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LASER BALLOON ABLATION FOR ATRIAL FIBRILLATION: A PROSPECTIVE EVALUATION OF SHORT AND LONG TERM EFFECTIVENESS AND SAFETY

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ABSTRACT

Background: In the landscape of interventional treatment for atrial fibrillation new forms of energy are emerging as alternatives to transcatheter ablation with radiofrequency and cryoenergy. The third generation of laser balloon (Cardiofocus Heartlight X3) with its compliant balloon and endoscope allows visualization of the ostium of the pulmonary veins and delivery of laser energy in a rapid semi-automatic mode, achieving a linear, continuous, and durable isolation of the pulmonary veins.

Purpose: To evaluate the efficacy and safety of AF ablation with the Laser Balloon X3 system through a prospective observational study in a contemporary patient population, and secondly the impact of RAPID mode on procedural and clinical endpoints.

Methods: We prospectively enrolled consecutive patients with symptomatic paroxysmal or persistent atrial fibrillation, indicated for pulmonary vein isolation according to current guidelines at the Policlinic Sant'Orsola-Malpighi Hospital between September 2020 and December 2022. Two operators performed all procedures using the laser balloon Heartlight X3. All intraprocedural and follow-up data were collected. Efficacy was defined as freedom from clinical or significant subclinical atrial fibrillation recurrence (burden >5 hours) at 3, 6, 12, and 24 months, excluding the AF recurrence in the first three months of post-procedural blanking period. To assess safety, all procedure-related complications were recorded.

Results: We enrolled 126 patients with a mean age of 61 years (+/-10), including 25% women. 76.2% of patients suffered from paroxysmal atrial fibrillation, 23,8% persistent AF; 90.5% were on DOAC anticoagulant therapy, and 9.5% on VKA. Patients underwent laser balloon ablation and were followed for an average of 18 months (+/- 6). At 3-6-12 and 24 months respectively 93%, 88%, 80%, and 74% of patients were free from atrial fibrillation. Among patients with paroxysmal AF at baseline, 83% and 78% were free from AF at 12 and 24 months, while for persistent AF patients, the figures were 73% and 63%, respectively. Among patients free from AF recurrence, 61% discontinued antiarrhythmic therapy, and 22% stopped anticoagulation. Among patients with AF recurrence, 16% underwent a redo ablation procedure, 32% switched to rate control therapy, 52% changed rhythm control strategy (antiarrhythmic drugs, electrical cardioversion). The Rapid mode utilization > 70% correlated with significantly shorter procedural

times and a lower rate of late AF recurrence. Four serious adverse events (3.1%) were recorded with no life-threatening complications, two phrenic nerve palsies and one pericardial effusion without cardiac tamponade, one venous access complication, all resolved during the index hospitalization.

Conclusions: In our single-centre experience, the Laser Balloon X3 System demonstrates an excellent efficacy and safety profile in terms of AF recurrence and procedure-related complications. The novel Rapid Mode was associated with shorter procedural time and lower AF recurrence rate. Further Large, multicentre RCTs with a control group and extended follow-up are ongoing to enhance scientific understanding of this ablative treatment for atrial fibrillation.

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1. ATRIAL FIBRILLATION

1.1 Definition and epidemiology

Atrial fibrillation (AF) is the most common arrhythmia in adults, and its frequency is increasing globally, the currently estimated prevalence of AF in adults is between 2%-4%. A 2.3-fold rise is expected owing to extended longevity, increasing burden of comorbidities and better detection of silent AF[1,2].

Diagnosis requires an electrocardiogram (ECG) of at least 30 seconds of single strip or an entire 12-lead ECG documenting AF. Electrocardiographic features of AF are irregularly irregular R-R intervals, absence of distinct repeating P waves, and irregular and chaotic atrial electrical activations with ineffective mechanical activity.

Comorbidities, including heart failure (HF), coronary artery disease (CAD), hypertension, diabetes mellitus (DM), obesity, obstructive sleep apnoea (OSA) and chronic kidney disease (CKD), are co- and related to AF development, recurrence, and persistence. The treatment of atrial fibrillation cannot ignore the intervention on these factors.

AF significantly increases the risk of stroke, death, HF and cognitive decline. Therefore, it has a high impact on healthcare-associated costs[3]. AF is among the most frequent causes of stroke, causing 20-30% of all ischaemic strokes and 10% of all cryptogenic strokes. Moreover, AF is a risk factor for dementia, conferring a hazard ratio of 1,4-1.6[6,7].

Due to its strong association with multiple comorbidities and complications, AF is also a substantial economic burden for healthcare systems[4.].

1.2 Clinical features

ESC guidelines[1] classify atrial fibrillation according to its onset and duration into:

1) First diagnosed AF: AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
2) Paroxysmal AF: Paroxysmal AF that terminates spontaneously or with intervention within seven days of onset.

3) Persistent AF: AF lasting beyond 7 days. It includes episodes terminated by cardioversion (drugs or electrical cardioversion) after >_7 days.
4) Long-standing persistent AF: Continuous AF of more than12 months when deciding to adopt a rhythm control strategy.
5) Permanent AF: There are no further attempts to restore/maintain sinus rhythm, the rate control strategy is applied to symptoms relief.

AF related symptoms are highly variable. Thus, AF could range from an asymptomatic to a disabling condition. The most frequent symptoms are palpitation and dyspnea on exertion. Further, the first symptoms of AF could be due to a related thrombo-embolic event, such as stroke or acute limb ischemia[1,5].

Symptom burden influences the decision to begin a rhythm control treatment (including catheter ablation). Therefore, clinicians should accurately characterize symptom status using the European Heart Rhythm Association (EHRA) symptom scale[8]:

- EHRA CLASS 1: AF does not cause any symptoms
- EHRA CLASS 2: Symptoms are mild: Normal daily activity not affected by symptoms related to AF (2a). Moderate: Normal daily activity not affected by symptoms related to AF, but the patient is troubled by symptoms (2b)
- EHRA CLASS 3: severe symptoms, Normal daily activity affected by symptoms related to AF
- EHRA CLASS 4: disabling when Normal daily activity discontinued due to AF.

1.3 Treatments and Guidelines

The ESC 2020 guidelines provided the Atrial fibrillation Better Care (ABC) algorithm ('A' Anticoagulation/Avoid stroke; 'B' Better symptom management; 'C' Cardiovascular and Comorbidity optimization). This approach deals with all the main aspects of AF and has effectively reduced morbidity, mortality and healthcare costs related to this condition in some studies[9, 10]. The prevention of thromboembolic events (A) and comorbidities control (C) have prognostic implications. The "B" component of this algorithm (Better symptom management)

deals with those strategies proven to ameliorate symptoms burden in patients with AF. These include rate and rhythm control therapies (including catheter ablation of atrial fibrillation). Instead, rate or rhythm control strategies mainly target the control of symptoms. Before the 2020 AF guidelines, no study had shown a superiority of one of the two choices in terms of prognosis[1]. Rate control is integral to AF management and is often sufficient to improve AF-related symptoms. Pharmacological rate control implies using beta-blockers, digoxin, diltiazem, verapamil, or combination therapy. Some antiarrhythmic drugs (AADs) also have rate-limiting properties (e.g., amiodarone, dronedarone, sotalol), but they should be used only for rhythm control. Finally, ablation of the atrioventricular node and subsequent pacemaker/cardiac resynchronization therapy implantation (ablate and pace strategy) is an irreversible and non-pharmacological option for patients with medication failure to achieve rate control[1].

The 'rhythm control strategy' refers to attempts to restore and maintain sinus rhythm. It may engage a combination of treatment approaches, including cardioversion, antiarrhythmic medication (amiodarone, dofetilide, dronedarone, flecainide, propafenone, and sotalol), and catheter ablation.

As regards chronic antiarrhythmic management, either with drugs (chronically administered or with a "pill-in-the-pocket" strategy) or catheter ablation, the ESC 2020 guidelines recommend rhythm control therapy to reduce AF-related symptoms and improve quality of life (class of recommendation I, level of evidence A or in specific patient subgroups (tachycardia-induced cardiomyopathy (IB) or HF with reduced ejection fraction (IIaB)) who may benefit from a rhythm-control strategy (in this case through catheter ablation of AF)[1].

Regarding hard clinical endpoints, a rhythm control strategy in unselected patients seemed to confer no advantage over rate control, based on so-called "rate versus rhythm control" randomized trials conducted >2 decades ago. The PIAF (Pharmacological Intervention in Atrial Fibrillation), AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management), RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation), AF-CHF (Atrial Fibrillation and Congestive Heart Failure), STAF (Strategies of Treatment of Atrial Fibrillation), and J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation)) trials

showed that fewer hospitalizations were necessary to deliver simple rate control therapy because of the necessary monitoring and adverse events (AEs) associated with AAD, catheter ablation of AF and cardioversion procedures[11-15].

Nevertheless, these randomized trials showed several methodological weaknesses (small sample size, lack of a control group, short-term follow-up periods (<6 months) and high level of patient crossover from rate to rhythm control). Sub-analysis showed that when treatment adjustments for rhythm control were excluded, hospitalization rates were similar in both cohorts[16]. Further, maintenance of sinus rhythm during follow-up was associated with lower mortality[17], and even if stroke, systemic embolism, and major bleeding rates did not differ between treatment strategies, event-free survival from these events was significantly better for rhythm control arm[18].

Finally, recent improvements in rhythm control strategies made it necessary to re-assess their impact on major adverse cardiovascular outcomes through randomized trials, and ESC 2020 guidelines had not considered their results.

In recent years, various studies have demonstrated a possible benefit of a strategy of rhythm control. Further, they showed the possible importance of early adoption of this approach. This way, rhythm control could prevent the negative effect of atrial remodeling, which occurs early after AF onset, and, subsequently, the progression from paroxysmal to persistent AF.

The ATHENA study (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with AF/atrial flutter) showed a reduction of the primary composite outcome of death or cardiovascular hospitalization with dronedarone compared to placebo in patients with paroxysmal or persistent AF or atrial flutter within six months before randomization. Furthermore, there was a significant reduction in secondary outcomes, including cardiovascular death and stroke[19]. Post hoc analyses suggested that the effect was more evident among patients with short (<3 months) and intermediate (>3 months to <24 months) AF/atrial flutter history than those with longer (>24 months) history[20].

The EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) study has recently been published, altering the view on early rhythm control as a general treatment

concept. In the study, patients were randomized to usual care (oral anticoagulation plus rate control or rhythm control as per ESC and AHA/ACC/HRS guidelines) or guideline-recommended care plus early rhythm control treatment, consisting typically of AAD therapy or catheter ablation. The composite of death from cardiovascular causes, hospitalization with worsening HF or acute coronary syndrome (ACS) or stroke was reduced by 21% in patients assigned to early rhythm control. Each component of the first primary outcome was numerically less common in the early rhythm control arm. Furthermore, there was no safety difference between randomized groups[21].

After the publishment of the EAST-AFNET study, large healthcare databases or registries confirmed the results of this study[22]. The use of amiodarone and dronedarone as AAD, the availability of ablation in patients who failed AAD therapy, and better use of AADs may have contributed to the outcome of these studies.

AAD therapy should be improved, and catheter ablation must be simplified to increase availability. Nevertheless, results from these recent trials support rhythm control as an essential strategy in the early stages of AF. Appropriate use of rhythm control will portend to a paradigm shift towards offering early rhythm control to all patients with recently diagnosed AF.

Pharmacological therapy for AF evolved substantially, and AAD therapy became the foundation of AF clinical management[1]. In general, AADs approximately double the likelihood of maintaining sinus rhythm compared with no rhythm-control therapy[23].

Initial enthusiasm for AADs was dampened after their association with excess mortality in specific subgroups (prior myocardial infarction, reduced EF, and ventricular ectopy), likely attributable to their proarrhythmic or negative inotropic effects. These effects were evident in the CAST (Cardiac Arrhythmia Suppression Trial), CAST II, SWORD (Survival With Oral d-Sotalol in Patients With Left Ventricular Dysfunction After Myocardial Infarction), and ALIVE (Azimilide Post-Infarct Survival Evaluation) studies in the 1990s[24-27].

However, more cautious use of these drugs following the results of these studies and the development of more modern AADs (see dronedarone above) improved their safety and efficacy.

As regards rhythm control in patients with chronic HF, several studies compared this approach to rate control. In the last decade, catheter ablation of AF has proved to be a safe and effective strategy in patients with HF. The ESC 2020 AF guidelines indicate ablation with a Class IIa recommendation, level of evidence B, in selected AF patients with HF with reduced ejection fraction (HFrEF) to improve survival and reduce HF hospitalization[1].

The AF-CHF trial failed to prove that pharmacological rhythm control could improve rates of cardiac death in comparison with rate control[28].

However, in the recent EAST-AFNET-4 trial, which compared a rhythm-control strategy with usual care for patients with AF diagnosed in the last 12 months, the rhythm-control strategy improved cardiovascular outcomes also in the subgroup of patients with HF (28.6%)[29]. Compared with the AF-CHF trial, in the EAST-AFNET-4, a significant proportion of patients (19.4%) underwent catheter ablation of AF.

As regards recent specific trials regarding catheter ablation in AF patients with HF, two trials, the AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device) and the CASTLE AF (Catheter Ablation for Atrial Fibrillation with Heart Failure)[30,31] showed a benefit on hospitalization and mortality. These results were counterbalanced by those from two other randomized clinical trials: the AMICA (Catheter Ablation Versus Best Medical Therapy in Patients with Persistent Atrial Fibrillation and Congestive Heart Failure) and the RAFT-AF (Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients With Heart Failure and Atrial Fibrillation)[32,33].

The AATAC trial compared catheter ablation to amiodarone and showed the superiority of the first in primary and secondary endpoints, including a positive effect on rates of death and hospitalization.

The CASTLE-AF trial was the first trial powered enough to evaluate hard endpoints for catheter ablation of AF. It enrolled patients with symptomatic paroxysmal or persistent AF, not tolerating antiarrhythmic drugs. Patients were on optimal medical therapy for HF. All had a NYHA class II-IV, ejection fraction (EF) ≤35% and an implanted device. Compared to medical

therapy (rate or rhythm control), catheter ablation led to a lower rate of a composite end point of death from any cause or hospitalization for worsening HF[31].

The AMICA trial included patients with persistent/long-standing persistent AF and EF≤35% and assigned them to a catheter ablation or a conventional therapy arm. At one year, patients in the ablation arm did not significantly improve EF or quality of life. Results from the AMICA trial could be due to patients with more advanced HF enrolled in the study (lower EF, worst NYHA class or persistent/long-standing persistent AF)[32].

The recent RAFT AF compared ablation-based rhythm control and rate control in patients with high-burden AF and HFrEF. The study showed no difference in all-cause mortality or HF events between groups; however, there was a non-significant trend for improved outcomes in the CA group[33].

In addition to these trials, we should again mention the CABANA study, the largest trial to compare catheter ablation and drug therapy as a first-line rhythm control therapy in patients with atrial fibrillation. While the primary composite endpoint of disabling stroke, death, serious bleeding, or cardiac arrest was not different between study arms, a sub-analysis showed beneficial effects of CA in all-cause mortality in patients with HFrEF[34].

These trials showed a clear benefit of ablation compared with pharmacological intervention, with significant reductions in mortality, stroke, and hospitalization within the setting of HF with reduced EF.

Finally, as regards HF with preserved ejection fraction (HFpEF), there are only a few observational studies which suggested that catheter ablation could be as safe and effective in maintaining sinus rhythm in HFpEF as in patients with HFrEF[35]. However, there is no prospective, randomized, long-term study.

2 TRANSCATHETER ABLATION OF AF: STATE OF THE ART

According to ESC 2020 guidelines, catheter ablation of AF is a second-line treatment after failure or intolerance to antiarrhythmic drug therapy. The level of evidence is different in patients with symptomatic paroxysmal (IA), persistent (IIa, C), and long-standing persistent AF (IIa, C). As first-line treatment for paroxysmal AF, ablation modestly improved rhythm control compared to drug therapy in previous randomized trials (IIa, B)[1].

Results from the **ATTEST** (Atrial Fibrillation Progression Trial) showed that early ablation as part of standard care was superior to AAD therapy alone in delaying progression from recurrent paroxysmal AF to persistent AF[36]. There were similar benefits of ablation as a first-line therapy across other various trials. The **STOP-AF** (A Clinical Study of the Arctic Front Cryoablation Balloon for the Treatment of Paroxysmal Atrial Fibrillation), **EARLY-AF** (Early Aggressive Invasive Intervention for Atrial Fibrillation), and **CRYOFirst** (Cryoballoon catheter ablation vs AADs as a first-line therapy for patients with paroxysmal atrial fibrillation) trials show that AF ablation is as safe as AAD therapy and more effective in maintaining sinus rhythm when used as a first-line rhythm control therapy[37-39].

The **CABANA** study (Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients with Atrial Fibrillation) showed that ablation might be more effective in maintaining sinus rhythm compared to drug therapy even if the primary composite endpoint of hard clinical outcomes was not different between the study arms. Moreover, in the ablation group, there was a significant decrease in symptoms and an increase in the quality of life. However, the proportion of patients with persistent or long-standing AF and total AF burden were lower in the ablation group[40].

2.1 Anatomic basis and electrophysiological mechanisms

The pathophysiology of AF involves multiple factors[41,42]:

- Triggers, which are responsible for AF initiation.
- Substrate, which is necessary for AF induction and maintenance.
- Perpetuators, which also facilitate the progression from paroxysmal to persistent forms.

The trigger mechanisms can include enhanced focal automaticity, reentry or triggered activity. It could be facilitated and subsequently maintained by parasympathetic and sympathetic activation. The transition is due to structural and electrical changes in both atria that make induction and maintenance of the arrhythmia more stable[43].

However, the general mechanisms still need to be fully understood, which can explain why treatment of AF, particularly long-standing persistent AF, remains suboptimal.

2.2 Pulmonary Veins

The leading theory on AF origin theorizes that the origin of this arrhythmia could be rapid firing focuses in the PVs or alternative anatomical structures.

Nathan and Eliakim first described sleeves of cardiac tissue extending from the left atrium (LA) into all pulmonary veins (PVs) for 1–3 cm[44]. The thickness of these sleeves is highest proximally (1–1.5mm) and then gradually decreases[45].

In vitro studies using diffusion tensor imaging have described how rapid firing from the PVs can initiate AF after interaction with the complex fiber anatomy of the LA[46]. Studies with cardiac magnetic resonance imaging (MRI) confirmed these findings[47]. Fiber orientation seems to play an important role, and future research and in vivo implementation of this knowledge in 3D mapping systems could allow new ablation strategies[48].

PV-sleeve cardiomyocytes have properties that predispose them to increased automaticity (i.e., a small background IK1 current and a reduced coupling to atrial tissue) [32, 33]. Further, data show susceptibility to Ca2þ-dependent arrhythmia mechanisms[34].

The anatomy of the PVs is variable. Four separate ostia are present in only 60% of patients[49].

The orifices of the left veins are slightly superior to that of the right ones. Superior veins project forward and upward, whereas inferior veins project backwards and downward. In almost 80% of patients, there is a shared anterior part of the ostia of the left veins. The most frequent type of variant anatomy is a common trunk for the left PVs, and the second most frequent variant is a right middle PV. Further, additional PVs can originate from the roof of the LA[50].

Other studies have provided evidence to suggest that the PVs and the posterior LA are also preferred sites for reentrant arrhythmias[51].

We previously explained that rapidly firing foci in the PVs are essential triggers of AF and can also contribute to its persistence. Isolation of the PVs, especially in paroxysmal forms of atrial fibrillation, could result in prolonged AF remission.

After recognizing the importance of the PVs, studies showed that a variety of sites other than the PVs potentially harbor AF-maintaining sources[52].

In the last decades, the complex interplay between these potential sources of AF and the atrial electroanatomic structure has been an object of debate. Numerous theories have been subsequently proposed.

For many years, three concepts competed to explain the mechanism of AF: multiple reentrant wavelets, rapidly discharging automatic foci, and a single reentrant circuit with fibrillatory conduction[53]. Some of the most recent theories are the leading circle reentry and the rotor or spiral wave theory. Finally, detailed human atrial mapping studies have suggested that AF is maintained by the dissociation between epicardial and endocardial atrial layers, with mutual interaction producing multiplying activity that maintains the arrhythmia.

