Research Article

Characterization of "Super-Responders" to Cryoballoon Ablation

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Abstract

Background: Pulmonary Veins Isolation (PVI) is the cornerstone in the treatment of atrial fibrillation. Recurrence rate is common in the long-term follow-up (FU); nevertheless, some patients maintain Sinus Rhythm (SR) for more than 5 years after the index ablation. The aim of this study is characterize this kind of patients so called "super-responders".

Methods: This is a retrospective single-center study including all patients summited for cryo-balloon ablation in our hospital from January 2011 to September 2020. We investigated clinical, electrocardiographic, echocardiographic variables and those linked to the ablation procedure. A univariate and multivariate logistic regression was performed.

Results: During this period, 422 patients underwent PVI; however, 193 were excluded: 21 lost in the FU, 30 got radiofrequency ablation and 142 did not reach a minimum 5 years FU. Of the 229 finally included, 85 (group 1) did not have any recurrence during the follow-up, in front of 144 (group 2) with AF recurrences. In the multivariate analysis the p wave duration: OR: 0.92; 95% CI (0.89-0.94); p <0.001, BMI kg/m^2: OR: 0.74; 95% CI (0.65-0.85); p <0.001, a temperature <-40ºC in all the targeted veins: OR: 3.52; 95% CI (1.45-8.54); p=0.005 and SR on the ablation index day OR: 7.29; 95% CI (1.53-34.71); p=0.012, maintained statistical significance.

Conclusions: In our series the p wave duration, BMI, the presence of SR the ablation index day and achieving a temperature <-40ºC in all the targeted veins, resulted as protective factors to maintain SR in the long term follow-up. An adequate selection of patients probably could improve results and optimize resources.

Keywords: Cryo-balloon ablation; Atrial fibrillation; Super-responders; Obesity; P wave duration

Introduction

Pulmonary Vein Isolation (PVI) is the cornerstone of symptomatic Atrial Fibrillation (AF) treatment and it has been proven clearly superior to Antiarrhythmic Drugs (AAD) either for paroxysmal or persistent presentation [1]. The energy source used to achieve isolation either point by point Radiofrequency Ablation (RFA) or single shot Cryo-Balloon Ablation (CBA) has shown a similar efficacy [2,3], but the learning curve of the former is much slower than CBA. That simple fact contributed to the great spread of CBA all over the world.

Recurrence rate during the Follow Up (FU) after the blanking period is high [1,4,5]. Factors related to acute recurrence as advanced age, hypertension, obesity, enlargement of left atrial size, non-paroxysmal presentation and the presence of obstructive sleep apnea, have been extensively described [6]. However, few studies have focused in for long term FU recurrences (>5 years) [4,5]. By the other hand, a non-negligible number of patients persist in Sinus Rhythm (SR) many years after the index PVI procedure, without any further recurrence.

The aim of this study is to characterize these so-called "super-responders" patients, defined by those in whom no recurrence have been detected after a minimum FU period of 5 years after the index ablation, comparing them to those with recurrences.

Methodology

Study population and data collection

This is a retrospective single-center study including all consecutive patients undergoing a CBA for PVI from January 2011 to September 2020. All patients signed an informed consent for the procedure approved by the local Ethics Committee in our center, and the institute's committee on human research has approved the study protocol. During this period both first-generation (CB1) and second-generation (CB2) cryo-balloon catheters (Medtronic inc. Minneapolis. USA) were used.

Data collection included clinical and demographic variables, as age, sex, history of hypertension, diabetes, coronary artery disease, CHA$_2$DS$_2$VASc score, significant structural heart disease, Body Mass Index (BMI), presence of Obstructive Sleep Apnea (OSA). In this regard, a screening Polysomnography (PSG) was performed in all patients with a BMI ≥30 or if there were symptoms related with OSA. We also collected time from diagnosis to AF ablation, type

of atrial fibrillation and patient rhythm the ablation index day. Echocardiographic variables included Left Ventricular Ejection Fraction (LVEF), left atrial size (anteroposterior diameter in parasternal view). Electrocardiographic variables included p wave duration in lead DIII in milliseconds (ms) and p wave amplitude in DII in millivolts (mv). Both variables were obtained using a specific software (Philips Inc Eindhoven. NL) able to increase tenfold the EKG, using manual calipers by two experienced electrophysiologists. In case of discrepancy over 10ms or 0.01mv, a consensus was reached by the intervention of a third electrophysiologist. The EKG registries used for this study, were obtained after AAD withdrawal. Only in patients in AF in whom AF persisted in the first control after the blanking period, the measures were performed using the EKG recorded just after ablation.

