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Impact of Ablation Index Settings on Pulmonary Vein Reconnection.

Lepillier A, MD ^a, Strisciuglio T, MD^{b,c}, De Ruvo E, MD,^d Scaglione M, MD,^e Anselmino M, MD,^f Sebag FA, MD,^g Pecora D, MD,^h Gallagher MM, MD,ⁱ Rillo M, MD,^j Viola G, MD,^k
5 Pisanò E,MD,^l Abbey S,MD,^m Lamberti F,MD,ⁿ Pani A,MD,^o Zucchelli G,MD,^p Sgarito G,MD,^q De Simone A, MD,^r Bertaglia E, MD,^s Solimene F, MD,^b Stabile G, MD,^{b,r,t}.

^aCentre Cardiologique du Nord, St Denis, Paris, France; ^bClinica Montevergine, Mercogliano (AV), Italy; ^c University of Naples Federico II, Naples, Italy; ^dPoliclinico Casilino, Roma, Italy; ^eOspedale Cardinal Massaia, Asti, Italy; ^fA.O.U. Citta della Salute e della Scienza di Torino, Department of Medical Sciences, University of Turin, Italy; ^g Institut Mutualiste Montsouris, Paris, France; ^hFondazione Poliambulanza, Brescia, Italy; ⁱSt George's Hospital, London, United Kingdom; ^jCasa di Cura Villa Verde, Taranto, Italy; ^kOspedale San Francesco, Nuoro, Italy; ^lOspedale Vito Fazzi, Lecce, Italy; ^mHôpital Privé Du Confluent (HPCN), Nantes, France; ⁿOspedale Sant'Eugenio, Roma, Italy; ^oOspedale di Lecco, Italy; ^pAzienda Ospedaliera Pisana, Pisa, Italy; ^qA.R.N.A.S. Civico Cristina Benfratelli, Palermo; ^rClinica San Michele, Maddaloni (CE), Italy; ^sDepartment of Cardiac, Thoracic, and Vascular Sciences, University of Padova, Italy; ^tAnthea Hospital, Bari, Italy.

PVI reconnection

Corresponding Author:
Dr Giuseppe Stabile,
Clinica San Michele, via Montella 16, 81024 Maddaloni (CE), Italy,
Tel.+393488960534; e-mail: gmrstabile@tin.it

ABSTRACT

Purpose Ablation Index (AI) is a radiofrequency lesion quality marker. The AI value that allows effective and safe pulmonary vein isolation (PVI) is still debated.

45 We evaluated the incidence of acute and late PV reconnection (PVR) with different AI settings and its predictors.

Methods The Ablation Index Registry is a multicentre study that included patients with paroxysmal/persistent atrial fibrillation (AF) underwent first time ablation. Each operator performed the ablation using his preferred ablation catheter (ThermoCool® SmartTouch or
50 Surround Flow) and AI setting (380 posterior-500 anterior and 330 posterior-450 anterior). We divided the study population in two groups according to the AI setting used: Group 1 (330-450) and Group 2 (380-500). Incidence of acute PVR was validated within 30 minutes after PVI, whereas the incidence of late PVR was evaluated at repeat procedure.

Results Overall, 490 patients were divided in Group 1 (258) and 2 (232). There was no
55 significant difference in the procedural time, fluoroscopy time, and rate of first-pass PVI between the two study groups. Acute PVR was observed in 5.6% PVs. The rate of acute PVR was slightly higher in Group 2 (64/943, 6.8%, PVs) than in Group 1 (48/1045, 4.6% PVs, $p=0.04$). Thirty patients (6%) underwent repeat procedure and late PVR was observed in 57/116 (49%) PVs (number of reconnected PV per patient of 1.9 ± 1.6). A similar rate of late
60 PVR was found in the two study groups. No predictors of acute and late PVR were found.

Conclusion Ablation with lower range of AI is highly effective and is not associated with higher rate of acute and late PVR. No predictors of PV reconnection were found.