In summary, although the presently available data leave several questions open, they indicate that ectopic activity and reentry play essential roles in AF. The specific mechanisms and determinants remain to be elucidated, along with their implications for therapy.

2.3 Autonomic nervous system and alternative substrates

The heart is richly innervated by the autonomic nerves. The ganglion cells of the autonomic nerves are located either outside the heart (extrinsic) or inside the heart (intrinsic). Both extrinsic and intrinsic nervous systems are important for cardiac function and arrhythmogenesis. The intrinsic cardiac nerves are found mostly in the atria and are intimately involved in atrial arrhythmogenesis. Histological study of human pulmonary vein (PV)–left atrium (LA) junction showed that numerous autonomic nerves are present. The nerve densities are the greatest in the LA within 5 mm of the PV–LA junction and are higher in the epicardium than endocardium. Adrenergic and cholinergic nerves are strongly co-located at tissue and cellular levels. A significant proportion (30%) of ganglion cells expresses dual adrenocholinergic phenotypes (ie, stain positive for both tyrosine hydroxylase and choline-acetyltransferase). Because these nerve structures are highly colocalized, it is difficult to perform radiofrequency catheter ablation that selectively eliminates purely sympathetic or parasympathetic arms of the autonomic nervous system[54].

The autonomic nervous system (ANS) plays an important role in the initiation and maintenance of AF, and modulating autonomic nerve function may contribute to AF control. Potential therapeutic applications include ganglionated plexus ablation, renal sympathetic denervation, cervical vagal nerve stimulation, baroreflex stimulation, cutaneous stimulation, novel drug approaches, and biological therapies. In the future, novel approaches for ANS mapping and modulation could increase the efficacy of AF ablation[55, 56].

The vein of Marshall (VOM) is not a simply a continuation of the ligament of Marshall, it also contains abundant innervation, both parasympathetic and sympathetic; functions as a true atrial vein, collecting venous return from atrial tissues; and contains a myocardial bundle connected to underlying myocardium. The VOM contains innervation, myocardial

connections, and arrhythmogenic foci that make it an attractive target in catheter ablation of atrial fibrillation. Additionally, it co-localizes with the mitral isthmus, critical to sustain perimitral flutter, and is a true atrial vein that communicates with underlying myocardium. Retrograde balloon cannulation of the VOM from the coronary sinus is feasible and allows for ethanol delivery, which results in rapid ablation of neighboring myocardium and its innervation. Perimitral flutter (PMF) is a mechanism of clinical recurrence after AF ablation, which can account for 33%-60% atrial tachycardias (AT) following ablation procedures. The anatomical location of the VOM in the epicardial aspect of the posterior mitral isthmus, between the CS and the left inferior pulmonary vein leads to a unique opportunity to create epicardial ablations in the mitral isthmus, which is notoriously difficult to ablate via an endocardial approach and that often requires ablation inside the CS.

IN THE **VENUS-AF** (Vein of Marshall EthaNol in Untreated perSistent AF) trial adding VOM ethanol infusion to catheter ablation resulted in improved rhythm control of persistent AF. VOM ethanol infusion is feasible, safe, and achieves rapid ablation of LA tissue and local innervation, including the epicardial myocardium sustaining PMF. The technique is reproducible and further confirmatory trials are under way[57].

Atrial fibrosis is a common finding in patients with AF. Whether atrial fibrosis originates from AF, AF-related risk factors or a specific fibrotic atrial cardiomyopathy is still in doubt. Further, there is significant variability in the amount of fibrosis in patients with AF. Some patients with paroxysmal AF have massive fibrosis, and some patients with persistent AF show mild fibrosis. Nevertheless, diffuse atrial fibrosis is related to poor outcomes after catheter ablation of atrial fibrillation[58,59]. Fibrosis affects electrical propagation through slow, discontinuous conduction with “zigzag” propagation, reduced regional coupling, abrupt changes in fibrotic bundle size, interruption of bundle continuity, and micro-anatomical reentry[60].

Another potentially critical factor in AF-related atrial remodeling is fatty infiltration, which increases in several pathological conditions and is potentially arrhythmogenic[61].

Amyloidosis could also play a role in AF genesis and maintenance. It could act as isolated heart disease (senile form), sometimes with specifically atria involvement (atrial amyloidosis), or as

part of a systemic process, as in immunoglobulin-derived light-chain disease. Notably, there is an inverse correlation between isolated atrial amyloidosis and atrial fibrosis[62].

The extracellular matrix remodeling plays an essential role in these histological processes. It is due to a complex process involving diverse factors, including oxidative stress, calcium overload, atrial dilatation, microRNAs, inflammation, and myofibroblast activation[63].

2.4 Ablation techniques: cryoballoon and radiofrequency

The cornerstone of all AF ablation strategies is electrical isolation of the pulmonary veins (PVs) while ablation strategies going beyond PV isolation (PVI) might be considered in the setting of recurrent AF despite durably isolated PVs or in case of atrial tachycardia. Since the PVs have been identified as the major trigger for initiation and perpetuation of AF, different strategies and technologies were developed aiming at durable PVI.

Traditionally, PVI is accomplished by **point-by-point RadioFrequency** (RF) ablation to produce a circumferential lesion around the antrum of the PVs[64].

Antral lesions surrounding the ipsilateral PVs with a single wide area circumferential ablation line based on 3D mapping with the goal to electrically isolate the PVs from the left atrial myocardium became the mainstay of RF-based AF ablation. The addition of contact force to time, temperature, and power as another physical variable into RF ablation (enclosed in the "ablation index"), improved lesion formation, and lesion quality significantly.

Nevertheless, despite improvements in mapping systems and the design of ablation catheters, the rate of PVs reconnection and AF relapse during follow-up is still high. According to long-term studies, it can reach a rate of up to 30%, mainly due to technical reasons, which lead to the generation of non-homogeneous lesions at the PV ostia[65]. Further, a complication rate of around 3% associated with RF catheter ablation is non-negligible. Severe complications include stroke/transient ischemic attack (including silent cerebral embolism), cardiac tamponade, pulmonary vein stenosis, atrial-oesophageal fistula, vascular complications, and phrenic nerve injury[66].

The **cryoballoon** (CB) technology represented the first attempt to improve procedural, clinical and safety outcomes of ablation of AF. It introduced the concept of a *single shot* technique, based on placing a specific balloon at the antrum of a PV, where it obtains a single circumferential lesion in a small amount of time through cooling of the equator or the distal hemisphere of the balloon to a low or extremely low temperatures[64].

Trials comparting CB and RF catheters have reported comparable arrhythmia-free survival. CB also showed shorter procedural time but longer fluoroscopy, with a slightly lower overall complication rate (except for phrenic nerve injury, which resulted more frequently with CB)[67,68].

CB systems are limited by catheter flexibility and balloon non-compliance that can lead to an inaccurate adherence, thereby causing incomplete lesions and explaining a PVs reconnection frequency similar to RF ablation[69].

Novel technologies aim to enhance complete PVI at the first procedure, increasing the safety profile and shortening procedure and fluoroscopy time. Other additional goals are to shorten the learning curve of the operators and improve our understanding of the underlying mechanism of AF, especially of persistent and long-standing persistent AF[64].

The Laser balloon system and the electroporation or pulsed field ablation (PFA, a non-thermal energy source) were recently introduced. Some trials are already available[70].

New mapping systems will not only provide anatomical and electrical information such as unipolar, bipolar, and activation analysis but also real-time information on lesion formation, lesion quality, and wall thickness. One platform is KODEX-EPD (EPD-Philips), a 3D imaging system that is not based on impedance or electromagnetism but on tissue dielectricity. Changes in the dielectric tissue properties can be used for real-time assessment and visualization of ablation lesions.

2.5 Endoscopic Laser Balloon Systems

The first endoscopic laser balloon system (ELBS; CardioFocus) was validated for clinical use in 2015[71]. The laser balloon catheter CardioFocus HeartLight EASAC with Excalibur Balloon (EAS; HeartLightTM; CardioFocus, Inc., MA, USA) aims to ensure greater effectiveness in the isolation of the pulmonary veins and improve patient safety.

This system consists of a compliant balloon at the tip of the catheter which can conform to the PV ostium, leading to its occlusion. The catheter handle allows the balloon inflation to be controlled and the laser energy beam to be directed (Fig.1).

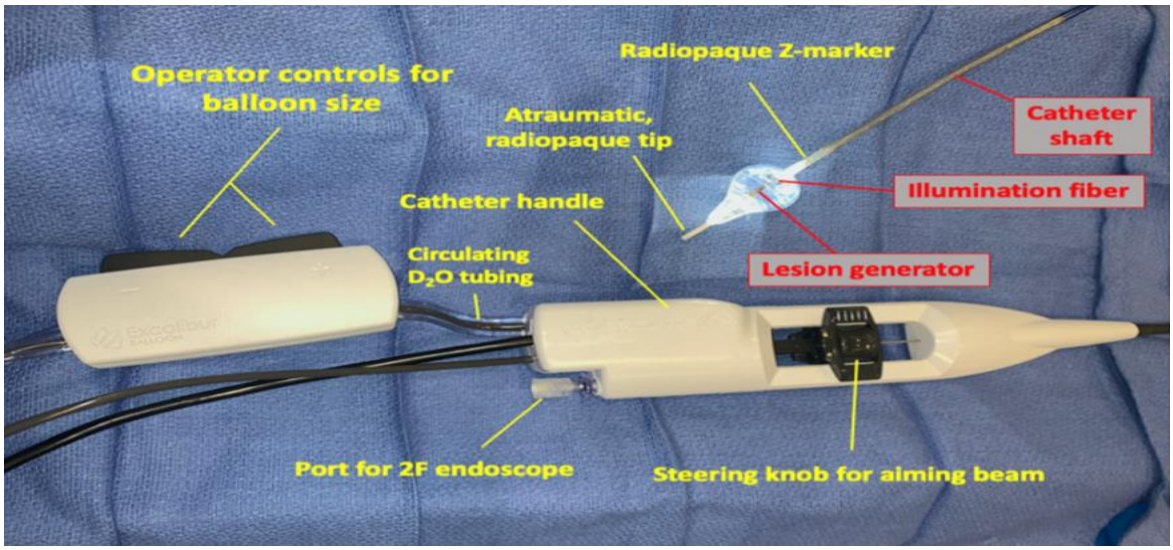
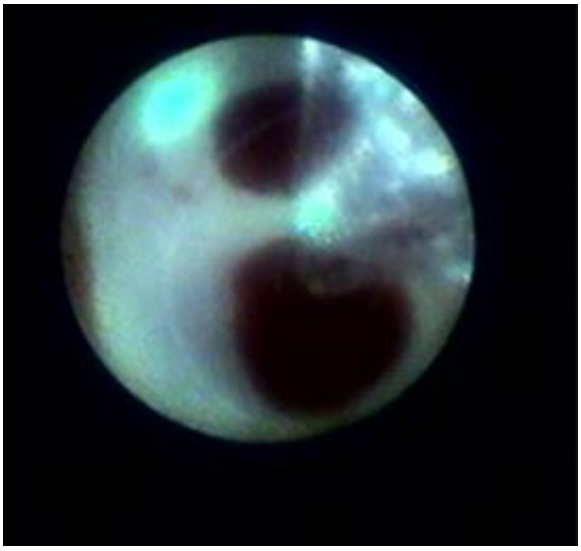


Figure 1. *Components of the laser balloon system.*

The operator then has a real-time view of PV ostia via a 2 F endoscope introduced via the shaft. Thereby, the ablation substrate may be directly visualized (Fig.2).