Intra-procedure characteristics as anatomy of PV, minimal temperature in all PV above or below -40ºC, entrance/exit block of PV, and cavotricuspid isthmus block if performed, were also collected.

Ablation procedure

CBA procedures were performed under conscious sedation. All patients had a previous imaging technique (computed tomography, magnetic resonance or rotational angiography) to assess left atrium and PV anatomy. All procedures were guided by intracardiac echocardiography, and since 2013, all procedures were monitored with an esophageal temperature probe. After having achieved left atrial access with a single transeptal puncture a 100IU/kg heparin bolus was given and a continuous perfusion is maintained through the Flex Cath sheath (Medtronic Inc) in order to obtain an ACT between 250-300 seconds. A 20mm diameter Achieve inner lumen-mapping catheter (Medtronic Inc) was sequentially positioned in the ostium of each PV to obtain baseline electrical information. Then a 28mm double-walled cryoballoon (Arctic Front or Arctic Front Advance. Medtronic Inc) was advanced over the Achieve catheter, inflated and positioned in the PV ostium of each vein. Optimal vessel occlusion was considered to have been achieved when selective die injection showed total contrast retention with no back flow to the atrium. For the right side, PV a continuous pacing with a tetrapolar catheter placed in the superior vena cava was used to pace the phrenic nerve to avoid phrenic nerve palsy. Application times varied along time, in the first-generation balloon, we performed at least two applications per vein, over 300 seconds each, with the second-generation balloon, we performed two applications over 240 seconds each, since 2018 we moved to a double 180 seconds application. Extra bonus application was performed in any case if PV potentials remain visible. Twenty minutes after performing the last application, we rechecked entrance and exit block of PVI repositioning the Achieve catheter in all the veins. If reconnections were detected, extra applications were performed until bidirectional block. In case of absence of PV potentials at the beginning of the procedure we considered the vein was isolated if when a temperature under -40ºC during at least 120 seconds was reached.

In those patients in AF after PVI, an electrical cardioversion was performed, at the end of the procedure. All patients were maintained under oral anticoagulation for at least two months after the procedure, and AAD were maintained during the blanking period (three months for paroxysmal and six months for persistent AF).

Follow-up

After discharge, patients were scheduled for FU visits at 1, 3, 6, 12 and 24 months, with at least four 24 h Holter monitor recordings (one during the blanking period, a second after AAD withdrawal, a third at 12 months and the last at 24 months). If no recurrences were detected during this time the decision of prolonging the FU was left to discretional decision of the treating doctor. Eighteen patients had an implantable loop recorder or pacemaker with atrial leads. Recurrences during the blanking period were not considered following the consensus publish in 2017(7). After this period, an AF recurrence was considered as documented atrial tachycardia lasting more than 30 seconds.

For the present analysis symptomatic recurrences, new AAD prescription, and weight evolution (to recalculate BMI) were collected by phone interview in all the patients from September 2020 to January 2021. In addition, the Shared Clinical History from the Catalan health system was reviewed in order to complement information regarding arrhythmia recurrence and new AAD prescription during the FU. Finally, their general practitioner obtained a recent EKG in all the patients.

