RESEARCH ARTICLE

PREDICTORS OF ATRIAL FIBRILLATION RECURRENCE AFTER CRYOBALLOON-BASED PULMONARY VEIN ISOLATION.

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Abstract

The study was designed to explore the role of imaging and clinical parameters as predictors of atrial fibrillation recurrence at 1 year after cryoballoon ablation. We included 70 patients who underwent their first cryoballoon ablation with available pre-procedural cardiac MRI study. We divided them into two groups according to AF recurrence at one year. Group A included 14 patients who developed AF recurrence at one year, while group B included 56 patients who remained arrhythmia-free at one year. Univariate analysis revealed a significant difference between both groups in; age (66±10 years and 55±10 years, for group A and B respectively, \( p < 0.05 \)), left atrial diameter (47.8 ±6.6 mm and 40.5 ± 5.6 mm, for group A and B respectively, \( p < 0.001 \)), hypertension (71.4% and 28.6% of group A and B patients respectively, \( p < 0.03 \)), persistent AF (50.0% and 19.6% of group A and B patients respectively, \( p < 0.05 \)) and ERAF (57.1% and 12.5% of group A and B patients respectively, \( p < 0.001 \)). In subsequent multivariate regression analysis, the most significant predictor for recurrence is age. The odds of recurrence increased by 20% per one year increase in age. Moreover, one unit increase in left atrial diameter increased the chance of recurrence by 13%. Conclusion; We concluded that age and left atrial diameter are independent predictors for AF recurrence after cryoballoon ablation. We highlight the importance of proper assessment of the risk of arrhythmia recurrence before referring the patient for ablation.

Introduction:

AF is a common cardiac rhythm disturbance that increases in prevalence with advancing age. Approximately 1% of patients with AF are <60 years of age, whereas up to 12% of patients with AF are 75 to 84 years of age. \textsuperscript{(1)} More than one third of patients with AF are >80 years of age. \textsuperscript{(2,3)} Since its introduction into clinical practice in the late nineties,\textsuperscript{(4)} catheter ablation of atrial fibrillation (AF) has become a well-established therapeutic option for the treatment of patients with symptomatic drug refractory AF.

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Pulmonary venous isolation (PVI) remains the cornerstone of most AF ablation procedures since PV foci were discovered as the trigger for AF. (5) Variety of energy modalities (most commonly radiofrequency and cryoenergy) have been used nowadays for AF catheter ablation. Point-by-point ablation using radiofrequency current is technically complex, demanding and dependent on electroanatomical mapping system (EAM) reconstruction of the left atrium and pulmonary veins (7). Balloon-based cryoenergy creates a complete circumferential lesion around the pulmonary veins (PV) with a limited number of applications. (8) Furthermore, cryoablation in the experimental setting is associated with less tissue architecture disruption and could reduce complications such as pulmonary venous stenosis and atrio-oesophageal fistula. (9,10) Cryoballoon ablation has been demonstrated to have efficacy and safety profile comparable to RF ablation. (11) A recent meta-analysis of 16 clinical trials comparing cryoablation with RF ablation concluded that cryoballoon ablation (CBA) was non-inferior to radiofrequency ablation (RFA) for paroxysmal AF. RF ablation was associated with a higher groin complications and pericardial effusion/cardiac tamponade, whereas CBA was associated with higher rates of transient and persistent phrenic nerve injury. (12)

Acute procedural success after AF ablation does not necessarily translate into long term arrhythmia-free survival, which is lower in persistent than paroxysmal AF. Moreover, AF ablation procedures are not free of complications. Therefore the need for proper risk assessment to predict recurrence after ablation is of paramount importance. There are many studies which have explored the predictors of recurrence after the index AF ablation. (13-16) In the present study, we retrospectively assessed the value of several imaging and clinical tools to predict 1-year recurrence of AF after balloon cryoablation.

Materials and Methods:-
Seventy patients who underwent their first cryoballoon ablation of pulmonary veins for symptomatic drug-refractory atrial fibrillation (AF) in electrophysiology laboratory, Spedali Civili Di Brescia, Italy, in the period between January 2013 and November 2015, with available cardiac MRI study done before the ablation procedure, had been divided into two groups: group A included patients who developed AF recurrence at one year post-ablation, while group B included patients who remained arrhythmia-free.