Ablation is performed with a 980-nm diode laser housed in the central lumen. Energy can be titrated (from 5.5 to 12 W) in predefined levels. ELBS lack recording of intracardiac signals. Therefore, the ablation procedure is visually guided, and PVI must be checked with a multipolar catheter introduced after laser balloon removal[72].

Figure 2. *An endoscopic image during the PVs occlusion by Laser Balloon with the visualization of two PVs ostia.*



The first two generations of laser catheters (LB1, HeartLight; CardioFocus; LB2, HeartLight Excalibur Balloon; CardioFocus) performed a circular ablation around each PV in a point-by-point way[73,74].

The latest generation of laser balloons (LB3; HeartLight X3) introduced a motor control system (RAPID feature) that enables uninterrupted, high-speed, circumferential lesion at 13 W, leading to a change of the technique from point-to-point to a potentially single sweep technology[75].

There are differences between the types of tissue injuries caused by various forms of thermal energy. RF uses tissue heating and the 90% of the power is absorbed in the first 1-1.5 mm of the myocardium, requiring high heating levels for a full transmural lesion[76]. Cryothermal lesions cause freezing with subsequent necrosis and replacement fibrosis[77].

ELBS is based on photonic energy that can penetrate tissue beyond the endocardium. Here it is absorbed by water, causing deeper heating and necrosis (Fig.3). Nevertheless, the first layers of the surrounding tissue absorb most of the energy, reducing the probability of collateral damage. Thus, lesions are well-defined and transmural, with no or minimal endocardial damage nor charring[78], as confirmed by cardiac MRI studies, which show well-defined lesions with less aggressive scarring into the LA[79].

Transmural, well-defined lesions could lead to a less acute pulmonary vein reconnection rate with a better safety profile. Studies have shown a stable PVI one year after the ablation[73].

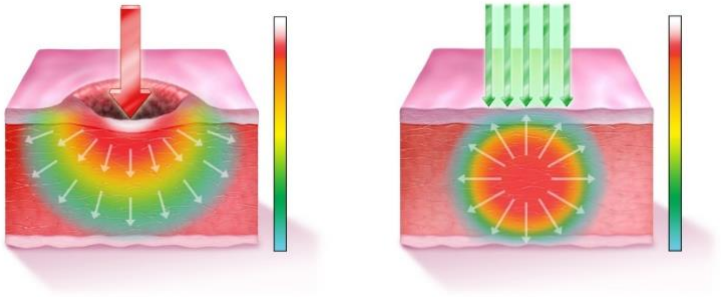


Figure 3: *Comparison of radiofrequency vs. laser energy delivering to tissue.*

Regarding efficacy data, the first two generations of laser catheters, which perform ablation point-by-point, resulted in similar efficacy but longer procedural times compared to RF and CB in paroxysmal and persistent atrial fibrillation[73,74].

A meta-analysis from 17 studies showed that these systems obtain acute PVI in 98% of cases, with freedom from recurrences after withdrawal of antiarrhythmic drugs in the range of 70-75% at 12 months. As regards safety, adverse events appear similar to other technologies. The most common complication is phrenic nerve injury (2.6%). No cases of PV stenosis were reported[80]. The learning curve of the procedure, even first-time users may achieve acute PVI in a high number of patients with a favorable outcome after one year[81].

The latest generation of laser balloons (X3) introduced the abovementioned RAPID feature, which could change the technique from point-to-point to a potentially single sweep technology resulting in significantly reduced procedure times[75,82].

Nevertheless, data regarding this modern system is scarce. No study analyses the Rapid mode impact on long-term outcomes, and there is no comparative study with RF or CB.

2.6 AF recurrence after transcatheter ablation

It still remains a challenge to achieve durable PVI and prevent AF recurrences. The lack of persistent PVI, however, limits the opportunities to perceive the real impact of PVI on AF suppression and to fully understand the benefit of extended ablation strategies going beyond PVI in non-responders to PV. Additional ablation of alternative substrates has not proven

beneficial or reproducible in real-world data[64]. In patients with more advanced forms of AF, alternative lesions are considered as tailored therapy.

Recurrences after ablation are classified into three types according to the phase after ablation in which they appear: (1) early recurrence (within three months); (2) late recurrence (from three months to one year); and (3) very late recurrence (more than one year).

Recurrences within the first three months after the procedure (blanking period) are due to local inflammation, alteration of the local function of the ANS and maturation of the local lesion. Usually, they do not need any additional redo intervention, except for those patients who experience a high burden of early recurrences.

Late recurrences are predominantly linked to the recovery of electrical conduction between the PVs and the LA and usually require a new intervention. The predominant mechanism of very late recurrences (after more than 12 months post-ablation) includes PV reconnection, the development of non-PV triggers, and the development and maturation of substrate[83].

Pulmonary vein isolation is crucial in treating symptomatic atrial fibrillation but not a universal remedy. Patients exhibiting risk criteria for recurrence should be considered for a redo procedure with personalized lesion customization (additional lines, neuromodulation).

3 STUDY SECTION

3.1 POURPOSE

Previous studies on first and second-generation ELBS have already shown similar efficacy and safety as irrigated RF catheters. However, their use resulted in longer procedural times compared to CB and RF catheters.

The third generation (X3) of ELBS has an improved structure and a novel function: the feature (RAPID), which potentially performs a full 360 degrees lesion for single-shot PVI. Nevertheless, there is a paucity of data on its feasibility and impact on procedural and clinical outcomes.

In this monocentric, prospective, non-randomized study, we analyze the use of the X3 ELBS, assessing its efficacy, safety, and long-term results in a contemporary cohort of patients with atrial fibrillation eligible for transcatheter ablation.

3.2 METHODS

3.2.1 STUDY POPULATION AND INCLUSION/EXCLUSION CRITERIA

We prospectively enrolled all consecutive patients who underwent catheter ablation of atrial fibrillation with the X3 system at our Institution (U.O. of Cardiology, Policlinic Sant'Orsola Malpighi PAD23) between September 2020 and December 2022.

INCLUSION CRITERIA

- Patients aged 18 to 75 with indications for the ablation procedure (ESC guidelines)
- Drug-refractory paroxysmal or persistent AF (failure or intolerance to at least one antiarrhythmic drug)
- AF causing tachycardia-induced cardiomyopathy
- AF affecting patients with HF with reduced ejection fraction (HFrEF)
- No prior AF transcatheter ablation.

Exclusion criteria

- LA thrombus (transesophageal or intracardiac echocardiogram)
- A left ventricular ejection fraction <25%
- ACS within the prior 60 days
- Any cardiac surgery in the prior three months
- Uncontrolled bleeding or active infection
- Severe comorbidities which affected patients' prognosis
- Pregnancy, or lactation.

3.2.2 STUDY PROTOCOL, DATA MANAGEMENT AND BASELINE EVALUATION

This study is non-pharmacological interventional, monocentric, prospective, and non-randomized. The local ethics committees approved the study protocol, and the study was registered and conducted following the Helsinki Declaration and all relevant national and international regulations.

We extracted all demographic, patients' medical history, procedural, and follow-up data. Then we de-identified them and collected them into a database.

Participants signed informed consent and underwent a baseline evaluation. We obtained a medical history, a physical exam, a 12-lead ECG, transthoracic echocardiography (TTE), routine laboratory exams and a pregnancy test for females of childbearing potential.

We calculated the estimated baseline glomerular filtration rate (eGFR) according to the Chronic kidney disease epidemiology collaboration (CKD-EPI) formula.

As regards TTE, we performed cardiac chamber quantification and estimation of left ventricular function, valvular dysfunction, and pulmonary artery systolic pressure (PASP) according to European Association of Cardiovascular Imaging (EACVI) recommendations[85,86].

We made a baseline diagnosis of HF with subsequent classification (HFrEF, HFrEF and HF with mildly reduced EF (HFmEF) according to ESC guidelines on HF[87].

If not already on OAC, we prescribed an anticoagulation therapy for at least 30 days before the ablation procedure. When necessary, we continued the antiarrhythmic therapy.

An experienced electrophysiologist at the involved center performed the study monitoring and assessed and recorded any relevant adverse event related to the procedure or during follow-up.

3.2.3 LASER BALLOON ABLATION PROCEDURE

Two operators performed all the ablations. We calculated procedural time from the moment of venous access to the removal of the electrophysiology catheters.

Procedures were under general anesthesia or deep sedation, using intravenous propofol, midazolam, and fentanyl.

After femoral venous access, the operator performed a transseptal puncture using an 8F sheath and a Brockenbrough needle under fluoroscopy and transesophageal (TEE) or intracardiac echocardiographic (ICE) guidance. Subsequently, unfractionated intravenous heparin boluses were administered to reach and maintain an activated clotting time ≥300 seconds.

The operator changed over guidewire the transseptal sheath with a 12F deflectable sheath and used it to position the X3 catheter at the ostium of the target PV. Finally, the balloon was inflated, and ablation was performed under fluoroscopic and endoscopic guidance.

The X3 system consists of a compliant balloon which conforms to the PV ostium. A 2F endoscope introduced via the shaft allows for a real-time view of PV ostia. Thereby, the operator may directly visualize the ablation substrate. However, due to a blind point of the endoscope, the operator has a ≈300° view.