KEY WORDS: Atrial fibrillation, catheter ablation, ablation index, pulmonary vein
65 reconnection

Declarations

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Conflicts of interest/Competing interests: Nothing to declare

70 **Ethics approval:** As this is a multicentre study, the ethical committee of each centre approved the study

Consent to participate: Before inclusion in the study every patient signed the informed consent

Consent for publication: all authors consent to the publication of the manuscript in JICE

75 **Availability of data and material (data transparency):** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability: NA

80 **Author contributions**

Concept/design: Solimene F, Lepillier A, Anselmino M, Bertaglia E, Stabile G.

Data analysis/interpretation: Solimene F, Lepillier A, De Ruvo E, Scaglione M, Anselmino M, Sebag FA, Pecora D, Gallagher MM, Rillo M, Viola G, Pisanò E, Abbey S, Lamberti F, Pani A, Zucchelli G, Sgarito G, De Simone A Bertaglia E, Strisciuglio T, Stabile G.

85 Drafting article: Solimene F, Lepillier A, Anselmino M, Gallagher MM, Rillo M, Viola G, De Santis V, Landolina M, De Simone A, Bertaglia E, Strisciuglio T, Stabile G.

Critical revision of article: Solimene F, Lepillier A, De Ruvo E, Scaglione M, Anselmino M, Sebag FA, Pecora D, Gallagher MM, Rillo M, Viola G, Pisanò E, Abbey S, Lamberti F, Pani A, Zucchelli G, Sgarito G, De Simone A Bertaglia E, Strisciuglio T, Stabile G.

90 Approval of article: Solimene F, Lepillier A, De Ruvo E, Scaglione M, Anselmino M, Sebag FA, Pecora D, Gallagher MM, Rillo M, Viola G, Pisanò E, Abbey S, Lamberti F, Pani A, Zucchelli G, Sgarito G, De Simone A, Bertaglia E, Strisciuglio T, Stabile G.

Statistics: Bertaglia E, Strisciuglio T, Stabile G.

Data collection: Solimene F, Lepillier A, De Ruvo E, Scaglione M, Anselmino M, Sebag FA,
95 Pecora D, Gallagher MM, Rillo M, Viola G, Pisanò E, Abbey S, Lamberti F, Pani A, Zucchelli G, Sgarito G, De Simone A, Bertaglia E, Strisciuglio T, Stabile G.

INTRODUCTION

100 Ablation Index (AI) (Biosense-Webster, Diamond Bar, California) is a new marker of
radiofrequency (RF) lesion quality, that incorporates stability, contact force, time and power
in a weighted formula. When the AI has been used in an ablation protocol respecting strict
criteria for lesion contiguity (1), a high rate of first pass pulmonary vein (PV) isolation (1-5)
and a high single-procedure arrhythmia-free survival at 1 year (1-6) have been reported. The
105 AI value that allows effective and safe PV isolation remains to be defined. An AI value
ranging from 330 to 400 has been proposed for posterior/inferior segments of PVs, and from
450 to 550 for anterior/roof segments (1,2,4,7,8).

In the present study, we compared the efficacy and the safety of two AI setting (330 for
posterior/inferior segments and 450 for anterior/roof segments vs 380 for posterior/inferior
110 segments and 500 for anterior/roof segments) during acute PV isolation (PVI) and at repeat
procedure in a multicenter, prospective, and observational trial.

METHODS

The Ablation Index Registry (AIR) (ClinicalTrials.gov Identifier: NCT03277976) is a
115 prospective, multi-center, research study designed to evaluate the acute achievement of PV
isolation with ThermoCool SmartTouch (ST) (Biosense-Webster, Diamond Bar, California)
or ThermoCool SmartTouch SF (STSF) (Biosense-Webster, Diamond Bar, California)
catheter using the AI Module. Enrollment started in November 2017 and ended in July 2018.
The study was approved by local Ethics Committees and complied with the Declaration of
120 Helsinki guidelines. Written informed consent was obtained from all patients.

Study population and ablation protocol. Enrollment criteria and ablation protocol has been
already described (7). Briefly, we enrolled patients with paroxysmal or persistent atrial
fibrillation (AF) who underwent their first AF ablation. Each operator performed AF catheter

ablation using its own ablation technique as concerning the ablation catheter (ST or STSF)
125 and the AI setting (380 posterior-500 anterior and 330 posterior-450 anterior). No
randomization was required nor was there any deviation from the clinical practice of each
center and operator. Therefore the enrolled population was divided in 4 groups: ST 330-450,
ST 380-500, STSF 330-450, and STSF 380-500. For the purpose of this analysis on lesion
quality, we divided the study population in two groups according to the AI setting used:
130 Group 1 (330 for posterior/inferior segments and 450 for anterior/roof segments) and Group 2
(380 for posterior/inferior segments and 500 for anterior/roof segments).