Pre-procedural Preparation:-
For each patient, the CHA2DS2-VASc was calculated. To rule out the presence of left atrial (LA) and LAA thrombi, all patients underwent two dimensional (2D) transoesophageal echocardiography (TEE) the day before the procedure, along with a transthoracic echocardiogram for the assessment of LA dimension, left ventricular ejection fraction (LVEF), and valvular function. Class IC antiarrhythmic drugs were discontinued prior to ablation. Procedures were performed either with continued oral anticoagulation using warfarin and therapeutic INR (2.0 to 3.0) or NOACs. Patients with left atrial diameter > 55 mm were excluded.

Pulmonary vein isolation procedure:-
Briefly, all procedures were carried out in conscious sedation. A deflectable decapolar catheter was inserted through right femoral vein and positioned into the coronary sinus to guide the transseptal puncture and was subsequently moved to the superior vena cava to stimulate the right phrenic nerve during treatment of the right PVs. A single transseptal puncture was performed using a needle system (BRK, St. Jude Medical, St. Paul, MN, USA) and a standard transseptal sheath (SL0 8F or 8.5F, St. Jude Medical, St. Paul, MN, USA), subsequently exchanged with a steerable 15F sheath (FlexCath Advance®, 15F, Medtronic®, Inc., Minneapolis, MN, USA). Before transseptal puncture, heparin was administered intravenously as bolus (10000 U) followed by a continuous infusion (1000 U/hr) to obtain ACT level > 350 sec. The FlexCath was continuously irrigated with heparinized saline (2 mL/hr). In cases of difficulty to achieve a complete venous occlusion due to the persistence of leak at the inferior portion of the PV’s ostium, a “pull down” maneuver as well as other changes of the balloon orientation were attempted. (17) After treatment of all PVs, bidirectional block was confirmed with pacing maneuvers through the Achieve® mapping catheter (Medtronic®, Inc., Minneapolis, MN, USA) and the distal poles of the coronary sinus catheter. Any residual conduction into the PVs was treated by further cryotherapy applications. Successful PVI was confirmed when all PV potentials were abolished or were dissociated at least 20 minutes after the last cryotherapy application to that vein.

Post-procedural care and Management:-
Transthoracic echo was done immediately after the procedure to rule out pericardial effusion. The patients were then monitored by continuous ECG recording in the following 48 hours. Anticoagulation (whether VKA or NOACs) was restarted the evening of the same day and continued for at least 3 months. The patients were discharged 48 hours...
post procedure provided that a pre-discharge echocardiogram ruled out pericardial effusion. Antiarrhythmic drugs were administered throughout the blanking period (first 3 months); afterwards the therapy could be stopped or continued according to the follow up and preference of the referring electrophysiologist. The follow up data are obtained from the records at 3 months and one year post-procedure. Some patients, according to a clinical indication, received implantable loop recorder. Patients were asked to record their 12-lead electrocardiogram whenever they experienced symptoms suggestive of AF.

The clinical data and echo measurements (including LA diameter and left ventricular ejection fraction) were collected from the patient records. All patients were assessed by pre-procedural Contrast enhanced MRI (CMR was performed on a 1.5 Tesla Philips Achieva® MRI scanner (Amsterdam, Netherlands) using a five-element phased-array cardiac coil) to obtain the following informations:

1. **PV drainage pattern**: A common PV ostium was deemed to be present if the superior and inferior veins coalesce prior to the inflection point at which the PV ostia meet the left atrial wall, thereby forming a single atrio-pulmonary venous junction (18,19). An accessory or supernumerary PV was identified by the presence of a vein other than the superior or inferior lobe veins entering the atrium via a distinct ostium. (20)

2. **PV ostial size and shape** (Figure 1 and 2): To describe the shape we calculated the ovality index of every individual pulmonary vein at the ostial level: Ovality means to what extent the ostial shape deviated from the perfect circularity.

\[
\text{Ovality or non-circularity index} = 2 \times \frac{a - b}{a + b}
\]

Where a is the length of the major axis and b is the length of the minor axis.

The follow up of the patients at 3 months and 1 year post-procedure were collected from the records. Early recurrence of AF will be defined as detection of AF (at least 30 s duration when assessed with ECG monitoring) within 3 months of ablation. One year recurrence of AF will be defined as detection of AF (at least 30 s duration when assessed with ECG monitoring) at 1 year following AF ablation.

