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Hybrid Therapy for Atrial Fibrillation: Where the Knife Meets the Catheter

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Abstract

During the past decades there has been a consistent evolution of both surgical and catheter-based techniques for the treatment of stand-alone atrial fibrillation, as alternatives or in combination with anti-arrhythmic drugs. Transcatheter ablation has significantly improved outcomes, despite often requiring multiple procedures and with limited success rates especially in presence of persistent atrial fibrillation. Surgical procedures have dramatically evolved from the original cut-and-sew Maze operation, allowing nowadays for closed-chest epicardial ablations on the beating heart.

Recently, the concept of a close collaboration between the cardiac surgeon and the electrophysiologist has emerged as an intriguing option in order to overcome the drawbacks and suboptimal results of both techniques; therefore, the hybrid approach has been proposed as a potentially more successful strategy, allowing for a patient-tailored therapeutical approach.

we reviewed the recent advancements either from the transcatheter and surgical standpoint, with a peculiar focus on the current option to merge both techniques along with an up-to-date review of the preliminary clinical experiences with the hybrid, surgical-transcatheter treatment of stand-alone atrial fibrillation.

Introduction

The pharmacological approach with Anti Arrhythmic Drugs (AADs) has not achieved optimal results in the long-term maintenance of sinus rhythm in patients with stand-alone Atrial Fibrillation :[1-5] often, the majority of patients with AADs will evolve from paroxysmal to a continuous form of atrial fibrillation.[6] Therefore, given the aforementioned limitations of the medical therapy, during the past decades there has been an upsurge in terms of surgical and catheter-based techniques as an alternative or in combination with pharmacological strategies.[7, 8]

Both surgery and catheter ablation following parallel and independent tracks in the past, recently there has been an increasing interest in the possibility to merge the advantages of either approaches, in an hybrid approach, which could be associated with an increased rate of success while reducing the drawbacks and complications of either techniques. The aim of current review is therefore to address the issue of a hybrid approach combining surgical and transcatheter ablation for the treatment of stand-alone atrial fibrillation.

Key Words:
Lone Atrial Fibrillation, Hybrid Approach, Trans-catheter Ablation, Surgical Ablation, Minimally Invasive Surgery

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Surgical AF Treatment

The original Cox Maze Procedure (CMP-I) consisted of a cut-and-sew approach, with multiple biatrial incisions being performed in order to interrupt potential macro reentrant circuit occurring in both atria.[9] Although extremely effective, this technique was associated with significant chronotropic dysfunction and conduction delays between the right and left atrium: [10,11] these issues led to a progressive evolution of the cut and sew maze technique into the Cox Maze Procedure III (CMP-III).[11, 12] In particular, from 1992 to 2002, 112 consecutive patients underwent a stand-alone cut-and-sew CMP-III, with a median sternotomy and cardiopulmonary bypass. The median duration of preoperative AF was 7.0 years (ranging from 3.2 to 13.0 years), with 56% paroxysmal (63 patients) and 44% persistent and long-standing persistent AF (49 patients). Of the patients, 95% were in the New York Heart Association class

I or III and 2% had experienced a previous catheter ablation failure. The perioperative events consited of 2% of 30-day mortality, 8% of pacemaker implantation and 34 % of early atrial tachicardias. The median follow-up was 5.9 years and the freedom from symptomatic AF was 96% (95% CI, 86%–98%) at last follow-up, with a freedom from AF off antiarrhythmic drugs of 83% (95% CI, 68%–88%). There was no significant difference in late success rates for patients with paroxysmal AF (96%) compared with those with persistent or long-standing persistent AF (93%, P0.556). Follow-up at 6 months was conducted by office visits and included a medical history, a physical examination and a 24-hour Holter monitoring, while the long-term follow-up consisted of a retrospective cross-sectional analysis performed in 2001. This included a mailed questionnaire or telephone interview and contact to either the cardiologist or the primary care physician to evaluate recurrence of AF. So, freedom from AF was mainly defined by the absence of symptoms (very few of these patients underwent electrocardiographic or Holter Monitoring at 12 or 24 months), with the exception of patients with pacemakers whose rhythms were costantly monitored by the devices.. Despite the impressive and probably quite overstimated results in terms of sinus rhythm restoration (up to 96%), the widespread use of this technique has been mainly hampered by the technical complexity, the use of cardiopulmonary bypass, the risk of bleeding, the high rate of pacemaker dependence (up to 15%) [13] as well as the poor aesthetic results of surgical scars especially in younger patients (since a full sternotomy was required): for these reasons, the Cox-Maze III has been barely adopted as a stand-alone therapy, instead it was mostly utilized during a concomitant mitral valve surgical procedure.[14]