Study Procedures. The ablation procedure has been already described (7). Briefly, ablation
was usually performed under effective oral anticoagulation, and antiarrhythmic drugs were
usually withdrawn before scheduled procedure. Ablation was carried out under conscious
135 sedation or general anesthesia according to operators' preference. One or two transseptal
accesses to the left atrium were achieved using a standard approach. Then, the LASSO
catheter and the ablation catheter (ST or STSF) were placed in the left atrium. Left atrium
mapping was performed in sinus rhythm. Patients with AF at the beginning of the index
procedure underwent electrical cardioversion. After left atrium reconstruction the effective
140 PV-left atrium electrical connection was checked by LASSO catheter. RF pulses were
delivered using the 3.5-mm Thermocool ST or STSF Catheter in power control mode. RF
power was set between 20 and 35 W depending on different left atrial sites and the catheter
tip was irrigated by saline at a flow rate of 2 mL/min during mapping and of 8 mL/min
(STSF) or 17 mL/min (ST) and 15 mL/min (STSF) or 30 mL/min (ST) for outputs of less
145 than and greater than 30 W, respectively (7). RF energy was delivered to produce a
circumferential ablation around the proximal part of each PV's ostium or around ipsilateral
PVs according to the patient's anatomy or operator's preference. The lesion around the PV
ostium was created by sequential point-by-point application of RF energy. Real-time

automated display of RF applications (Carto VISITAG™ Module, Biosense Webster) was
150 used with predefined settings of respiration adjustment, catheter stability (3 mm for 3 s),
minimum contact force (3 g over minimum 25% of time), with the lesion tag display size of 3
(radius of 1,5 mm), and AI thresholds: 450 for anterior wall and 330 for posterior wall, for
Group 1, and 500 for anterior wall and 380 for posterior wall, for Group 2, respectively. In
case of dislocation, a new RF application reaching the AI target was applied. Maximal inter
155 lesion distance (ILD) between 2 neighboring lesions was ≤ 6 mm (1,9). Upon completion of
circumferential ablation a circular mapping LASSO catheter was used to confirm PV
isolation (first-pass isolation). In the absence of isolation after completing the circle, LASSO
guided touch-up ablation was delivered until PV isolation was achieved. Resumption of left
atrium to PV conduction was evaluated at 30 minutes after ablation. The administration of
160 adenosine/isoproterenol was not part of the protocol and was left to operators' discretion. In
case of reconnection PVs were newly isolated targeting the points of electrical breakthrough.
All patients underwent a post-procedural ECG. Post-procedure echocardiography or other
imaging was at the operators' discretion.

Follow-up. After ablation, patients underwent a 30 days visit including a detailed history,
165 physical examination, 12-lead standard electrocardiography, and 24-h Holter monitoring. In
case of symptomatic arrhythmia recurrence, patients were treated with a repeat procedure or
with anti-arrhythmic drugs, based on patients' choice.

Repeat procedure. Repeat ablation was performed using the same modalities as the
first procedures. After left atrium reconstruction the effective PV-left atrium electrical
170 connection was checked by LASSO catheter. In case of reconnection PVs were newly
isolated targeting the points of electrical breakthrough. In case the 4 PVs were still isolated,
the operator proceeded with the search of non-PV triggers and went for a "box lesion" to
isolate the posterior wall.

Statistical analysis. Continuous variables are expressed as mean \pm standard deviation or median and interquartile range according to their distribution. Normality of data distribution was tested with Shapiro-Wilk test. Categorical variables are expressed as absolute number with percentage (%). Comparison among groups for continuous variables was performed by the unpaired Student T test or Mann-Whitney U test. Comparison of categorical variables among groups was performed by Chi square test. Statistical significance was set at a 2-tailed probability level of <0.05 . All statistical analyses were performed using SPSS software (Version 24.0, IBM, Armonk, NY, US).

