF subtype, n
60
50
40
30
20
10
0
Paroxysmal
Persistent
Long-standing
PVs reconnection
No PVs reconnection
p<0.001
D
AF ablation protocol, n
PVI alone
Left isthmus line
Roof line
CFAEs
PVs reconnection
No PVs reconnection
p=0.001