A specific filling media (D2O) circulates in the central shaft and cools the balloon.

The catheter has a flexible tip to minimize trauma, and the shaft contains a radiopaque marker. The latter allows visualization of the catheter on fluoroscopy. This way, the operator has both an endoscopic and fluoroscopic reference.

Ablation is possible with a 980-nm diode laser housed in the central lumen. The optical fiber inside the shaft generates an arc of light that can be positioned at any location on the balloon to allow aiming and ablation with the diode laser. The operator can utilize energy delivery with predefined power levels (from 5.5 to 13W) and duration (20-30 seconds).

As already mentioned, the X3 system introduced a motor control system (RAPID feature) that enables uninterrupted, high-speed (2.25° per second) circumferential lesion at 13 W, which should result in reduced procedure times since it potentially leads to a change of the technique from point-to-point to a “single sweep”.

During each PVI, we first attempted to complete the circumferential lesion at 13 W using only the RAPID feature. If completion of the lesion with the RAPID feature was not possible, the operator used additional point-by-point energy delivery at 5.5, 8.5 or 13 W to achieve a visually complete circumferential lesion. For every procedure, we calculated the mean percentage of use of the RAPID feature for each circumferential lesion and on total lesion distance.

In the isolation of the right-side PVs, we performed high-output right phrenic nerve pacing from the superior vena cava to induce diaphragmatic movement and promptly recognize potential phrenic nerve injury. We immediately interrupted energy delivery if there was a transient loss of diaphragmatic movement.

The operator performed an additional cavo-tricuspid isthmus block with an RF catheter in those patients with a history of typical atrial flutter.

At the operator’s discretion or as a random control, 15 minutes after PVI, we used a circular mapping catheter to assess for PVs electrical isolation (absence of PV potentials and/or entrant/exit block pacing). If a PV was not isolated, the operator used the X3 to repeat the PV isolation.

3.2.4 FOLLOW-UP

We identified the first three months after the ablation as a blanking period, during which we related AF recurrences to local inflammation, ANS deregulations and maturation of the lesion, and not to a failure of the procedure.

After discharge, patients stayed on OAC and AAD for at least three months. After this time, we continued OAC only if the patient had a specific indication (CHA2DS2-VASc score > 1 in men or > 2 in women) or if the assessing physician deemed it necessary based on the patient's clinical status and comorbidities. Moreover, we also interrupted AAD therapy if the patient did not present a significant arrhythmia burden.

We performed follow-up visits at 3, 6, 12, 18 and 24 months to assess for AF recurrences, procedural-related long-term complications and major adverse cardiocerebrovascular events (MACCES).

Visits included a physical exam, a 12 lead ECG, and an evaluation of blood test. Additionally, we performed a device interrogation in carriers of implantable cardiac devices.

A week before each visit, the patients needed to complete a 24-hour Holter ECG monitoring.

During the 12- and 24-month visits, the assessing physician performed a TTE to evaluate valve function, chamber dimensions, pulmonary artery systolic pressure, left ventricular EF and diastolic function. In comparison with the baseline, we defined an improvement in EF and PASP as an increase of at least 5% and a decrease of 10 mmHg, respectively, and we identified an improvement of LA enlargement and mitral regurgitation (MR) as a reduction in severity class. Finally, we collected additional data from hospitalizations or unscheduled ambulatory or Emergency Department accesses.

3.2.5 PRIMARY ENDPOINTS

The primary endpoint was the evaluation of the efficacy and safety of performing an ablation procedure with the X3 system.

The treatment will be considered efficient if no atrial fibrillation relapse will occur: any clinical AF or subclinical AF with arrhythmia burden >5 h. We identified a recurrence as an ECG, Holter strip or a recording of an implantable device of at least 30 seconds documenting AF. We distinguished recurrences within three months (blanking period) from those after three months following the ablation procedure.

→ **Primary endpoints**: Freedom from AF recurrence at 1 and 2 year in overall patients population and in paroxysmal and persistent AF subgroups.

We evaluated safety as the rate of procedure-related serious adverse events (AE). We considered the following as serious AE: transient ischemic attack/stroke (within one month after the ablation), vascular access complications (pseudoaneurysm, arteriovenous fistula, hematoma requiring transfusion, intervention or lengthening of the hospital stay), clinically significant pericardial effusion (within one month after the ablation), cardiac perforation or cardiac tamponade, phrenic nerve injury, atrio-esophageal fistula, death (related to the procedure or its complications). We also evaluated the number of pinhole balloon ruptures. Finally, we also considered the rate of the MACCES.

3.2.6 SECONDARY ENDPOINTS

We analyzed the impact of RAPID MODE feature on procedural and clinical outcomes:

→ We evaluated the impact of the RM feature on procedural outcomes as the difference in procedural and fluoroscopy times between patients with utilization of RM for more than 70% of total circumferential lesions and those with less than 70%. We selected this as the best cut-off after statistical analysis.

→ We evaluated the impact of the RM feature on AF recurrences between the same two populations.

3.2.7 STATISTICAL ANALYSIS

The data collected in the database were expressed differently depending on categorical and continuous variables.

Categorical variables were expressed as absolute frequencies (the number of patients exhibiting the considered variable) and relative frequencies (calculated as the percentage of patients with the variable in question relative to the total population under examination).

Continuous variables were presented in terms of mean ± standard deviation (SD).

Continuous variables were compared using the non-parametric Mann-Whitney test in the case of a non-normal distribution and the Fisher's test in the case of a normal distribution. Categorical variables were compared using contingency tables, and the significance of the obtained data was evaluated with Pearson's χ^2 test. A p-value of <0.05 was considered the threshold for statistical significance.

The statistical analysis and Kaplan-Meier curves were generated using Stata/SE 17.

4 RESULTS

4.1 BASELINE CHARACTERISTICS

We enrolled a total of 126 consecutive patients between September 2020 and December 2022 undergoing transcatheter laser balloon ablation.

All baseline demographic characteristics, risk factors, therapy, comorbidities, and echocardiographic parameters are summarized in tables 1-4.

The average age of the population was 61 ± 10.2; 74,6% of patients were male. 26 patients (20,6%) were obese (BMI>30 kg/m^2). The mean eGFR and body max index were 80.5 ± 20.2 mL/min/1.72 m^2 and 26,7 ± 4.2 kg/m^2, respectively. At baseline 93 patients (73.8%) had paroxysmal AF, 33 (26.2%) persistent AF.

Table 1: Baseline Characteristics:

Age, mean ± s.d. (years)	61 ± 10.2
Female Sex, n (%)	32 (25.4%)
Body Max Index, mean ± s.d. (kg/m^2)	26,7 ± 4.2
Obesity, n (%)	26 (20.6%)
Atrial Fibrillation type	
Paroxismal, n (%)	93 (73.8%)
Persistent, n (%)	33 (26.2%)
Atrial Fibrillation Duration, mean ± s.d. (months)	64.5± 67.2
CHA2DS2-VASc score	
0 n (%)	34 (26.9)
1 n (%)	27 (21.4)
2 n (%)	31 (24.6)
3 n (%)	18 (14.2)
4 n (%)	9 (7.1)
5 n (%)	4 (4.1)
6 n (%)	3 (2.4)
Creatinine, mean ± standard deviation (mg/dL)	1 ± 0.3
Glomerular filtration rate (CKD-EPI), mean ± s.d. (mL/min.1.72 m^2)	80.5 ± 20.2

The most prevalent cardiovascular risk factor was hypertension (51.6%).

25 patients (19.8%) had a history of HF (including HFrEF, HFmEF and HFpEF).

16 pts suffered from diabetes (12.7%).

Mean left ventricular EF (55.6 ± 12.9%) was normal. We observed a LA enlargement in 95 (75.3%) patients, 39 (41%) mild, 34 (35.8%) moderate, and 22 (23.2%) severe.

Table 2: Baseline Comorbidities and Risk Factors

Heart Failure, n (%)	25 (19.8%)
Coronary Artery Disease, n (%)	12 (9.5%)
Dilated Cardiomyopathy, n (%)	14 (11.1%)
Hypertrophic Cardiomyopathy, n (%)	12 (9.5%)
Hypertensive heart disease, n (%)	11 (8.7%)
Valvular Heart Disease, n (%)	8 (6.3%)
Hypertension, n (%)	65 (51.6%)
Dyslipidemia, n (%)	71 (56.3%)
Diabetes, n (%)	16 (12.7%)
Obstructive Sleep Apnoea Syndrome, n (%)	6 (4.7%)
High Intensity Physical Exercise, n (%)	9 (7.1%)
Peripheral Artery Disease, n (%)	4 (3.2%)
Previous Stroke/TIA, n (%)	8 (6.3%)
Chronic Obstructive Pulmonary Disease, n (%)	6 (4.7%)

Table 3: Baseline Echo parameters

EF, mean ± s.d. (%)	55.6 ± 12.9
LVEDV, mean ± s.d. (mL)	121.8 ± 57.9
Left atrial enlargment, n (%)	95 (75.3%)
Mild, n (%)	39 (41%)
Moderate, n (%)	34 (35.8%)
Severe, n (%)	22 (23.2%)
Mitral regurgitation, n (%)	80 (63.5%)
Mild, n (%)	61 (76.2%)
Moderate, n (%)	13 (16.3%)
Severe, n (%)	6 (7%)
PASP, mean ± s.d. (mmHg)	28.4 ± 8.7
EF, Ejection fraction; LVEDV, Left ventricular end diastolic volume; PASP, Pulmonary artery systolic pressure; s.d. standard deviation.	

All patients were on oral anticoagulation therapy for at least a month, either on a direct oral anticoagulant (90.5%) or a Vitamin k antagonist (9.5%).

The most used drugs were beta-blockers, in 66 patients (52.4%).

104 patients (82.5%) were on antiarrhythmic drug for rhythm control strategy, and the most frequently used was Flecainide (50.8%), followed by amiodarone (18.6%).

29 patients (23%) were receiving rate control therapy with digoxin or calcium-channel blockers.