RESULTS

Study population. A total of 490 patients were enrolled: 258 patients in Group 1, 232 in Group 2. A ST catheter was used in 96/258 (37%) Group 1 patients and 81/232 (35%) (p=0.60) Group 2 patients. The clinical characteristics of the study population are summarized in the table I. Group 1 patients had a higher mean body mass index and a lower left ventricle ejection fraction. The incidence of hypertension was higher in Group 2, whereas the incidence of dilated cardiomyopathy was higher in Group 1.

Procedural data. In table II are summarized the main procedural data. There was no statistically significant difference in the mean procedural time, fluoroscopy time, contact force, and impedance drop between the two study groups. Also the rate of first-pass PV isolation was similar. A LASSO guided touch-up ablation was required to isolate 193/1988 (9.7%) PVs (Figure 1), with no significant differences between left or right, superior or inferior veins nor between anterior and posterior segments. In table III are summarized the main procedural data of PVs isolated after the first-pass isolation compared with those of PV that required a touch-up ablation. No difference in mean contact force was observed, whereas

a touch-up ablation was required to isolate PVs in which lower mean power and impedance drop and longer mean RF pulse duration were used.

200 **30 minutes PV reconnection.** Resumption of left atrium to PV conduction 30 minutes after ablation was observed in 5.6% PVs (Figure 2), with no significant differences between left or right, superior or inferior veins nor between anterior and posterior segments. The rate of 30 min PV reconnection was slightly higher in Group 2 (64/943, 6.8%, PVs) as compared to Group 1 (48/1045, 4.6% PVs, $p=0.04$). In table IV are summarized the main procedural data
205 of PVs that showed a 30 min reconnections compared with those of PVs that did not. No difference in mean contact force, impedance drop, mean power and mean RF pulse duration was observed.

Repeat procedure and late PV reconnection. Thirty patients (6%) underwent repeat procedure for symptomatic arrhythmia recurrence (Table V): in 9/30 (30%) (5 in Group 1
210 and 4 in Group 2) a durable PVI was observed whereas in the others with PVR ($n=21$) the mean number of reconnected veins was 1.9 ± 1.6 . Overall, 57/116 (49%) PVs were reconnected and reconnections were more likely in the right veins and in the anterior segments (Figure 3). No difference was found in the rate of reconnection between Group 1 and 2 (72% vs 68%; $p=0.6$). Compared to patients with PVR, patients with 4 isolated veins
215 had similar first procedural and RF characteristics (RF time, force time integral, power, contact force, or impedance drop) (Table VI). The time to arrhythmia recurrence was longer in patients with durable PVI compared to those with reconnections (4.8 ± 4.7 months vs 10.2 ± 6.6 months, $p=0.05$) (Figure 4). Furthermore, the AI setting didn't influence the time to recurrence in patients with PVR (4.6 ± 4.8 months vs 5.1 ± 4.8 , $p=0.8$; in Group 1 and Group 2
220 respectively).

Complications. A complication (4 pericardial effusions, 2 transient phrenic nerve palsy, 1 cardiac tamponade, 1 pneumonia) was observed in 8 (1,6%) patients without any difference among the two study groups (1.5% vs 1.7%, p=0.88).

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DISCUSSION

Main findings. This study, evaluating the impact of two AI settings on the rate of first pass PV isolation, and acute and late PV reconnection, shows that lower AI values were as safe and effective as higher ones. With both AI settings a high rate of first pass PV isolation and a low rate of acute PV reconnection were achieved irrespective of patient and operator characteristics. The probability of finding 4 isolated veins at repeat procedure was 30%. No predictors of acute and late PVR were found.