**Statistical Analysis:**
Statistical analysis was done using IBM SPSS statistics program version 21 and Medcalc programs. Quantitative data were described by mean and median as measures of central tendency & standard deviation, minimum and maximum as measures of dispersion, while categorical variables were summarized by frequency and percent. A P-value of < 0.05 was considered statistically significant. Multivariate stepwise logistic regression using backward (Wald and Likelihood ratio) methods was done for statistically significant risk factors by bivariate analysis.

**Results:**
Of the total of 70 patients who were included in the present analysis, Fourteen (20%) patients of the whole study population developed AF recurrence (group A) versus Fifty-six (80%) who remained free from arrhythmia recurrence at one year (group B). Table 1 describes the clinical and demographic data of both study groups. Compared to group B, the patient in group A were significantly older (p = 0.05) , with more arterial hypertension (p = 0.03) , persistent atrial fibrillation (p = 0.05) and early recurrence of atrial fibrillation (p = 0.001).

**Echocardiography parameters:**
- **Left atrial diameter**: the mean left atrial anteroposterior diameter was 47.8 ± 6.6 mm and 40.5 ± 5.6 mm in group A and B respectively (p = 0.001).
- **Left ventricular ejection fraction**: the mean left ventricular ejection fraction measured by M-Mode was 57.7±5.5 in group A and 57.3±3.2 in group B (P = 0.83).

**MRI assessment of pulmonary vein drainage pattern**: There was no difference between group A and group B in the presence of common left or right pulmonary veins as well as supernumerary right pulmonary veins (Table 2).

**Pulmonary vein (PV) ostial ovality index**: After exclusion of the patients with common pulmonary veins; The ostial ovality index , assessed at each individual pulmonary vein ostium, was not significantly different between both groups (Table 3). The mean ovality index of the left pulmonary veins (0.41± 0.15) was significantly higher than the mean ovality index of right pulmonary veins (0.21 ± 0.09), p = 0.001. So, left pulmonary veins were more oval than right pulmonary veins.
A multivariate analysis using logistic regression model was done with the following variables which are statistically significant by univariate analysis: Hypertension; Age; Left atrial diameter; Persistent AF and ERAF. According to wald statistics, the most significant predictor for recurrence is age. The odds of recurrence increases by 20% (OR 1.19; 95% CI: 1.06 to 1.34) per one year increase in age. One unit increase in left atrial diameter increases the chance of recurrence by 13% (OR: .87; 95% CI .768 to .985).

**Figure 1:** shows the manual alignment of both longitudinal and transverse axes of the right superior pulmonary vein (RSPV) at the ostial level. So index of ovality at the PV ostial level = 2 x (maximal diameter− minimal diameter) / (maximal diameter + minimal diameter).

**Figure 2:** short axis view at the level of RIPV ostium shows the manual measurements of maximal diameter, minimal diameter in mm and ostial area in mm².

**Table 1:** Comparison between both study groups concerning the clinical variables

<table>
<thead>
<tr>
<th></th>
<th>Group A (n= 14)</th>
<th>Group B (n= 56)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>64.3</td>
<td>50</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>35.0</td>
<td>20</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>60.0 – 80.0</td>
<td>35.0 – 76.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>66.86 ± 10.64</td>
<td>55.16 ± 10.38</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66.0</td>
<td></td>
<td>52.50</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>25.0</td>
<td>10</td>
</tr>
</tbody>
</table>
### Table 2: Comparison between the two study groups according to drainage pattern of the pulmonary veins in the left atrium

<table>
<thead>
<tr>
<th></th>
<th>Group A (n= 14)</th>
<th>Group B (n= 56)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common right PV</td>
<td>2</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Common left PV</td>
<td>4</td>
<td>6</td>
<td>0.72</td>
</tr>
<tr>
<td>Supernumerary right PV</td>
<td>3</td>
<td>5</td>
<td>0.10</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of both study groups regarding the mean ovality index of each individual pulmonary vein.