Statistical analysis

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as mean ±SD or median and range as appropriate. Patients were divided in two groups. Group 1 included patients with a FU longer than 5 years, without recurrences. Group 2 included patients with any recurrence, regardless of FU time. A univariate analysis was performed between both groups, for categorical variables using the χ2 de Pearson or the Fisher's exact test when appropriate. For continuous variables, the t student test was used.
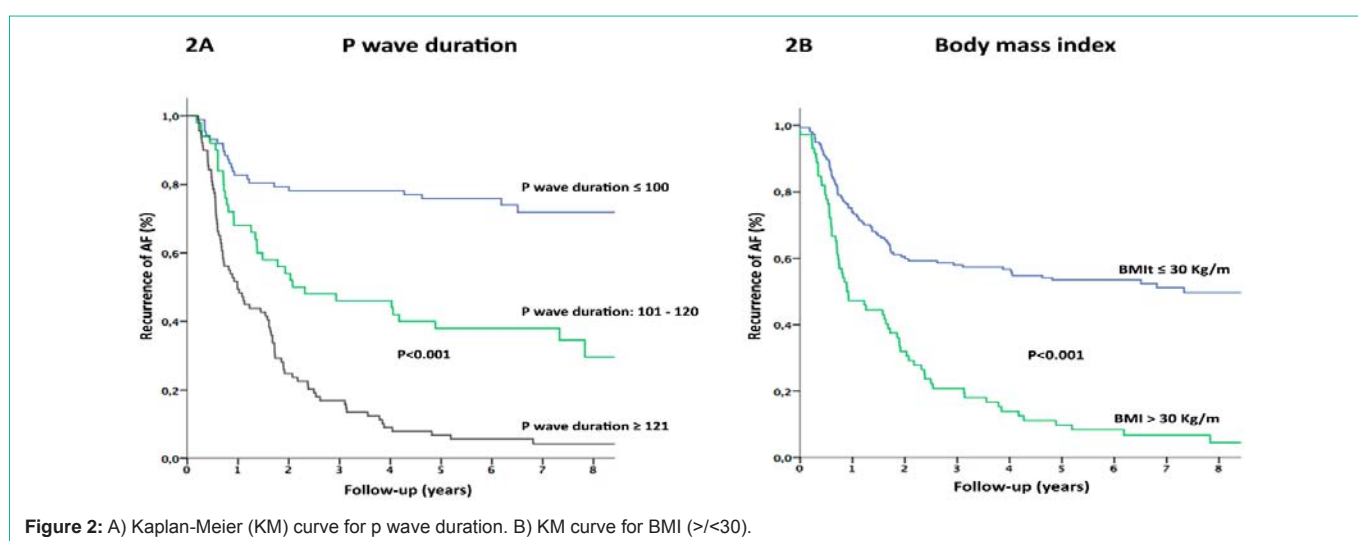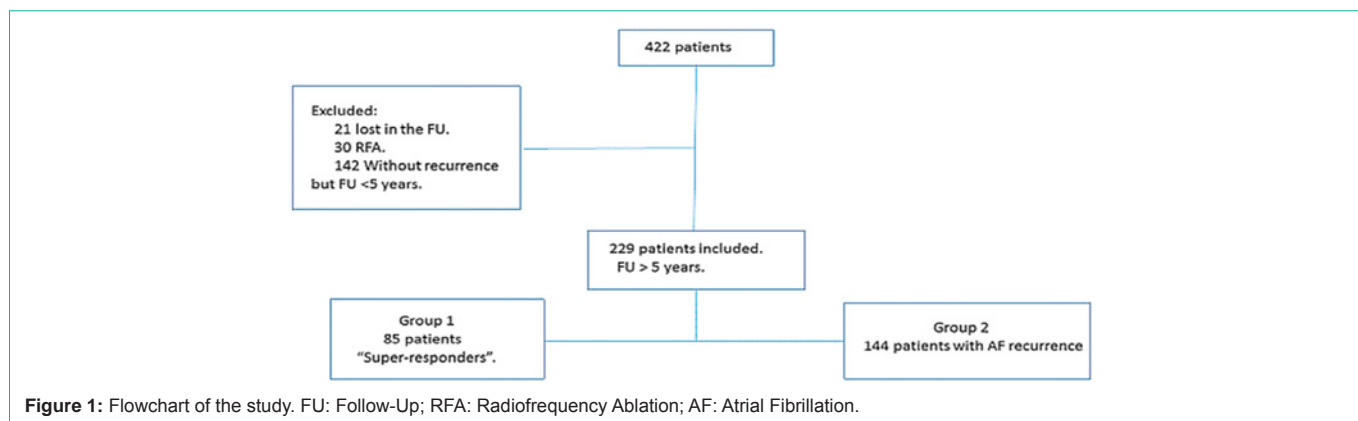
A multivariate logistic regression analysis using a backward modeling with significant variables (p <0.05) was performed, to determine prognostic factors of absence of AF recurrence (group 1). Variables were removed one by one, if their exclusion did not modify significantly the likelihood ratio statistics of the model. When removal of any variable changed the estimated parameters of the remaining variables by >15%, it was considered a confounding effect and that variable was retained in the model regardless of its statistical significance. Results are presented as odds ratio (OR) or 95% confidence interval (95% CI). Area under the ROC curve (AUC) was calculated for this model.