AI setting in acute PV isolation. The AI is a novel marker of RF application quality that incorporates stability, contact force, time and power in a weighted formula, and has shown to accurately estimate lesion depth and diameter (11). Not well defined are the best AI values that allow effective, safe and durable PV isolation. Das et al (8) studied the relationship between the AI and PVR at repeat electrophysiology study. From receiver operating characteristic (ROC) curve analysis, optimal cutoff points (Youden Index) were calculated. For AI, the optimal cutoff for anterior/roof segments was 376 (sensitivity 63.6%, specificity 77.8%, and positive predictive value 97.2%) and for posterior/inferior segments was 340 (sensitivity 52.9%, specificity 94.3%, and positive predictive value 98.2%). No late reconnection was seen in anterior/roof segments where the minimum AI value was ≥ 480 or in posterior/inferior segments where the minimum AI value was ≥ 370 . El Haddad et al (12) studied acute and late PV reconnection. By ROC curve analysis they found the highest (90%) specificity to predict durable PV isolation with an AI >550 on the anterior wall and >417 on

245 the posterior wall. Based on an initial survey within the 25 centers involved in our Registry, two most used AI settings (330 posterior/450 anterior and 380 posterior/500 anterior) were compared as regarding the rate of first pass PV isolation, rate of acute and late PV reconnection, and safety. No differences were observed between the two AI settings. Our findings, that a higher AI setting is not acutely superior than a lower one might be justified by 250 Ullah et al (11) series. They showed that ablation beyond 430 AI provides minimal additional biophysical efficacy, suggesting an upper limit to use for clinical ablation. Recently, Lee et al (13) evaluated the optimal AI threshold for avoiding acute PV reconnection. AI values of ≥ 450 at the anterior/roof segments and of ≥ 350 at the posterior/inferior/carina segments were identified as the optimal AI thresholds for avoiding acute PV reconnection, confirming 255 present results.

First pass PV isolation. The most common technique for PVI is creating circular RF lesions in a point-by-point manner around the PV ostia (14). The introduction of the AI to guide the RF delivery greatly improved the rate of first pass isolation from about 50% (15,16) to above 90% (1-3). In particular, in a previous analysis of the multicenter AIR Registry we 260 observed that PVI guided by AI allows every operator to achieve a rate of first-pass PV isolation $\geq 84\%$, thus concluding that the AI improves the “operator variable” by generalizing and standardizing physicians’ skills and experience applied to the AF ablation procedure. Few data are available on the site of persistent atrium-PV connection that requires a touch-up ablation until PV isolation is achieved. In Hussein et al series (2) first pass PV isolation with 265 wide area circumferential ablation (WACA) circle was achieved in the AI group in 173/178 (97%) circles, of the 5 (3%) WACA circles in which first pass isolation failed to occur, 4 (80%) were related to the right ipsilateral PVs and required further RF delivery. In Dillon et al series (17) first pass isolation occurred in 82% WACAs, with first-pass isolation occurring in both left and right WACAs in 68% (34/50) of patients. Further ablation was required on

270 the inter-venous ridge between the PVs in order to isolate them in 16% (16/100) WACAs. In
our series we observed that a touch-up ablation was required to isolate 193/1988 (9.7%) PVs,
with no significant differences between left or right, superior or inferior veins nor between
anterior and posterior segments. No difference in mean contact force was observed, whereas
a touch-up ablation was required to isolate PVs in which lower mean power and impedance
275 drop and longer mean radiofrequency pulse duration were used. This finding suggests a
higher impact of RF biophysics over anatomical characteristics in achieving a first-pass PV
isolation.

Acute PV reconnection. More data are available on the sites of acute PV reconnection. In
Hussein et al series (2) either spontaneous or adenosine-induced PV reconnection was
280 identified in 11 (6%) circles in the AI group (3 on the left and 8 on the right). In Das et al (8)
series acute reconnection was seen after the minimum 20-min waiting period in 28 (6%)
segments (14 spontaneous and 14 adenosine-induced) in 20 (50%) patients, affecting 21
(26%) WACA circles. In El Haddad et al series (12) acute PV reconnection occurred in 11/48
(23%) patients, 14/96 (15%) circles, and 25/980 (2.6%) PV segments. In Lee et al series (11),
285 in the AI guided PV isolation group 4.2% of PV segments showed acute PV reconnection
with a mean of 0.6 ± 0.9 segment per patient. Similarly, in our series, resumption of left
atrium to PV conduction 30 minutes after ablation was observed in 5.6% PVs, with no
significant differences between left or right, superior or inferior veins nor between anterior
and posterior segments. No predictors of acute PV reconnection were found.

