International Journal of Cardiology 259 (2018) 82–87

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Impact of prophylactic cavotricuspid isthmus ablation in atrial fibrillation recurrence after a first pulmonary vein isolation procedure

João Mesquita [a,*], António Miguel Ferreira [a,b], Diogo Cavaco [a,b], Pedro Carmo [a,b], Márcio Madeira [c], Pedro Freitas [a], Francisco Moscoso Costa [a,b], Francisco Morgado [a], Miguel Mendes [a], Pedro Adragão [a,b]

[a] Cardiology Department, Hospital de Santa Cruz, Lisbon, Portugal
[b] Cardiology Department, Hospital da Luz, Lisbon, Portugal
[c] Cardiothoracic Surgery Department, Hospital de Santa Cruz, Lisbon, Portugal

ARTICLE INFO

*Article history:*
Received 2 December 2017
Received in revised form 6 January 2018
Accepted 8 January 2018

*Keywords:*
Atrial fibrillation
Cavotricuspid isthmus
Pulmonary vein isolation
Radiofrequency catheter ablation
Prognosis

ABSTRACT

*Introduction:* PVI is a well-established therapy for patients with drug refractory atrial fibrillation (AF). However, it remains unclear whether prophylactic cavotricuspid isthmus (CTI) ablation at the time of PVI improves long-term freedom from AF.
*Objective:* To compare the outcomes of patients who underwent PVI alone vs. PVI + prophylactic CTI ablation.
*Methods:* Propensity score (PS) matching analysis based on a registry dataset of 1931 consecutive patients who underwent a first AF catheter ablation. After excluding those with documented/inducible atrial flutter (n = 233), 1698 individuals were available for matching. Following adjustment for age, gender, body mass index (BMI), hypertension, smoking, diabetes, LA volume, type of AF, and type of navigation (magnetic vs. manual), PS matched 411 patients who underwent PVI + CTI ablation with 411 receiving PVI alone.
*Results:* PS analysis yielded a study population of 822 matched patients (58 ± 11 years, 69% males, 64% with paroxysmal AF). Over a median 2 years follow-up period there were 278 AF recurrences (34%). Survival free of AF (Log rank p = .965) and annual relapse rates were similar in the two groups - 10.9%/year vs 10.1%/year (PVI vs PVI + CTI, respectively, p = .97). CTI ablation remained unassociated with AF-free survival (HR 1.09, 95%CI: 0.84–1.41, p = .54) after Cox regression adjustment for age, sex, type of AF, LA volume, hypertension, diabetes, BMI and center. Female gender, current smoking, indexed LA volume and non-paroxysmal AF were identified as independent predictors of relapse after matching.
*Conclusions:* Prophylactic CTI ablation at the time of a first PVI does not seem to improve long-term freedom from AF.



## Acronyms

ACGME – Accreditation Council on Graduate Medical Education
REDUCE-AF
TRIPLE-A

## Ethical standards

All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The patients signed an informed consent both for the procedure and publication of any relevant data.

## 1. Introduction

Pulmonary vein isolation (PVI) is a well-established treatment for patients with drug-refractory atrial fibrillation (AF) [1,2]. However, recurrence rates after a first catheter ablation procedure are still significant [3,4].

An increasing body of research has shown that PV reconnection is an important mechanism of AF relapse following catheter ablation [5]. Nevertheless, some patients remain free from AF despite showing PV reconnection, while others present with AF relapse regardless of complete PV isolation, prompting the question of whether pulmonary vein triggers are the only culprits in AF and if additional ablation sites should be targeted [6,7]. Several strategies to reduce AF recurrence after ablation have been proposed, such as performing additional lines [8,9] or

*Abbreviations:* AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CT, computerized tomography; CTI, cavotricuspid isthmus; ESC, European Society of Cardiology; HR, hazard ratio; IQR, interquartile range; LA, left atrium; LV, left ventricle; LVSD, left ventricular systolic dysfunction; PS, propensity-score; PSM, propensity-score matching; PV, pulmonary vein; PVI, pulmonary vein isolation; RF, radiofrequency; SDM, standardized difference of the means; USA, United States of America.

* Corresponding author at: Av. Prof. Reinaldo dos Santos, 2790-134 Carnaxide, Portugal.
*E-mail address:* jpmesquita@chlo.min-saude.pt (J. Mesquita).

https://doi.org/10.1016/j.ijcard.2018.01.025
0167-5273/

atrial substrate modification [10–12] albeit without significant prognostic improvement [13–15]. In this setting, ablation of the cavotricuspid isthmus (CTI) is sometimes performed. Although there is a well-established association between atrial flutter (AFL) and AF [16–18], it remains unclear if this procedure improves the outcomes of AF patients without previously documented or induced AFL undergoing PVI [8].