<table>
<thead>
<tr>
<th></th>
<th>Mean ovality index of Group A</th>
<th>Mean ovality index of Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSPV</td>
<td>0.41±0.22</td>
<td>0.33±0.14</td>
<td>0.26</td>
</tr>
<tr>
<td>LIPV</td>
<td>0.47±0.22</td>
<td>0.46±0.19</td>
<td>0.89</td>
</tr>
<tr>
<td>RSPV</td>
<td>0.16±0.14</td>
<td>0.24±0.13</td>
<td>0.09</td>
</tr>
<tr>
<td>RIPV</td>
<td>0.16±0.10</td>
<td>0.24±0.08</td>
<td>0.06</td>
</tr>
</tbody>
</table>

LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

### Figure 3: Shows the difference in the mean ovality index between right and left pulmonary veins in both groups.

**Mean ovality index**

**Discussion:**

Efficacy and safety of pulmonary vein isolation by means of balloon-based cryoablation has been established by several observational studies. In a systematic review of 23 studies, most of them including only patients with paroxysmal AF, Andrade et al. reported a successful acute PVI in more than 98% of the patients, with 73% of paroxysmal and 45.1% of persistent AF patients having 1 year freedom from AF recurrence out of the blanking period. Despite the constant improvement in the procedural efficacy and safety with cryoballoon ablation, a certain failure rate still remains, and this could be partially attributed to patient selection. As such, the preoperative estimation of the recurrence probability may aid in the patient selection process, particularly considering the
heterogeneous follow up modalities, leading to asymptomatic AF episode missing, and the highly variable use and
definition of predictors for AF recurrence.

In this study, we investigated the predictors of AF recurrence in patients undergoing cryoballoon ablation for
paroxysmal or persistent AF. The main findings were as follows: clinical success in regard to the freedom from
recurrent AF was 80%. Patients who experienced AF recurrence at one year (Group A) were older, with more
frequent hypertension, persistent AF, early recurrence of atrial fibrillation and larger left atrial diameter. Other
comorbidities (diabetes mellitus, coronary artery disease, heart failure, renal dysfunction) , history of atrial flutter,
atypical pulmonary vein drainage pattern and ostial ovality index , did not predict arrhythmia recurrence at one year.
Multivariate analysis of our five significant variables showed that age and left atrial diameter were the two
independent predictors for AF recurrence after cryoablation.

Khoueiry Z et al (23) , evaluated the mid-term outcomes of cryoballoon ablation in an unselected population with
paroxysmal AF who underwent a first procedure of cryoballoon ablation or radiofrequency from a pulmonary vein
anatomical viewpoint. Comparisons between both techniques were performed regarding safety and efficacy
endpoints, according to pulmonary vein (PV) anatomical variants. They found no difference in the incidence of
relapse (17.0% cryoballoon ablation vs. 14.1% radiofrequency, P = 0.25). Moreover, no interaction of PV
anatomical variants on mid-term procedural success. In the present study, we observed no difference between both
groups regarding the presence of common left pulmonary venous ostium , common right ostium or accessory right
pulmonary vein.

Schmidt M et al (24) , investigated the role of Ovality index of each individual pulmonary vein ostium on
PV occlusion grading and AF recurrence rate during PVI with cryoballoons (both 23 and 28 mm balloons). They
used cardiac computed tomography prior to procedure to assess PV ostial diameter in 168 consecutive AF patients.
The success rate at 12 ± 6 months follow-up was 69%. They observed that, left-sided PVs were significantly “more
oval” than right sided PVs. Complete PV occlusion was more often achieved in patients with a “less oval” PV ostial
anatomy and corresponded to a lower AF recurrence rate at long term follow-up. Furthermore, ostial PV anatomy
had an important impact on clinical outcome; Patients with AF recurrence had "more oval" left-sided PVs compared
to patients free from AF recurrence , whereas no significant association was found for right sided PVs. In the present
study, the left pulmonary veins were found to be more oval than the right veins. We did not observe statistical
significant relationship between 1-year recurrence of AF after cryoablation and the mean ovality index of every
individual pulmonary vein.

Many studies also show that increased left atrial diameter (LAD) is an important predictor of the recurrence of AF
after pulmonary vein isolation. Ejima K et al. (25) followed 80 patients with non-paroxysmal AF refractory to
antiarrhythmic drugs after PVI For about 3 years. They observed that left atrial volume (LAV) was the only
independent predictor of atrial tachyarrhythmia recurrences not only after single procedures, but also after the final
procedures. Moreover, Repeat ablation procedures increased the best cut-off value for predicting recurrences. In the
present study, the mean left atrial diameter was higher in patients who developed AF recurrence than in patients
who remained free of recurrence at 1-year follow-up post procedure.