Significant continuous variables from EKG were divided in tertiles and Kaplan-Meier curves were performed in order to evaluate the best cut off point predicting the absence of AF recurrence. Those cut off points were included in a logistic regression to obtain the best predictive value for each variable independent or as a whole adjusted by sex and age.

A two-tailed probability value ≤0.05 was deemed significant. Statistical analysis were conducted using the SPSS software v 25.9 (SPSS inc. Chicago. Illinois. USA).

Results

A total population of 422 patients underwent PVI in our center during this period, nevertheless 21 were lost in the FU, 30 were

Figure 1: Flowchart of the study. FU: Follow-Up; RFA: Radiofrequency Ablation; AF: Atrial Fibrillation.

Figure 2: A) Kaplan-Meier (KM) curve for p wave duration. B) KM curve for BMI (>/<30).

excluded because the ablation was done by a point-by-point RFA. Finally, 142 patients had not reached the minimum 5 years FU period. Therefore, for the final analysis we got 229 patients. Figure 1 shows the flowchart of the study.

There were 85 patients, with a median FU of 6.94 (5.77-8.12) years, in whom no AF recurrence was documented. This group was designed as "super-responders" (Group 1) and was compared with the 144 patients with AF recurrences (Group 2).

We didn`t find PV potentials in 26% of the veins. The median time to recurrence was 10.69 (6.69-22.74) months, being significantly shorter in persistent vs paroxysmal AF 6.90 (2.79-8.08) vs 12.06 (6.77-25.23) months (p=0.003).

We missed the EKG information in three patients in whom no SR was recorded at anytime. One patient with moderate OSA was treated with Continuous Positive Airway Pressure (CPAP) for other concomitant comorbidities, at the same time one patient with severe OSA was not treated for intolerance to CPAP. Only seventeen patients showed a weight decrease achieving a BMI under 30kg/m^2, among them three summited to bariatric surgery.

We did not find differences between Groups 1 and 2 by using the CB1 or CB2. This is probably due to a selection bias. CB1 was initially used mainly in paroxysmal forms of AF, while with CB2 we

performed also in persistent and long-standing AF. Even knowing that only PVI will be not enough in these patients, it was used as a first approach, advising patients that probably a second approach will be needed in the future.

Table 1 shows clinical, echocardiographic, electrocardiographic differences and those related with the procedure in both groups. Univariate analysis showed that patient's in group 1 were younger; hypertension rate, CHA_2DS_2VASc score, moderate OSA rate, BMI, p wave duration, time from diagnosis to ablation and left atrial size, was lower than in group 2. By the other hand LVEF, p wave amplitude, were higher and the temperature under -40ºC was achieved in a greater number of cases in group 1 *vs.* group 2.

In a logistic regression multivariate analysis we observed that the factors related with long-term maintenance of SR were the p wave duration, BMI, being in SR the ablation index day and finally achieving a minimal temperature in all PV of less of -40ºC (Table 2).

As Figure 2A and 2B show, a p wave duration <100ms and maintaining a BMI <30Kg/m^2 in the FU, was associated a significant reduction in AF recurrence (Log-rank p <0.001).

From a practical and clinical point of view, those variables that significantly predicted long-term maintenance in SR, individually or in combination, either if the minimal temperature lower than -40ºC

Table 1: Univariate analysis comparing Group 1 *vs.* Group 2.