290 **Late PV reconnection.** Prior studies investigated the durability of PVI after a CF-guided
ablation protocol aiming to enclose the veins with stable, contiguous, and optimized RF
lesions. De Pooter et al. (18) reported a likelihood of finding 4 isolated veins at repeat
ablation of 62% and no clinical and procedural differences between patients with or without
PV reconnections and also time to AF recurrence from the first PVI was similar. However,

295 this was a single-centre study, and all the PVI procedures were performed by highly skilled operators. Recently, Duytschaever et al. (6) reported the data of the multicenter prospective VISTAX study, and described a 41.2% rate of durable PVI, that reflects some variability across different sites. In our series of patients, we found a durable PVI in 30%. The inclusion of persistent AF patients (37%) in our case series may partly explain this lower rate compared
300 to the VISTAX study, however there are other possible reasons. First, we cannot exclude the resumption of dormant PV conduction (19), as the adenosine/isoproterenol was not given in all patients at the end of the first procedure. Nonetheless, a recent meta-analysis by Chen (20) demonstrated that the adenosine test does not reduce the rate of AF recurrence. Second, the persistence of PV potential at the carina that reflects the connections between ipsi-lateral
305 veins may be the cause of PV reconnection (21). In our study in patients requiring touch-up ablations the choice to perform an ablation at the carina was left to each operator. However the data about the efficacy of this approach are still controversial as the study by Higashiya demonstrated no clear benefit (22).

As for the predictors of durable PVI, similarly to De Pooter et al. we didn't find any distinct
310 clinical nor procedural characteristics in patients with 4 isolated veins at repeat ablation.

Limitations. First, this is a non randomized study. No deviation from the clinical practice of each center and operator was required. This might justify the clinical and procedural differences in the two study groups. Nevertheless, the high and comparable rate of first-pass PV isolation that we observed in the two study groups, with different tools and operators, is a
315 strong point of our study. Second, the target ILD during the ablation procedure was ≤ 6 mm (1,6), because the study was conducted before the publication of the randomized trial by Hoffmann et al. (23), that demonstrated that the target ILD should be 3-4 mm. Third, after the circumferential ablation after a waiting period of 30 minutes the decision whether to

administrate adenosine/isoproterenol was left to each operator, thus we cannot exclude that
320 the cause of the late PV reconnection was the resumption of dormant conduction.

CONCLUSIONS

In conclusion, lower AI (330-450) values were as safe and effective as higher ones (380-500)
in obtaining acute PV isolation in patients with paroxysmal/persistent AF who underwent
325 first catheter ablation. With both AI settings a high rate of first pass PV isolation and a low
rate of acute and late PV reconnection were achieved irrespective of patient and operator
characteristics. No predictors of acute and late PV reconnection were found.

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FIGURE LEGENDS

Figure 1 Anatomic distribution of touch-up lesions required to isolate the pulmonary veins. LSPV= left superior pulmonary vein; LIPV= left inferior pulmonary vein; RSPV= right superior pulmonary vein; RIPV= right inferior pulmonary vein. PA view: postero-
435 anterior view.

Figure 2 Anatomic distribution of 30 min pulmonary vein reconnections. LSPV= left superior pulmonary vein; LIPV= left inferior pulmonary vein; RSPV= right superior pulmonary vein; RIPV= right inferior pulmonary vein. PA view: postero-anterior view.

Figure 3 Anatomic distribution of late pulmonary vein reconnections at repeat ablation.
440 LSPV= left superior pulmonary vein; LIPV= left inferior pulmonary vein; RSPV= right superior pulmonary vein; RIPV= right inferior pulmonary vein. PA view: postero-anterior view.

Figure 4 Box plots showing the mean time to arrhythmia recurrence in patients with and without pulmonary vein reconnections

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Table I. Patient demographics for the total cohort of subjects, and for each study group.