Age was proved to be a significant predictor for AF recurrence after catheter ablation. Lee SH et al (26) investigated
the factors affecting the rhythm outcomes after the maze procedure in patients with a giant LA and AF-associated
mitral valve disease to determine the best candidates for the maze procedure in this population. The 5-year AF-free
rate was 87.1% ± 4.3% in patients 50 years or younger and 77.3% ± 4.1% in patients older than 50 years (P = .001).
On multivariate analysis, advanced patient age was the only significant, independent risk factor for AF recurrence.
In our study, age was an independent predictor, on multivariate analysis, of arrhythmia recurrence after
cryoablation. The odds of recurrence increases by 20% (OR 1.19; 95% CI: 1.06 to 1.34) per one year increase in age.

Early recurrence after catheter ablation of AF is fairly common: Bertaglia found 46% of atrial tachy-arrhythmias
relapse during the first three months of follow-up. (27) Moreover the incidence of ER is maximum soon after the
procedure, which decreases in the following days. (28) Although, the prevalence of ER is not negligible, it has been
widely recognized that a good proportion of patients experiencing ER are free of significant atrial arrhythmias at
prolonged observation. Nevertheless, the occurrence of LR is more frequent in the subgroup with ER. (29) Similar
findings were reported by Themistoclakis and coworkers (30) They investigated the predictors of AF recurrence and
the relationship between early recurrence (EAT) and late recurrence (LAT) after AF ablation in 1298 mixed AF patients. After a single ablation procedure, EAT developed in 514 (40%) patients and LAT in 292 (22%) patients. EAT was an independent predictor of LAT. The risk of LAT was inversely related to the time to first EAT occurrence (LAT occurred more frequently in patients who experienced the first EAT in the third month than in those who experienced the first EAT in the second or first month (98% vs 69% and 44%). Notably, 49% of patients with EAT did not experience LAT. Moreover, ERAF was the most important predictor for late AF recurrence in a study (29) of 61 paroxysmal AF patients who underwent balloon cryoablation.

Canpolat U et al. (31) proposed a new scoring system in the prediction of recurrence after AF ablation with cryoballoon in 236 patients. According to univariate Cox proportional hazard regression analysis, hypertension, BMI, current smoking, left atrium diameter, nonparoxysmal AF type, duration of AF history and early recurrence were significantly associated with AF recurrence (p < 0.05). Concordant with the previous results, patients who developed recurrence of AF at 1 year after cryoballoon ablation, in the present study, had more hypertension and persistent AF.

Proper patient selection could avoid unnecessary procedures and so the expenditure, especially in the light of the currently increased procedure costs, and could prevent potential ablation-related complications. Moreover, the decision to refer a patient with AF for catheter ablation should balance the indication with the procedure outcomes. Therefore, proper assessment of the procedure risks including the recurrence risk could be useful in daily practice, facilitating the decision making process of the AF patients and can be a part of the discussion with the patient. With a low risk profile for recurrence i.e. young patient with paroxysmal AF, no or minimal structural heart disease and refractory symptoms, physicians may be more enthusiastic to early patient referral to ablation by virtue of low anticipated arrhythmia recurrence and better long-term outcomes. In asymptomatic patient, ablation is not indicated even with a very low risk for recurrence. On the other hand, patients with a high risk profile, i.e. old patient with persistent AF, hypertension and significant structural heart disease should be thoroughly informed about the high risk of recurrence and the importance of maintaining regular follow up and monitoring after ablation. However, in such type of patients, ablation may be decided despite anticipated high recurrence risk in the presence of refractory symptoms. Furthermore, in a patient with a high risk of recurrence, the decision may be taken to avoid redo-ablation considering the increased risk of further recurrences.

Conclusions:-
Age and left atrial diameter are independent predictors for AF recurrence after cryoballoon-guided pulmonary vein isolation. We highlight the importance of proper assessment of the risk of arrhythmia recurrence before referring the patient for ablation.

Conflict of Interest:-
Mohamed Sanhoury received research grant form Alexandria University, Egypt.
Antonio Curnis is a consultant to Boston Scientific, Biotronik, Medtronic, St Jude Medical, and Sorin Group.

References:-