Clinical Variables	Group 1 (n=85)	Group 2 (n =144)	P
Age	53.01 ± 9.81	55.47 ± 9.90	0.07
Male Sex	65 (76.5%)	98 (68.1%)	0.174
HTA	27 (31.8%)	88 (61.1%)	<0.001
DM	6 (7.1%)	19 (13.2%)	0.15
CAD	2 (2.4%)	8 (5.6%)	0.252
CHA$_2$DS$_2$VASc score	0.96 ± 1.09	1.42 ± 1.14	0.003
OSA			>0.001
Severe OSA (CPAP)	7 (8.2%)	12 (8.3%)	
Moderate OSA	4 (4.7%)	56 (38.9%)	
No or Mild OSA	13 (15.3%)	19 (13.2%)	
PSG Not performed	61 (71.7%)	57 (39.6%)	
Initial BMI	27.02 ± 3.95	29.61 ± 4.33	>0.001
Final BMI	26.86 ± 3.93	29.87 ± 4.35	<0.001
Final BMI <30Kg/m²	81 (95.3%)	76 (52.8%)	<0.001
Time Diagnosis-Ablation (months)*	24(12.06-48.3)	34.28 (18.78-66.28)	0.03
Type of AF			<0.001
Paroxysmal AF	80 (94.1%)	96 (66.7%)	
Persistent AF	4 (4.7%)	33 (22.9%)	
Long standing persistent AF	1 (1.2%)	15 (10.4%)	
Echocardiographic Variables			
LA Size (mm)	37.78 ± 4.69	42.66 ± 4.83	<0.001
LVEF (%)	64.60 ± 6.17	61.40 ± 8.37	<0.001
Electrocardiographic Variables	**Group 1 (n=85)**	**Group 2 (n=141)****	**p**
P wave amplitude (mv)	0.124 ± 0.029	0.103 ± 0.036	<0.001
P wave duration (ms)	98.2 ± 12.6	121.03 ± 14.45	<0.001
Ablation related Variables	**Group 1 (n=85)**	**Group 2 (n=144)**	**p**
SR the ablation index day	81 (95.3)	104 (72.2%)	<0.001
Minimal Temperature <-40ºC in all PV	69 (81.2%)	86 (59.7%)	0.001
Acute Efficacy (Bidirectional isolation)	84 (98.8%)	136 (94.4%)	0.075
Normal Anatomy (4 independent PV)	73 (85.9)	116 (80.6)	0.305
Associated CTI Ablation	25 (29.4%)	52 (36.1%)	0.3

HTA: Hypertension; DM: Diabetes Mellitus; CAD: Coronary Artery Disease; OSA: Obstructive Sleep Apnea; PSG: Polisomnography; BMI: Body Mass Index; AF: Atrial Fibrillation; LA: Left Atrium; LVEF: Left Ventricular Ejection Fraction; PV: Pulmonary Veins; SR: Sinus Rhythm; CTI: Cavo-Tricuspidid Isthmus. *Median (interquartile); **n for the electrocardiographic variables in group 2 was 141 patients because we missed 3 patients in AF in whom a p wave measure was not possible.

in all PV, is achieved or not, are reflected in Figure 3. In this figure, for example, we can observe that the five years probability of maintaining SR is 86% in a patient that presented in SR the ablation index day, had a p wave duration <100ms and maintained a BMI under 30Kg/m². However, it rise up to 94% if the ablation index day, the operator is able to achieve a temperature under -40ºC in all the PV during at least 120s.

Discussion

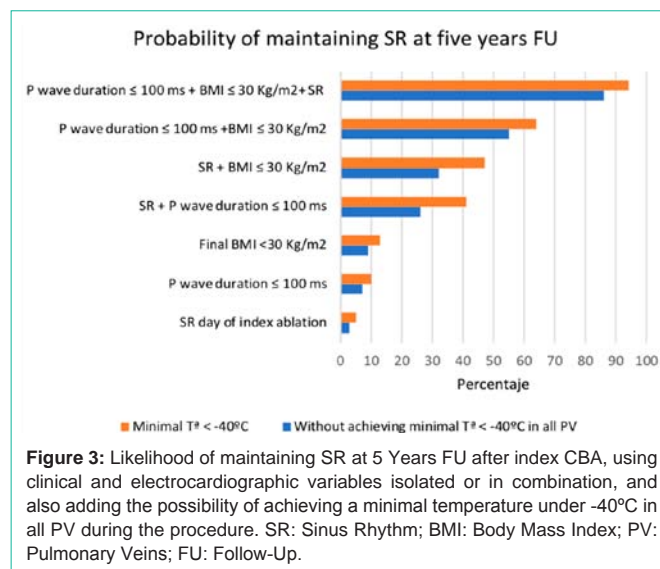The present study shows that in those patients in whom a CBA is

Figure 3: Likelihood of maintaining SR at 5 Years FU after index CBA, using clinical and electrocardiographic variables isolated or in combination, and also adding the possibility of achieving a minimal temperature under -40ºC in all PV during the procedure. SR: Sinus Rhythm; BMI: Body Mass Index; PV: Pulmonary Veins; FU: Follow-Up.