	Overall population (n=490)	Group 1 (n=258)	Group 2 (n=232)	P
Mean age (yrs)	59±11	58.81±10.9	59±11	0.96
Male sex (%)	71	69	74	0.31
BMI	27.1±4.2	28±5	26±4	0.004
LA volume (ml)	104±49	109±43	99±54	0.083
LVEF (%)	58±8	56±9	59±8	0.005
Paroxysmal AF (%)	80.4	80	81	0.85
Hypertension (%)	36.8	30.5	44	0.003
Ischemic heart disease (%)	6.3	6.2	5	0.487
Valvulopathy (%)	2.4	1.2	4	0.051
Dilated cardiomyopathy (%)	2.9	4.63	1	0.012
Previous TIA/Stroke (%)	2.7	3	2	0.521
Diabetes mellitus (%)	6.3	7.7	5	0.176
Chronic renal failure (%)	1.4	1.2	2	0.598

BMI= body mass index; LA= left atrium; LVEF= left ventricle ejection fraction; AF= atrial fibrillation; TIA= transient ischemic attack.

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Table II. Procedural data for the total cohort of subjects, and for each study group.

	Overall population (n=490)	Group 1 (n=258)	Group 2 (n=232)	P
Common ostium (%)	18.4	12	25	<0.001
Accessory PV (%)	5.7	5.03	6.47	0.57
Procedure time (min)	127±64	123±63	131±65	0.15
Fluoroscopy time (s)	400±404	367±357	436±446	0.06
Ablation time (min)	32±12	32±11	32±13	0.42
First pass isolation (%)	90±16	90±16	88±16	0.88
Mean CF (g)	11±4	10.7±5	10±4	0.15
Mean impedance drop (Ω)	10.4±4.7	10.3±3.7	10.6±4.3	0.36

PV= pulmonary vein; CF= contact force.

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Table III. Procedural data according to touch-up lesions.

	Overall PV (n=1988)	PVI without touch-up (n=1794)	PVI with touch-up (n=194)	P
Mean ablation time (min)	16±7	16±7	17±7	0.002
Mean contact force (g)	11.4±3.5	11.4±3.4	11.7±4.2	0.43
Mean impedance drop (Ω)	10.4±4	10.6±4	9.8±3.5	0.017
Mean power (W)	31±3	32±3	31±3	0.024

Mean ablation time= mean ablation time to isolate 2 ipsilateral PV; PV= pulmonary vein;
PVI= pulmonary vein isolated; CF= contact force; RF= radiofrequency time.

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Table IV. Procedural data according to acute pulmonary vein reconnections.

	Overall PV (n=1988)	PV without reconnection (n=1876)	PV with reconnection (n=112)	P
Mean ablation time (min)	16±7	16±7	16±6	0.88
Mean contact force (g)	11.4±3.5	11.5±3.4	11.3±4.1	0.68
Mean impedance drop (Ω)	10.4±4	10.6±4	9.8±3.5	0.07
Mean power (W)	31±3	31±3	32±4	0.1

Mean ablation time= mean ablation time to isolate 2 ipsilateral PV; PV= pulmonary vein;
PVI= pulmonary vein isolated; CF= contact force; RF= radiofrequency time.

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Figure 1.

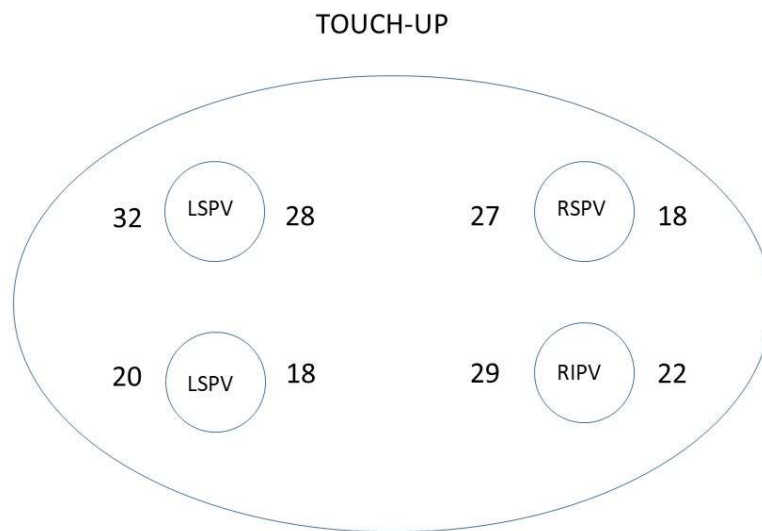


Figure 2.