The purpose of this study was to assess the impact of CTI ablation in patients without atrial flutter undergoing a first PVI procedure.

## 2. Methods

### 2.1. Patient population and study design

All consecutive patients with symptomatic drug-refractory AF who underwent a first PVI between December 2008 and December 2015 were included in a two-center observational registry (implemented in Hospital Santa Cruz, Carnaxide, Portugal; and Hospital da Luz, Lisbon, Portugal). To account for the learning curve effect, the initial 30 or 50 ablations with a new catheter or navigation system, respectively, were discarded.

Patients who [1] had previously documented or induced AFL during the study (n = 233), [2] were lost to follow-up <12 months after the procedure (n = 98), or [3] those without 3D quantification of left atrial (LA) volume neither by cardiac computerized tomography (CT) nor electroanatomical mapping (n = 317) were excluded from the analysis, resulting in a final study population of 1698 individuals. The absence of LA volume quantification was selected as an exclusion criteria due to its strong prognostic impact in patients with AF undergoing catheter ablation [19,20].

AF was categorized as paroxysmal if self-terminated in <7 days, persistent if episodes lasted ≥7 days or required cardioversion, or long-standing persistent if maintained for >12 months [2,21].

Most patients (n = 1240, 73%) underwent a 64-slice cardiac CT scan <48 h before the ablation procedure for exclusion of thrombi, quantification of LA volume, evaluation of pulmonary vein anatomy and integration with electroanatomical mapping [20]. LA volume was determined by tracing LA borders on CT images and then excluding both left atrial appendage and pulmonary veins. When cardiac CT could not be performed, LA volume estimation was derived from CARTO® (Biosense Webster Inc., Diamond Bar, CA, USA) electroanatomical mapping at the time of ablation. Data from 732 patients (43%) who had LA volume assessed by both modalities showed good correlation between these methods (Pearson's R = 0.76, p < .001).

### 2.2. Pulmonary vein isolation protocol

Intracardiac catheters were advanced through the right femoral vein and placed under fluoroscopy guidance: 1) a decapolar catheter placed at the coronary sinus to provide stable reference electrograms; 2) a variable circular mapping catheter placed at the ostia of the PVs for mapping and stimulation, and 3) an irrigated-tip ablation catheter for mapping and ablation. LA access was established by double transseptal puncture, after which a bolus of intravenous heparin (100 mg/kg) was administered, followed by additional dosages to achieve and maintain an activating clotting time > 350 s. Guided by electroanatomical mapping using either CARTO® or NavX® (St. Jude Medical® Inc., St. Paul, MN, USA) systems, radiofrequency ablation was performed >5 mm from the PV ostia, with continuous lesions enclosing the left and right pairs of PV. Radiofrequency energy was delivered using a catheter dragging technique. Power settings of 25–30 W and 30–35 W were applied on the posterior and anterior wall, respectively (power control mode). Impedance and temperature cut-offs were set at 250 Ω and 43 °C, respectively. Success was defined by achieving complete electrophysiological isolation of the PVs (entrance and exit block), evaluated using a circular mapping catheter. At Hospital Santa Cruz all patients underwent conventional manually guided ablation, while at Hospital da Luz a Niobe II magnetic navigation system (Stereotaxis® Inc., St. Louis, MO, USA) was used. The treatment was considered successful if complete electrophysiological PVI was achieved. When required, electrical cardioversion was performed at the end of the procedure.

Oral anticoagulation was resumed 4 h after the ablation, maintained for 6 months and then withdrawn or continued according to CHA2DS2-VASc criteria (CHADS2 before 2009). Patients on vitamin K antagonists with sub-therapeutic international normalized ratio were kept on subcutaneous enoxaparin 1 mg/kg every 12 h until an adequate INR was achieved. As a general rule, classes I/III antiarrhythmic drugs (AAD) were maintained in all patients for the first three months after the procedure and then withdrawn if there was no AF recurrence. A proton pump inhibitor was also prescribed for the first month after the ablation.