The introduction of various energy sources (Radiofrequency, Microwave, Cryoenergy, High-intensity focused ultrasound) as alternatives to the original "cut-and-sew" technique significantly expanded the application of the modified Maze operation .[15] The different types of energy sources differ mainly in the method by which they transfer energy to the tissue and how effectively such energy can potentially create a transmural lesion. To date, only radiofrequency (RF) and cryoenergy have proven to be safe and effective:[16,17,18,19]therefore, the original Cox Maze III has further been developed into the Cox Maze IV (CMP-IV), first introduced in 2002,[20] which replaced most of cut-and-sew incisions with linear lesions created with bipolar RF and cryoenergy. The Maze IV was associated with a significantly reduced incidence of major perioperative complications while offering a freedom from AF comparable to the Cox Maze III (90% for CMP-IV vs. 96% for CMP-III and 82% for CMP-IV vs. 83% for CMP-III off AADs);[18,21] nonetheless, sternotomy and cardiopulmonary bypass were still required. The above mentioned success rates about CMP-IV come from a single-center experience, that enrolled, from 2002 to 2010, 100 consecutive patients with symptomatic AF, in whom AADs and/or catheter ablation had failed . The median duration of preoperative AF was 6.0 years (ranging from 2.2 to 10.0 years), with 31% paroxysmal (31 patients) and 69% persistent and long-standing persistent AF (69 patients). Follow-up was conducted by office visits at 3, 6, and 12 months and annually thereafter. At each visit, a medical history, physical examination, and ECG were obtained. Since 2006, when new follow-up guidelines were established, 24-hour Holter monitoring or pacemaker interrogation was performed in 95% (62/65) of patients. Success was defined as the absence of any episode of atrial arrhythmias, including AF, atrial flutter, or atrial tachycardia, that lasted more than 30 seconds. Patients were only considered to be a success if they were both free of AF and free of antiarrhythmic drugs (class I or III) after 3 months postoperatively (blanking period). Any patient requiring an interventional procedure after the blanking period was deemed a permanent failure. The Cryo CMP-IV yielded an 88.5% rate of freedom from AF at 12 months, as best result.[22] Cryoablation preserves the architectural integrity of tissue collagen and it is an excellent energy source for ablation given its safety, efficacy and ease of use, given the low risk of bleeding, perforation, or collateral damage and lack of endocardial thrombus formation[14, 21,23] Still, the CryoMaze procedure required as well an arrested heart and cardiopulmonary bypass, since the "heat sink" effect of circulating intracavitary blood can "wash" the cold energy created by the cryoprobe thereby hampering an effective ice formation at the level of the endocardial tissue, especially on the full beating heart .[21,23]

Instead, an off-pump, beating heart surgical AF approach has gained growing interest during the past decade: consequently, novel approaches have been investigated and developed in order to perform an effective isolation of the pulmonary veins (PVs) on the beating heart in patients with lone AF.[24] Refinements in surgical techniques and technologies have nowadays allowed for a significantly less invasive, off pump AF ablation either via closed-chest, thoracoscopic or minithoracotomy approaches.[25,26] The minimally invasive surgical (MIS) approach using video-assisted PV epicardial ablation was first described in 2003 by Saltman.[27] Saltman et al. reported a case of pulmonary vein isolation (PVI) in which they devised and experimented with a bilateral completely thoracoscopic epicardial approach in order to deliver a wide isolation of all four PVs and the posterior aspect of the left atrium ("box" lesion set):[27] this preliminary experience proved that totally endoscopic PVI was a safe and effective procedure and paved the way for further technical refinements.