Table 2: Logistic regression multivariate analysis, adjusted by age, sex, p wave amplitude, AF type, HTA, LVEF and LA size.

Variable	OR	95% CI	p
Minimal Tª <-40ºC in all PV	3.52	1.45-8.54	0.005
P wave duration	0.92	0.89-0.94	<0.001
SR the CB index ablation day	7.29	1.53-34.71	0.012
BMI Kg/m²	0.74	0.65-0.85	<0.001

The AUC and ROC curve was 92% (95% CI: 89-96); p >0.001. PV: Pulmonary Veins; BMI: Body Mass Index; CB: Cryoballoon.

planned, some simple and feasible clinical and EKG variables allow to select a subgroup of patients that will have an excellent behavior in the long-term FU. Protector factors were having a p wave duration <100ms, a maintained BMI <30kg/m² and the presence of SR the ablation index day. The other protective factor found in this study was to achieve a minimal temperature less than -40ºC in all the PV the CBA day, despite this factor cannot be chosen by the referent clinician.

Obesity, is associated with an electrical and structural atrial remodeling and has been clearly related to the appearance and progression of AF from paroxysmal to persistent forms, and has also been related to an increase of recurrences after AF ablation [5,8]. Moreover, ablation alone does not stop AF progression in obese patients [9,10]. In addition, weight loss has been related to a reduction of left atrial size, left ventricular hypertrophy and even with a reduction of symptoms and AF burden [11]. Indeed weight loss is associated with better post ablation results. In the REVERSE AF [12] a 10% weight loss was associated with a long-term reduction of AF progression, with a significant decrease of AF burden or even with complete disappearance of AF. Similar conclusions were observed in the Winkle et al. [10] study on 2715 patients summited for AF ablation; in this study, a higher BMI was associated with more comorbidities and more long standing persistent AF forms. Indeed a BMI >35kg/m² was associated with worst outcomes.

In our series, although been a retrospective study, which did not include an specific intervention program, we were able to demonstrate that patients, with a maintained BMI <30kg/m² or with an initial BMI

>30kg/m², but who showed a weight reduction during FU, achieving a BMI <30kg/m², were most likely to keep SR, than those in whom BMI was maintained over 30kg/m².

P wave represents atrial depolarization and the endo-epicardial sinus wave propagation over natural barriers [13]. An increase of p wave duration reflects the presence of some kind of atriopathy or atrial myocardiopathy [14] may be favored for multiple risk factors as age, hypertension, coronary artery disease and obesity. In this sense is not surprising, that an increase of p wave duration had been related to an increase of AF prevalence [15,16], probably reflecting that AF is the final step of the atrial myocardiopathy. Mugnai P et al. [17] in a series of 426 patients after PVI, excluding those with left atrial dilatation, patients with pacemakers or patients in whom the EKG quality was not good enough, observed that p wave duration and dispersion were clearly related to an increase of AF recurrences after PVI, in patients with normal atrial size.

In our series, a p wave duration <100ms is a protective factor for no AF recurrence in the long-term FU, probably due to the fact, that those patients had not a substrate favoring AF, and reflecting that may be a focal trigger in PV was the driver of their AF. Suggesting at the same time that an early treatment on these kind of patients may be justified to avoid progression to atrial myocardiopathy.

Achieving a minimal temperature under -40ºC in all PV was a predictive factor of maintenance of SR in the long-term FU. To achieve that temperature in a single vein has been taken in our study as a surrogate of efficacy, when PV potentials were not recorded in the inner lumen catheter. Nevertheless efficacy between both groups was not different (indeed in most patients PVI was recorded with temperatures <-40ºC). Therefore, in our opinion, achieving less than -40ºC in all the PV may reflect a better PV occlusion with deeper or even more extensive lesions in order to avoid recurrence of conduction from the vein to the atria, which is usually the described mechanism of AF relapses [18].

In the study from Watanabe R et al. [19] in 130 patients who underwent CBA, a temperature <-44ºC was a predictor of recurrence at 13 months FU period. However, to our knowledge there are not studies validating if achieving a minimal temperature of -40ºC in all PV is a predictor of recurrence in the long term FU.