Table 4: Baseline Therapy/Device

DOAC, n (%)	114 (90.5%)
VKA, n (%)	12 (9.5%)
Antiplatelet therapy, n (%)	7 (5.5%)
ACE-I/ARB, n (%)	45 (35.7%)
Sacubitril/Valsartan, n (%)	6 (4.7%)
ARA, n (%)	20 (15.9%)
SGLT2-I, n (%)	4 (3.2%)
AAD, n (%)	104 (82.5%)
Propafenone, n (%)	5 (3.9%)
Flecainide, n (%)	64 (50.8%)
Amiodarone, n (%)	23 (18.2%)
Sotalol, n (%)	4 (3.2%)
Dronedarone, n (%)	8 (6.3%)
Beta-blockers, n (%)	66 (52.4%)
Non dihidropiridine Calcium-channel blockers, n (%)	26 (20.6%)
Digoxin, n (%)	3 (2.3%)
Statin, n (%)	47 (37.3%)
Device, n (%)	14 (11.1%)
PM, n (%)	0 (0%)
ICD, n (%)	2 (1.7%)
CRT-D, n (%)	3 (2.3%)
CRT-P, n (%)	9 (7.1%)

DOAC, Direct oral anticoagulant; VKA, Vitamin k antagonist; AAD, Antiarrhythmic drug; ACE-I/ARB, Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARA, Aldosterone receptor antagonist: SGLT2-I, Sodium-glucose cotransporter 2 inhibitor; PM, Pacemaker; ICD, Implantable cardioverter defibrillator; CRT-P, Cardiac resynchronization therapy pacemaker; CRT-D, Cardiac resynchronization therapy defibrillator.

4.2 PROCEDURAL AND SAFETY DATA

Table 5: Procedural data

Total Procedural Time, mean ± standard deviation (min)	160.7 ± 48.8
Total Fluoroscopy Time, mean ± standard deviation (min)	29 ± 14.7
Uninterrupted OAC, n (%)	53 (46.9%)
General Anaesthesia, n (%)	10 (8%)
Deep Sedation, n (%)	116 (92%)
Echo-guidance	
Transoesophageal echocardiography-guide, n (%)	9 (7.1%)
Intracardiac echocardiography, n (%)	117 (92.9%)
Variant Anatomy, n (%)	36 (28.5%)
Middle Pulmonary Vein, n (%)	24 (66.6%)
Common Ostium, n (%)	12 (33.4%)
Number of Pulmonary Veins	510
3, n (%)	15 (11.9%)
4, n (%)	85 (67.4%)
5, n (%)	25 (20.6%)
Mean RAPID use per Vein, mean ± standard deviation (%)	83.2 ± 20.3
Patients with PVs treated with RAPID Mode > 70%, n (%)	95 (75.3%)
Cavotricuspid isthmus blockade, n (%)	19 (15%)
Left superior pulmonary vein	
Time to ablate, mean ± standard deviation (min)	14.6 ± 10.7
Fluoroscopy time, mean ± standard deviation (min)	3.2 ± 3.4
Mean RAPID use, mean ± standard deviation (%)	81.5 ± 25.7
Left inferior pulmonary vein	
Time to ablate, mean ± standard deviation (min)	13.4 ± 7.5
Fluoroscopy time, mean ± standard deviation (min)	2.9 ± 2.6
Mean RAPID use, mean ± standard deviation (%)	83.3 ± 22.5
Right superior pulmonary vein	
Time to ablate, mean ± standard deviation (min)	13.1 ± 8.6
Fluoroscopy time, mean ± standard deviation (min)	2.8 ± 2.4
Mean RAPID use, mean ± standard deviation (%)	83.9 ± 26.5
Right inferior pulmonary vein	
Time to ablate, mean ± standard deviation (min)	16.6 ± 12.1
Fluoroscopy time, mean ± standard deviation (min)	4.9 ± 5.2
Mean RAPID use, mean ± standard deviation (%)	83.7 ± 24.5
Pulmonary veins assessed for electrical isolation, n (%)	101 (19.8%)
Absence of electrical isolation, n (%)	15 (14.8%)

Table 5 shows the procedural data.

The mean duration of procedure was approximately 160 minutes, from venous access placement to removal of laser balloon catheter via venous introducer sheath. Fluoroscopy mean time was 29 minutes.

92% of patients underwent deep sedation, the remainder underwent general anesthesia.

We identified and attempted to treat a total of 510 pulmonary veins.

Operators used the Rapid Mode motorized system to achieve an average of 83.2 ± 20.3% of pulmonary vein isolation. 95 patients (75.3%) were treated using RM for complete PV isolation in at least 70% by PVs. Within this group, rapid mode was used for at least 80% of all lesions in 87 (69%) patients and for 90% in 67 (53.1%) patients.

36 (28.5%) patients presented variant anatomy, of whom 24 (66.6%) had a middle pulmonary vein and 12 (33.4%) had a common ostium.

The operator checked for electrical isolation at the end of the procedure in 101 (20%) PVs, as a random check or when visually the vein had not been ablated correctly. 15 veins (14.8%) still presented an electrical connection to the LA with a subsequent need for further energy delivery.

19 (15%) patients received cavo-tricuspid isthmus block with RF at the end of PV isolation, with prolongation of procedural total time (187.7 ± 49 min).

Among baseline characteristics, only a history of HF showed a correlation with prolonged total procedural (155.5 ± 5.2 vs 178.0 ± 9.7, p=0.04) and fluoroscopy (29.0 ± 1.4 vs 37.2 ± 2.7, p=0.011) time.

The presence of an anatomical variant only resulted in prolonged procedural (153.2 ± 5.4 vs 177.5 ± 8.3, p=0.016) but not fluoroscopy (29.2 ± 1.5 vs 34.6 ± 2.3, p=0.06) time.

As regards procedural complications (table 6), we documented an episode of symptomatic pericarditis with associated effusion the day after the procedure that was successfully managed with medical therapy and did not require invasive intervention.

Two patients experienced a transient phrenic nerve palsy during energy delivery on the RIPV, and it resolved spontaneously before discharge. One patient reported a vascular access complication.

A pinhole balloon rupture occurred in 6 procedures (5.3%) and it occurred when laser energy was delivered to blood during an incomplete PV occlusion. This technical complication leads to loss of balloon pressure, with subsequently decreased view and the need for a change of the balloon with impact on the cost of the procedure.

Table 6. Procedural related Complications

Pinhole balloon rupture, n (%)	**6 (5.3%)**
Procedural complications, n (%)	4 (3.2%)
Phrenic nerve injury, n (%)	2 (1.6%)
Pericardial effusion, n (%)	1 (0.8%)
Cardiac perforation/tamponade, n (%)	0 (0%)
Stroke/TIA, n (%)	0 (0%)
Vascular access complications, n (%)	1 (0.8%)
Atrio-esophageal fistula, n (%)	0 (0%)
Death, n (%)	0 (0%)

4.3 AF RECURRENCE AND FOLLOW-UP DATA

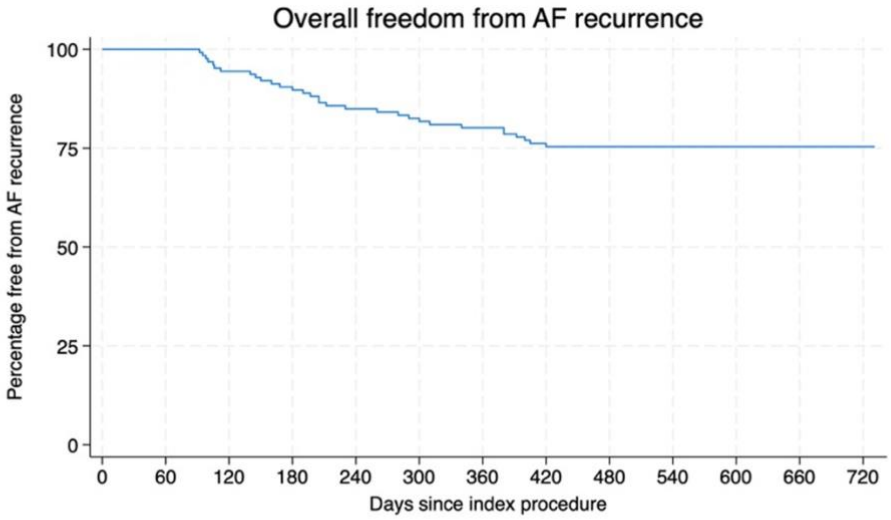
119 (94.5%) had at least 12 months of follow-up. The main findings are reported in Tables 7. The mean follow-up duration was 18 ± 5.6 months.

Table 7: Follow up clinical data

Patients with at least 12 months of follow-up	119 (94.5%)
Mean follow-up duration, mean ± s.d. (months)	18 ± 5.6
Patients with AF recurrence at 1 year, n (%) - In Paroxysmal AF group at baseline - In Persistent AF group at baseline	25 (20%) 16 9
Patients with AF recurrence at 2-year, n (%) - In Paroxysmal AF group at baseline - In Persistent AF group al baseline	33 (26%) 21 12
Patients with AF early recurrence (blanking period), n (%)	23 (18.2%)
Patients with both early and late AF recurrences, n (%)	15 (12%)
Types of first AF recurrence	
-Paroxysmal AF, n (%)	20 (66%)
-Persistent AF, n (%)	9 (27%)
-Permanent AF, n (%)	4 (12%)
Destination therapy for patients with AF recurrence at 12 months (n 25)	
Continuation of rhythm control strategy (AAD change/ECV)	13 (52%)
Redo Procedure, n (%)	4 (16%)
Switch to rate control strategy	8 (32%)
Atrial flutter newly diagnosed, n (%)	7 (28%)
Destination therapy for patients free from AF at 12 months (n 101)	
OAC interruption, n (%)	22 (23%)
Mean time to OAC interruption, mean ± s.d. (months)	8 ± 4
AAD interruption, n (%)	51 (50.5%)
Mean time to AAD Interruption, mean ± s.d. (months)	6 ± 3
OAC, Oral anticoagulation; AAD, antiarrhythmic drug; s.d., standard deviation. ECV, electrical cardioversion	

25 patients developed AF recurrence at 12 months, and 33 at 24 months, with a percentage of patients free from atrial fibrillation of 80% at 12 months and 74% at 24 months (Fig. 4).