To date, bipolar RF is the most commonly adopted energy source for bilateral MIS as it has been associated with more effective linear lesions on the beating heart .[15] however, most the use of bipolar RF in a minimally invasive fashion still required a double-sided approach to the chest in order to prevent the risk of unproper positioning of the catheter. The percentage of success with this technique ranged from 42 to 91% in published papers (excluding case reports) at follow-up ranging from 6 and 40 months.[26, 28]

Nevertheless, in an effort to further reduce the invasiveness of closed-chest AF surgery, a monolateral approach for thoracoscopic arrhythmia surgery has been described in 2005 by our group at the University of Brescia:[29] such novel approach meets the criteria of a true minimal invasive approach, since it avoids chest opening (only 3 mini-incisions on the right chest), the use of cardiopulmonary bypass while still allowing for a continuous linear lesion (box lesion set) being performed. The monolateral approach can significantly lessen the potential complication rates (such as bleeding), the degree of post-operative pain and allow for faster recovery. The right monolateral approach implies a monopolar RF device being utilized. In an animal lesion study, epicardial radiofrequency ablation with common unipolar irrigated probe (i.e. Cobra Cooled surgical probe - Boston Scientific Corporation, San Jose, CA) has demonstrated transmural coagulation only in 69% of the total specimens and it decreased according to the increase of wall thickness, especially over 3 mm. Transmural coagulation was seen in 64% of the specimens after RF

of less than 30 seconds, and 86% after ablation of ≥60 seconds.[29] Faced with these results, further technical improvements associated with new instruments were indispensable to improve transmurality of the epicardial RFablation procedures on a beating heart.

Thus a new type of probe have been designed: the Cobra Adhere XL (Estech, USA) is a multiple-electrode, temperature-controlled, monopolar radiofrequency probe with a vacuum-assisted stabilization system that improves the contact with atrial tissue and optimizes the power penetration in the myocardium, if compared to other unipolar RF devices. The Cobra Adhere XL probe can be used specifically on the beating heart, performing a single epicardial lesion encircling all four pulmonary veins, in a plane parallel to the mitral valve annulus.[30]

To give an example, in a study conducted by our group,[31] twenty-four consecutive patients with either persistent (three patients, 12.5%) or long-standing persistent (21 patients, 87.5%) lone AF were prospectively enrolled. After a mini invasive surgical ablation with the Cobra Adhere XL, the exit block was documented in all cases, whereas the entrance block was achieved in 87.5%(21 of 24 patients). No intensive care unit stay was required, and no complications occurred postoperatively; hospital mortality was 0%. At a mean interval of 33 ± 2 days after surgery, an EP study was performed: bidirectional block was confirmed in 79.1%(19 of 24 patients), whereas gaps at the level of the box lesion were observed in 20.8% of the patients (5 of 24 patients). Albeit overall good results in term of safety and efficacy were obtained, the potential to create complete and continuous transmural lesions with bidirectional conduction block indeed is suboptimal, when delivered epicardially on the beating heart. The reason for this is due to poor visibility and difficulty of contact where the probe curves, especially at the level of the left inferior pulmonary vein.[25, 31]

In animal lesion studies (on porcine hearts), transmurality was achieved at 137/141 evaluation sites, which corresponds to full thickness lesion achieved at 97.2% of the locations chosen; in particular transmurality was observed at 100% of sites at which tissue wall thickness was less than 6mm.[33]

The COBRA Fusion ablation system received FDA clearance in April, CE mark in May and has been in extensive clinical evaluations in the US and EU since then and early clinical results are now available from the UNC Center for Heart and Vascular Care (North Carolina, USA).[33] Upon completion of the surgical epicardial ablation via right thoracoscopy, patients were transferred to the electrophysiology laboratory and bidirectional block (in and out the posterior left atrium) was found in each of them. The posterior wall and pulmonary veins showed no electrical activity whereas the anterior wall and left atrial appendage were electrically active.[33] About this article, we must consider that the number of patients ablated has not been reported and also the maintenance of transmurality and the absence of reconnections and gaps remain to be evaluated over time, in the long term. The ATTAC-AF is a multicenter trial, designed demonstrate the safety and efficacy of the Estech COBRA Surgical in patients with irregular heart beats who are undergoing heart surgery. The enrollment of cardiac surgery patients who have a history of non-paroxysmal AF has begun in September 2012. During the cardiac surgical procedure for treatment of coronary or valve disease, patients will also be treated for their atrial fibrillation disease with Estech's COBRA® Ablation probes. Patients enrolled in the ATTAC-AF trial will be followed for a minimum of one year to determine the success rate for preventing recurrence of AF and to assess the patient's quality of life following the ablation procedure. [34]