The presence of SR the ablation index day, was reflecting in most cases patients with paroxysmal forms (only two patients with paroxysmal AF were in AF the ablation index day), nevertheless up to 18 patients with persistent AF were in SR the ablation index day, after an electrical cardioversion, performed several weeks before underwent CBA. The fact of maintaining SR in these persistent forms after cardioversion, might reflects that those patients had a not so ill atrium. Indeed a correlation of a higher recurrence rate after electrical cardioversion was observed in patients with a HATCH score >2 [20] (hypertension, age, chronic obstructive pulmonary disease, stroke and heart failure), suggesting more atriopathy in this group of patients. In another study, a worst atrial myocardial strain was able to predict future recurrences after cardioversion [21].

Despite having statistical significance in the univariate analysis for maintenance of SR, a p wave amplitude greater than 0.13mv lost it significance in the multivariate analysis. This fact probably happened

because the population included in our series was quite "healthy". P wave amplitude may correlate with endocardial voltage, and probably the more substrate in the atrium, the lower p wave amplitude. Park JK et al. [22], in a series of more than 500 patients who underwent PV ablation showed that a p wave amplitude <0.1mv in lead DI was a predictive factor of recurrence.

Moderate OSA, obviously not treated with CPAP, did not reach statistical significance in the multivariate, although it did, in the univariate analysis, may be due to the fact of confounding factors as obesity [23], or just due to the small number of patients included in this series. Nevertheless, non-treated severe OSA is a known factor related with an increase of AF recurrences after PVI, and treatment with CPAP in this kind of patients decreased recurrences [24]. Is interesting to highlight that sleep units carried out by pneumologists are not treating moderate OSA with CPAP, and they seem to have a higher risk of recurrence.

Conclusion

In our series having a p wave duration <100ms, BMI <30kg/m², the presence of SR the ablation index day and achieve a minimal temperature under -40ºC in all PV for at least 120s during CBA are associated with maintenance of SR in the long-term FU. A holistic treatment in AF patients, taking specifically care on decrease weight may improve outcomes. An appropriate selection of patients undergoing CBA can improve outcomes and resource optimization.

Limitations

Several limitations are present in this study. The main limitation of the present study is being a retrospective study, including patients with CBA with CB1 and CB2 and also with different application time per vein. Nevertheless, there were no differences in efficacy because of that issue. The second point is that this is not an interventional study, and this is the reason that weight loss was achieved in only 17 patients with an initial BMI >30kg/m², but even with this limitation, this variable appears as significant. The third point is that we do not have polysomnography in all the patients, and may be more patients with recurrences were non-detected OSA. The forth point is that we do not have study the atrial function by atrial myocardial strain, and this point is especially important in patients with recurrences and normal atrial size. Previous studies showed a correlation between atrial strain and p wave duration25. The fifth point is that we measured the p wave duration after CBA, once the ADD had been withdrawn. The reason to do it this way, was to avoid the effect of these drugs (only in four patients we used the ECG just after ablation, so under the effect of AAD, because in the first clinical control they were in AF). By the other hand, it should be impossible to measure the p wave in patients with persistent AF, except if they had been previously cardioverted. However, doing it after ablation can be also discussed, by the fact that CBA could have influence the measure. In order to discard this possibility we measured the p wave amplitude and duration in 50 patients (25 paroxysmal and 25 persistent) pre and post ablation both under the effect of AAD, and no significant differences between the values was observed. Finally, because of the retrospective nature of this study, not having continuous monitoring on heart rhythm with any device (only in 18 patients), may not discard asymptomatic AF recurrences. However, the Shared Clinical History of the Catalan Health system allowed us to review all the medical history of the

patients during FU, and we reassure that none "super-responder" patient received AAD during the FU time, and of course, neither the general practitioner nor cardiologist reported any recurrence.

Highlight Points

• After a long term follow up period some patients summited for cryo-balloon ablation either for paroxysmal or persistent atrial fibrillation remain in sinus rhythm. Characterize this kind of patients is the aim of the present study.

• Some simple and feasible clinical and EKG variables allow selecting a subgroup of patients that will have an excellent behavior in the long-term follow-up.

• A p wave duration <100ms, a maintained BMI <30kg/m^2 and the presence of SR the ablation index day and a minimal temperature less than -40ºC in all the pulmonary veins were related with better outcomes.

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