***Figure 4**. The Kaplan-Meier curve illustrates the success rate of laser ablation as the percentage of patients free from atrial fibrillation.*



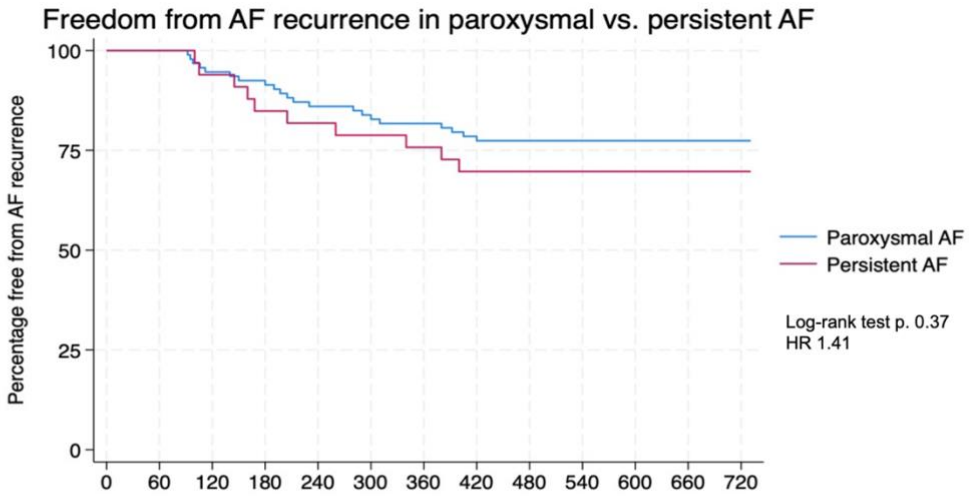
No. at Risk	126	117	112	101	93
Treatment success(%)	100	93	88	80	74

Analyzing the two subpopulations of patients with paroxysmal and persistent atrial fibrillation at baseline, at 3, 6, 12 and 24 months, they presented success rates of 94% vs. 90%, 90% vs. 85%, 83% vs. 73%, 78% vs. 63%, with a higher recurrence rate in patients with persistent AF, although not statistically significant (p = 0.37, HR = 1.41) (Fig.5).

In the group of patients with AF recurrences, 20 (66%) experienced episodes of paroxysmal AF, 9 patients (27%) had recurrences of persistent AF, for whom it was deemed appropriate to adjust medical therapy (change in AAD) and consider potential electrical cardioversion to pursue the rhythm control strategy. However, a new ablation procedure was required in 4 patients (12%).

In 4 patients (12%), the assessing physician deemed further attempts to restore sinus rhythm futile. Therefore, in these patients, AF was reclassified as permanent with rate control as destination therapy.

Figure 5. *The Kaplan-Meier curve illustrates the success rate of laser ablation in two different subgroups as the percentage of patients with paroxysmal or persistent AF at baseline free from atrial fibrillation during follow-up.*



No. at Risk					
Paroxysmal AF	93	87	84	77	72
Persistent AF	33	30	28	24	21
Treatment success (%)					
Paroxysmal AF	100	94	90	83	78
Persistent AF	100	90	85	73	63

In the blanking period 23 patients (18,2%) experienced early AF recurrence. No baseline nor procedural parameter showed an association with them, including AF type or performing an intraprocedural control of acute PVI.

Among patients free from AF recurrence, 51 (50.5%) discontinued antiarrhythmic therapy at month 6 ± 3.

Anticoagulation therapy was stopped in 22 patients (23%) at month 8 ± 4, in those with CHA_2DS_2VASC score = 0-1.

Atrial flutter was newly diagnosed in 7 patients.

Table 8: MACCES, Major adverse cardiocerebrovascular events

MACCES, n (%)	8 (6.4%)
HF episode, n (%)	6 (4.8%)
ACS, n (%)	1 (0.8%)
Acute Limb Ischemia, n (%)	0 (0%)
Stroke/TIA, n (%)	0 (0%)
Death, n (%)	1 (0.8%)
Transplant, n (%)	0 (0 %)
Major Bleeding, n (%)	2 (1.6%)
Ventricular Arrhythmias, n (%)	1 (0.8%)
Hospitalization for cardiovascular causes, n (%)	6 (4.8%)
Emergency Department/Unplanned Ambulatory Access, n (%)	27 (21.4%)
HF, Heart failure; ACS, Acute coronary syndrome; TIA, Transient ischemic attack.	

As regards MACCES, 8 patients (6.5%) had at least one major event. Of these, 6 had an episode of heart failure, one had an ACS, and one died for cardiovascular reasons (table 8).

Further, one patient had an episode of hemodynamically relevant ventricular tachycardia, while two had an episode of major bleeding.

An echocardiogram at 12 months was collected in 88 pts (70%). Of these patients, 14 had an improvement in EF, while 23 (18%), 20 (15.9%) and 9 (19.6%) had a decrease in LA enlargement, mitral regurgitation severity and PASP, respectively (table 9).

Table 9: Follow up echocardiographic parameters

Patients with echocardiogram at 12 months	88 (70%)
EF%, mean ± standard deviation	54 ± 13.5
Patients with EF Improvement, n (%)	14 (11.1%)
Left Atrial Dimension Improvement, n (%)	23 (18.2%)
Mitral Regurgitation Improvement, n (%)	20 (15.9%)
PASP improvement, n (%)	9 (19.6%)
EF, Ejection fraction; PASP, Pulmonary artery systolic pressure.	

4.4 RAPID MODE IMPACT ON OUTCOMES

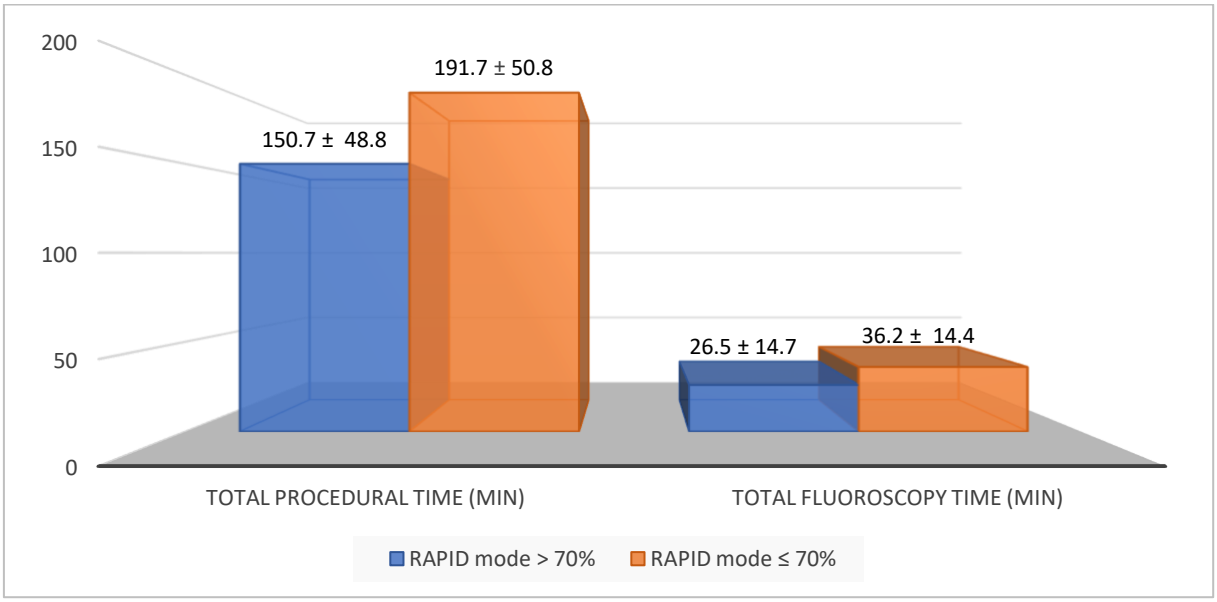
To evaluate the impact of the RAPID Mode on procedural and clinical outcomes a cut off of 70% of the total circumferential lesions was used. The comparison of main baseline demographic characteristics, risk factors, therapy, comorbidities, and echocardiographic parameters between the two groups is reported in Table 9. Regarding these characteristics, we found no significant difference between the two groups.

Table 9: Comparison of baseline and follow-up characteristic between patients with mean RAPID use above 70% and those with use below 70%.

	Mean RAPID use < 70%	**Mean RAPID use > 70%**	**p value**
Age, mean ± s. d. (years)	62.2 ± 10.4	60.7 ± 10.1	0.49
Female sex, n (%)	9 (31%)	23 (23.9%)	0.29
Body max index, mean ± s. d.	28.2 ± 4.6	26.5 ± 4.2	0.11
Obesity, n (%)	8 (27.6%)	14 (16.7%)	0.2
AF type			0.41
Paroxismal, n (%)	25 (83.4%)	68 (71.4%)	
Persistent, n (%)	5 (16.6%)	27 (28.6%)	
AF duration, mean ± s.d. (months)	55.7 ± 48.7	67.9 ± 67.2	0.8
CHA2DS2-VASc score			0.26
0 n (%)	5 (16.6%)	29 (30.5%)	
1 n (%)	5 (16.6%)	22 (23.2%)	
2 n (%)	8 (26.6%)	22 (23.2%)	
3 n (%)	6 (20%)	12 (12.6%)	
4 n (%)	4 (13.3%)	5 (5.2%)	
5 n (%)	2 (6.6%)	2 (2.1%)	
6 n (%)	0 (0%)	3 (3.1%)	
GFR (CKD-EPI), mean ± s. d. (mL/min.1.72 m^2)	75.5 ± 21.7	82.7 ± 19.0	0.15
History of HF, n (%)	10 (33.0%)	15 (16.0%)	0.036
Mean EF, mean ± s. d. %	52.7 ± 16.5	55.7 ± 12.3	0.62
AF recurrence at 12 months	14 (22%)	11 (38%)	0.015
AF recurrence in blanking period	16 (25%)	7 (25%)	0.44
CHA2DS2-VASc, Congestive heart failure, hypertension, age >_75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, sex category (female); CKD-EPI, Chronic kidney disease epidemiology collaboration; HF, Heart failure; EF, Ejection fraction, s.d. standard deviation.			

There was a significant reduction of procedural (150.7 ± 48.8 min vs 191.7 ± 50.8 min, p<0.001) and fluoroscopy time (26.5 ± 14.7 min vs 36.2 ± 14.4 min, p<0.01) in those patients with utilization of the RAPID feature for more than 70% of total circumferential lesions (Fig.6).