Nowadays none of the existing surgical ablation technologies can guarantee complete transmurality at 100%. Although minimally invasive epicardial PVI has been shown to be safe and effective, it is limited by the restricted lesions set that can be performed, if compared to the full Cox-Maze procedure, so that a completed isolation is difficult to achieve. Even the use of alternative sources of energy in a beating heart setting can reduce the effectiveness of the ablation itself due to blood cooling, epicardial fat and poor catheter–tissue contact, thus resulting in 'late' recovery of conduction.

Trans-Catheter Ablation

Following the introduction of more sophisticated tools and an improved understanding of the electrophysiologic (EP) mechanisms responsible for the initiation and perpetuation of AF, Haisseguerre and Swartz were the first to propose the trans-catheter ablation of atrial fibrillation.[35,36] The discovery of trigger points for AF (mainly for paroxysmal AF) located inside the pulmonary veins [37] has turned attention to this anatomic region inside the left atrium and led to the development of many types of transcatheter ablation techniques (focal, linear and circumferential lesions).[38,39,40] They all mainly aim at the complete anatomical disconnection of the common atrial myocardium from the myocardial fibers located in the wall of the pulmonary veins and mixed to the proper tissues of these vessels. At the beginning the electrophysiologists (EPs) began performing focal lesions, in particular the focal ablation of AF had been proposed by the Bordeaux's group, which, as already mentioned, was based on the observation that in 90% of cases the bouts of AF were triggered by ectopic foci located in the PVs.[37,41] About the site of origin of the AF triggers, noteworthy is the more recent study by Cuculich et al.,[42] testing a noninvasive way (electrocardiographic imaging - ECGI) to map epicardial activation patterns of AF on both atria continuosly, in a patient-specific manner. They demonstrated the coexistence of a variety of mechanisms and variable complexity among patients with diverse clinical type of atrial fibrillation and that AF is characterized by a dynamically changing activation sequence. The most common patterns of AF were multiple wavelets (92%), with pulmonary vein (69%) and non–pulmonary vein (62%) focal sites, while rotor activity was seen rarely (15%).[42] The observation that in the former study 90% of AF bouts were triggered by ectopic foci located in the pulmonary veins, while in the latter only the 69% comes from the PVs seems to be consistent with the finding of many dynamic mechanisms that coexist and randomly combine themselves into an even greater number of activation patterns, specific for each patient.

Anyhow, initially attempts were made to target exclusively the ectopic foci in a pinpoint fashion.[43] The technique, however, was not only extremely laborious but also often ineffective, given the frequent presence of multiple foci in the PVs and multiple wavelets in other regions of the atria;[44] moreover,pinpoint lesions also lacked of continuity and transmurality.

Therefore, the introduction of refined, ad-hoc catheters, provided EPs the possibility to reproduce the anatomical concept widely adopted in the cardiac surgery approach, i.e. performing the complete circumferential isolation of one or more PVs from the endocardial side, [45, 46] along with extended linear lesions to the wall of the atria .[47, 48] Most common sites of linear ablation lesions include a "roof

line" connecting the lesions encircling the left and/or right PVs, a "mitral isthmus" line connecting the mitral valve and the lesion encircling the left PVs at the level of the left inferior PV, and an anterior linear lesion connecting either the "roof line" or the left or right circumferential lesion to the mitral annulus anteriorly.

Transvenous PVI has become the cornerstone of catheter ablation for AF and is currently the therapy of first choice if patients affected by paroxysmal AF warrant rhythm control and fail antiarrhythmic drugs.[49] PVI is a proper therapeutical strategy in patients with paroxysmal short-lasting episodes of AF and is reported to be effective in 60–89% of them after 12 months.[50,51,52] The 89% was obtained in the A4 study by Jais et al.[52] and is meant without AADs and without redo ablations after the blanking period. Catheter ablation of AF was performed in 53 patients with paroxysmal AF, all patients were systematically followed up for 1 year after the first day of randomization (day 0) in each center, with a 12-lead ECG, Short Form-36 quality-of-life questionnaire, AF symptom frequency and severity checklist, and 24-hour Holter recording at baseline and 3, 6, and 12 months.[52] The primary end point of the study was the proportion of patients free of recurrent AF between months 3 and 12, therefore a 90-day treatment stabilization period after randomization (blanking period) allowed up to 3 ablation procedures (patients underwent a mean of 1.8 procedures within the blanking period). Treatment failure was considered a recurrent AF lasting more than 3 minutes, occurring after the stabilization period (episodes were qualified as AF were documented by ECG or reported by the patient as AF).[52]