### 2.3. Cavotricuspid isthmus ablation and bidirectional block

The decision to perform CTI ablation was made on case-by-case basis and left to the operator's discretion. The completion of a linear lesion was anatomically oriented – between the inferior vena cava and the tricuspid annulus – with the purpose of establishing a bidirectional conduction block through the CTI (endpoint). Radiofrequency energy was delivered using the same parameters as those previously described for PVI, albeit with a power setting of 40 W. Bidirectional block at the isthmus was assessed by pacing on both sides of the line (proximal coronary sinus and lateral wall of the right atrium) and then recording double potentials separated by >100 ms throughout its entirety [22].

### 2.4. Study endpoint and patient follow-up

The study endpoint was AF recurrence, defined as symptomatic and/or documented AF or other atrial arrhythmias, after a 3-month blanking period. Symptomatic AF was defined as the presence of symptoms considered to be likely due to AF episodes. Documented AF was defined by the presence of at least one episode of AF lasting >30 s in any ECG, 24 h Holter monitoring or event-loop recording. The follow-up protocol comprised outpatient visits with 12-lead ECG and 24 h Holter monitoring on the 1st, 3rd, 6th and 12th months post-ablation, followed by yearly assessments. Patients were encouraged to contact the department if they experienced symptoms of AF recurrence. Whenever clinical records were insufficient, a structured telephonic interview was conducted. Patients who were kept on AAD after the 3rd month of follow-up were not considered as failed ablation [23,24].

### 2.5. Statistical analysis

The propensity score (PS) is a conditional probability of receiving a particular treatment given a set of baseline-measured covariates [25]. In order to make treatment groups comparable, a propensity score (PS) was estimated by multivariable logistic regression with 'AF ablation + CTI ablation' as the dependent variable and the following baseline characteristics as covariates: age, gender, body mass index (BMI), hypertension, smoking, diabetes, LA volume indexed to body surface area (BSA), type of AF and type of navigation (magnetic vs manual). The resulting probabilities in the treatment group (PVI + CTI) were matched in a 1:1 ratio to the best corresponding control patient (undergoing PVI alone), with a maximal allowable difference of 0.05 (caliper width of 0.05 of the standard deviation of the logit of the PS). When two or more control patients had the same PS match, one was randomly selected for the matching. Paired subjects were removed from the pool and the next PVI + CTI (treatment) – PVI alone (control) pair was selected until no further matches could be performed, yielding a total of 822 paired subjects. Any remaining differences between matched pairs were assessed by standardized difference of the means (level of significance < 0.05).

Normally and non-normally distributed variables were expressed as mean ± standard deviation and median, respectively. Differences between groups were assessed using independent samples *t*-test and McNemar's test for continuous and categorical variables, respectively.

Kaplan–Meier curves were used to report AF relapse over time. Differences in the survival curves of both control and treatment groups were assessed with the log-rank test. Annual relapse rates were obtained by dividing the total numbers of first events by the total number of person-years of follow-up for each group.

Univariate proportional-hazards Cox regression was used to identify predictors of time to AF recurrence. The following characteristics were assessed: age, gender, type of AF (paroxysmal vs non-paroxysmal), diabetes, hypertension, indexed LA volume, cigarette smoking (categorical), hypercholesterolemia, known coronary heart disease and left ventricular (LV) systolic dysfunction (ejection fraction < 50%). Variables with a p-value ≤ .10 in univariate analysis were entered simultaneously in a multivariate Cox regression model and considered to be statistically significant if p < .05. Multicollinearity was excluded by assessing Pearson's correlation coefficient between pairs of continuous variables (all < 0.60).

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, IL) for Mac OS. Statistical significance was set at p-value < .05 (two-sided).

## 3. Results

Before matching, the two groups differed significantly in several baseline characteristics (Table 1). From the 1698 patients available for pairing, 411 (24%) underwent CTI ablation in addition to PVI. According to each patient's PS, all 411 individuals who received CTI + PVI were paired with 411 others who received PVI alone, yielding a total of 822 paired patients. After matching, all analyzed variables were well balanced between the control and treatment groups [standardized difference of the means (SDM) <5% for all characteristics] (Table 1; Supplementary Material Fig. I). Significant differences in the procedural characteristics between the two groups were also noted, with patients in the treatment group experiencing longer procedures [189 (131–240) vs 171 (123–223) min, P = .01)] with prolonged radiofrequency energy delivery [46 (28–61) vs 38 (22–54) min, P = .01)] (Supplementary material Table I). Complete antral PVI was achieved in all patients. At the end of the procedure, 148 (18%) patients underwent electrical cardioversion [74 (18%) individuals in each group (p = .81)].

During a median follow-up of 2 years (IQR 1.8–4.2) there were 278 (34%) atrial arrhythmia recurrences (AF accounting for 97% of the