Figure 6. *Comparison of fluoroscopic and procedural time between patients with mean RAPID mode use above 70% and those with use below 70%.*



Moreover, in the multivariate analysis, the use of the RAPID feature for more than 70% of total circumferential lesions also proved an independent predictor of reduction of both procedural duration (p <0.001) and fluoroscopy use (p=0.019) time. The analysis compared with other factors associated with longer procedural times, such as the presence of variant anatomy, performing an intraprocedural cavo-tricuspid isthmus block or an end-procedural control of acute PVI.

We also observed a significantly shorter ablation and fluoroscopy time for each singular PV if >70% of the circumferential lesion was made through RAPID mode (Table 10).

Table 10: Procedural and fluoroscopic time for single pulmonary vein	**Mean RAPID mode ≤ 70%**	**Mean RAPID mode > 70%**	**P value**
Right Inferior Pulmonary Vein (ablation time), mean ± standard deviation (min)	27.4 ± 12.8	13.9 ± 10.7	**<0.001**
Right Inferior Pulmonary Vein (fluoroscopic time), mean ± standard deviation (min)	5.4 ± 3.3	4.7 ± 5.8	**0.01**
Right Superior Pulmonary Vein (ablation time), mean ± standard deviation (min)	22.8 ± 9.0	10.4 ± 6.4	**<0.001**
Right Superior Pulmonary Vein (fluoroscopic time), mean ± standard deviation (min)	4.2 ± 3.4	2.3 ± 2.0	**0.05**
Left Inferior Pulmonary Vein (ablation time), mean ± standard deviation (min)	23.9 ± 14.6	12.5 ± 7.8	**<0.001**
Left Inferior Pulmonary Vein (fluoroscopic time), mean ± standard deviation (min)	5.0 ± 4.9	2.8 ± 2.7	**<0.001**
Left Superior Pulmonary Vein (ablation time), mean ± standard deviation (min)	23.9 ± 14.6	12.5 ± 7.8	**<0.001**
Left Superior Pulmonary Vein (fluoroscopic time), mean ± standard deviation (min)	5.0 ± 4.9	2.8 ± 2.7	**0.009**

Regarding clinical endpoint, the Rapid Mode group >70% demonstrated a statistically significant difference (p=0.015) in terms of the incidence of late recurrences of atrial fibrillation, which were more frequent in the Rapid Mode group ≤ 70% (Table 9).

5 DISCUSSIONS

In the scenario of transcatheter ablation of atrial fibrillation, the Laser Balloon system (X3 ELBS) has represented a paradigm shift. Thanks to the fibroscope, it has transformed the isolation of the pulmonary veins from a procedure guided by fluoroscopy and electrical signals into a semi-automatic visuo-anatomic ablation. The target of ablation with a one-shot balloon technique is now well-known, and the evolution of technology has enabled us to visualize the ostium of the pulmonary veins and to precisely complete cardiac tissue lesions.

In this study we report one of the most numerous monocentric experiences of the third generation Laser balloon X3 system in a contemporary cohort of patients.

The X3 ELBS has demonstrated both short and long-term effectiveness in reducing recurrent symptomatic atrial fibrillation, with an excellent safety profile.

In the overall population, we observed freedom from AF recurrence at 3, 6, 12, and 24 months, respectively, of 93%, 88%, 80%, and 74%. In the subgroups of patients with paroxysmal and persistent forms at baseline, we noticed a trend of lower recurrence rates in the paroxysmal group compared to the persistent group, particularly success rates at 3, 6, 12, and 24 months of 94% vs. 90%, 90% vs. 85%, 83% vs. 73%, and 78% vs. 63%, respectively.

These data align with what has been reported in the literature for other forms of energy and confirm a greater complexity in patients with persistent forms of atrial fibrillation.

In the recent ADVENT trial, the safety and efficacy of the novel pulsed field catheter ablation (PFA) for symptomatic paroxysmal atrial fibrillation were compared with conventional thermal ablation techniques, radiofrequency (RF) and cryoballoon (CB). This first randomized trial of pulsed field ablation has demonstrated non-inferior efficacy compared to conventional thermal ablation techniques. The AF recurrence rate was 17.2% in the PFA group vs. 16.4% in the thermal group at the 12-month follow-up. However, patients with persistent AF were excluded. The incidence of adverse events in both groups was 2.3% and 2%[70].

A recent meta-analysis, which included 7 trials comparing laser balloon (including first and second generation) and CB in the ablation of paroxysmal atrial fibrillation, demonstrated a recurrence rate of atrial fibrillation at 12 months ranging from 16% to 22%[84].

Currently, the efficacy of pulmonary vein isolation alone in reducing AF recurrences is around 80% for paroxysmal forms and 70% for persistent forms at one year. With laser balloon and pulsed field techniques, it has not been possible to further increase this efficacy, most likely because pulmonary vein isolation is the cornerstone of catheter ablation but not a panacea.

Further studies need to be conducted to integrate alternative lesion targets, which, as of today, are only achievable with radiofrequency or neuromodulation techniques. New technologies, such as laser and PFA, have shown a short learning curve and are, therefore, less operator-dependent, effectively standardizing the procedure.

These new technologies should, in fact, aim to not only improve efficacy but also reduce procedural times and complications. As for safety, in our population, the complication rate was 3.2%, with all complications being reversible and not life-threatening.

RF and CB procedures hold a mean complication rate of 3%, rarely irreversible and life-threatening, such as phrenic nerve paralysis and atrio-esophageal fistula. In our experience, we recorded one case of symptomatic post-procedural pericarditis and two episodes of transient phrenic nerve palsy, all of which resolved during the hospital stay and did not require an extension of the hospital stay or any further intervention. One access-related complication was attributed to the Seldinger technique and the complex arteriovenous anatomy of the patient itself, not to the laser balloon technology.

We could explain this low complication rate with the features of the X3: laser is photonic energy that penetrates tissue beyond the endocardium, and it is absorbed by water causing deeper heating and necrosis. Nevertheless, the first layers of the surrounding tissue absorb most of the energy, reducing the probability of charring and thrombosis[79].

The more compliant balloon allowed for a better conformation to the PV ostium and, subsequently, more antral and selective energy delivery[73]. Finally, the novel RAPID feature allows for a highly selective 13 W energy delivery, which could result in well-defined

transmural lesions[75]. These characteristics could lead to selective LA wall damage, sparing surrounding tissues and explaining the low complication rate we observed in our cohort.

As regards pinhole balloon rupture, the rate of its occurrence in our experience (5.3%) was lower than in previous studies with the X3 system[82]. Usually, it is a consequence of balloon overheating, which occurs when the operator uses high energy output, primarily when delivered over blood. To avoid this technical complication, it is necessary to optimize the contact of the balloon at the venous ostium to create an entirely bloodless field, and placing manual point to point lesions with reduced power (5.5W) when balloon adhesion is not optimal. Further, during the study course, the X3 system introduced a new coated balloon with better resistance to higher temperatures.

As regards MACCEs, during the follow-up 8 patients (6.4%) had at least one major event, mainly an episode of acute HF. They occurred in sicker patients with a higher cardiovascular risk burden (those with a history of HF, lower EF and eGFR, higher CHA2DS2-VASc score and persistent AF). Our study confirmed that in patients with AF, one of the predictors of serious cardiovascular events at follow-up is AF recurrence.

Regarding secondary endpoints, we have analyzed the impact of the Rapid Mode (RM) on procedural and clinical endpoints. The RM allows for precise, continuous, circumferential and semi-automatic energy delivery, potentially resulting in no lesion gaps during PVI.

There was a significant reduction of procedural and fluoroscopy time in those patients with utilization of the RM for more than 70% of total circumferential lesions.

Our multivariate analysis confirmed that using the RM is an independent predictor of reduction of procedural times, adjusting for other factors associated with the prolonged duration of the ablation procedure.

Furthermore, we noted reduction in late AF recurrences in those patients with more use of the RAPID feature, likely due to a more effective lesion with longer-lasting pulmonary vein isolation.

However, further analysis, a higher number of patients, multicentric experience and a longer follow-up could confirm our observation.

A final consideration should be made regarding the assessment of electrical isolation after the visual-anatomic lesion created with the laser energy.

The current laser balloon is not equipped with electrical poles for exploring PV potentials, while is available with CB, PFA, and RF catheters. Therefore, if the operator wishes to check the PV electrical signal, an additional catheter must be introduced into the pulmonary vein, such as the quadripolar or decapolar catheter used for coronary sinus cannulation or phrenic nerve stimulation.

Nevertheless, when the operators checked for acute electrical PV isolation, they found that of 101 PVs, 15 (14.8%) presented an electric gap with a subsequent need for further energy delivery. Even this rate is a relatively high number, at our center, the operators check acute PV isolation when there is suspicion of a potential gap in the circumferential lesions. Further, we found a residual gap in majority of the first 30 procedures when the operator was still inexperienced.

Previous studies showed that a visually guided approach, without mapping PVs, leads to a high acute PVI rate with both second and third generation ELBSs[82].

Besides, in our experience, we found no difference in AF recurrence rate when comparing those patients without acute checking of PVI with those who did.

Checking for acute PV isolation in all procedures could prove time-expensive and with implications for the duration of the procedure.

The latest generations of CBs can already record intracardiac signals via a circular mapping tip placed distally to the balloon via its shaft. In the future, a similar integration in the X3 system could allow checking for acute PV isolation in all patients without using an additional catheter.

6 STUDY LIMITATIONS

The present study has several limitations. First, it is observational, with no control group. We conducted a monocentric investigation; subsequently, the number of enrolled patients was low. We could not adequately assess the total subclinical AF burden at follow-up since only a

small number of our patients carried an implantable cardiac device. Finally the follow-up duration is incomplete at 24 months for patients who underwent ablation at the end of 2022 due to the current closure of the study, potentially influencing rates of AF recurrence and MACCEs.

7 CONCLUSIONS

In our monocentric experience, the novel X3 ELBS proved effective and safe, with a satisfactory long-term AF recurrence rate.

The Rapid Mode feature showed good applicability and impacted both procedural and clinical outcome in terms of total procedural and fluoroscopy time and AF late recurrences.

Larger, multicentric studies, with a control group and longer follow-up, could strengthen our observations and prove the RM feature's role in improving clinical outcomes.

Large, multicenter studies, including a control group and longer follow-up, could strengthen our findings and demonstrate the role of the RM feature in enhancing clinical outcomes.

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