To note the findings of Weerasooriya et al.[53] about the long term efficacy of catheter ablation for paroxysmal AF: the percentage of patients in sinus rhythm falls to 37 and 29% respectively 2 and 5 years after a single catheter ablation. Only when percutaneous ablation is repeated, rates of maintenance of sinus rhythm rise to 87%, 81% and 63% at 1, 2 and 5 years of follow up.[53]

Conversely, the long-term efficacy of the procedure is not satisfactory for patients with persistent and long-standing persistent AF (LSP AF). The success rates after a single ablation procedure, limited to the PVs, vary from 22% to 60% at one year of follow up in different series[54, 55, 56]

Pathogenetic mechanisms and atrial anatomic substrates are different in paroxysmal and persistent AF,[6,57] therefore leading to the observation that PVI alone is not enough when in LSP AF atrial remodelling occurs and sustains AF regardless of triggers firing within the PVs.[58]

Therefore, a more extensive lesion set beyond PVI, which could include targets along the LA remodelled substrate, is essential in persistent and LSP AF,[54] but more extensive transcatheter approaches can lead to time consuming ablations with a consistent degree of complexity, and finally leading to major X-ray exposure and increasing the risk of procedural complications associated with AF ablation.[49, 59]

Hybrid Ablation

The concept of a close collaboration between the cardiac surgeon and the electrophysiologist in order to overcome the drawbacks and suboptimal results of both catheter ablation and surgical AF treatment is intriguing and has been proposed in recent years as a potentially more successful strategy[14, 60] (Table 1). As this approach is still in its early developmental stages, there is no established consensus with respect to the patients that could benefit most: [61] in general, we believe it is of utmost importance to distinguish among patients with paroxysmal and persistent AF. The former may benefit from an EP approach in the first instance, and following at least a couple of failed transcatheter attempts, a surgical ablation may be considered; instead, in the latter instance, a surgical approach may considered first then followed by additional transcatheter touch-up.

The rationale of such strategy is based on the consideration that in presence of paroxysmal AF the majority of triggers are located within the four PVs while in presence of persistent AF surgical procedure in first instance allows for an extensive isolation of the PV and the posterior aspect of the left atrium, thereby excluding not only the ectopic foci within the PVs but also targeting the macro-reentrant circuits and the fragmented potentials usually located within this area. Moreover, from the EP standpoint, it is recommended to reduce RF energy delivery when treating the posterior left atrium as to minimize the potential collateral damage to the esophagus: such risk can be mitigated by the surgical box lesion which could also overcome such drawback of the transcatheter ablation. Conversely, the EP procedure, as a second step, can identify and treat any potential gap in the surgical ablation (endocardial "touch-up") and and create additional ablation lines, if required, in a patient-tailored fashion.[62] Furthermore, the risk of stroke and air embolism during such transcatheter ablations could be potentially minimized by reducing the total number of endocardial ablations and the overall time spent within the left atrium;[63] finally, there is also a reduction in fluoroscopy and overall procedural time.[64]

From the surgical standpoint, the collaboration with the electrophysiologists is extremely important especially in terms of intraoperative validation of the surgical ablation,[64,65] since the most reliable end point for an effective PVI is the confirmation of bidirectional conduction block through the box lesion.[59] The validation of entrance and exit block has consistently improved the quality of epicardial monopolar RF ablation, because the intraoperative EP assessment allows for a tailored delivery of RF applications, until such end-points are met, thereby reproducing the EP criteria for success also in the surgical setting.[64, 65, 66, 67]

When a hybrid approach is utilized, it can be performed as either a concomitant or a sequential procedure. In most instances[66, 68, 69, 70, 71] a single step (concomitant) procedure has been reported, advocating the potential advantage of a single hospitalization. However, the possibility to delay the EP assessment from the surgical procedure at least by 1 month[64,31] allows for important insights: first, the "delay" in the completion of the hybrid procedure allows for further evolution and stabilization of the ablative lesions (reabsorption of periprocedural edema and reduced atrial post operative irritation) which usually occurs within a few weeks, as to avoid false positive and negative results. The false positives consist in early inducible postoperative atrial arrhythmias, typically occurring within the blanking period and which could not necessary be due to the presence of gaps in the box lesion.[64, 31] Then false negatives may be minimized as acute demonstration of a bidirectional block could only be transient and not confirmed by delayed testing at one month after surgery.[64,71] Finally, additional potential drawbacks of the single-step, concomitant approach are patients' heparinization following the trans-septal puncture which could increase the risk of epicardial bleeding, the need of a hybrid operating theatre and the concomitant

Table 1: Clinical Studies Testing The Hybrid Approach

Study	Year Pub	Arms	N° Pts	AF Type	Surgical procedure	Lesion set	Intra-op Bidirect Block	Post-op Complic	Trans Catheter procedure	Gaps	Endocardial Additional lesions	Rhythm Monitoring	Follow up Additional Trans cath	Total Follow Up time	Success Definition	Follow Up Endpoints	Follow Up Results		
																	Parox	pers	LSP
Munere-tto et al. [64]	2012	Hybrid Abla-tion	36	Lone AF: Persist 22% LSP1 78%	Right Monolat-eral Thora-coscopic Epicardial approach Monopo-lar RF Cobra Adhere XL (Estech)	Box Lesion encyr-cling the 4 PVs2	100%	89%	0%	SEQUEN-TIAL 30-45 days after 3D Mapping CARTO AVAIL electro-physiology catheter RF ablator catheter	17%	Cavo Tricus-pid Isthmus line 58% CFAEs 17% Additional Pvs antral line 39% Mitral Isth-mus line 0% Overall pts treated: 61%	Continuous monitoring rhythm de-vice (Reveal XT) Remote Monitoring Carelink Network: monthly transmis-sion ECGs and cardiologist examina-tions at 1 – 3 – 6 – 9 – 12 – 18 – 24 – 30 months	NA	30 months (mean FU time)	Normal Sinus Rhythm - Absence of AF lasting > 5 min and monthly AF burden <0,5%	30-month success rate off AADs4 30-month success rate wtih AADs 30-month AADs preva-lence 30-month OACs5 prevalence	Overall: 78% Overall: 92% verall: 22% Overall: 11%		
Munere-tto et al. [31]	2012	Hybrid Abla-tion	24	Lone AF: Persist 12,5% LSP 87,5%	Right Monolat-eral Thora-coscopic Epicardial Approach Monopo-lar RF Cobra Adhere XL (Estech)	Box Lesion encyr-cling the 4 PVs	100%	87,5%	0%	SEQUEN-TIAL 30-45 days after 3D Mapping CARTO AVAIL electro-physiology catheter RF ablator catheter	20,8%	Cavo Tricus-pid Isthmus line 62% CFAEs 14% Additional Pvs antral line 38% Mitral Isth-mus line 0% Overall pts treated: 62,5%	Continuous monitoring rhythm de-vice (Reveal XT) Remote Monitoring Carelink Network: monthly transmis-sion ECGs and cardiologist examina-tions at 1 – 3 – 6 – 9 – 12 – 18 – 24 – 30 months	0	28 months (mean FU time)	Normal Sinus Rhythm - Absence of AF lasting > 5 min and monthly AF burden <0,5	28-month success rate off AADs 28-month success rate wtih AADs 28-month AADs preva-lence 28-month OACs preva-lence	Overall: 75% Overall: 87,5% Overall: 25% Overall: 9,5%		

La Meir et al. [68]	2012	Hybrid Ablation	19	Lone AF Parox: 26% Persist: 21% LSP: 53%	Right Monolateral Thoracoscopic Epicardial Approach Monopolar RF Cobra Adhere	Box Lesion encircling the 4 PV Ganglionated plexi ablation	100% 100%	0%	0%	CONCOMITANT Lasso mapping catheter; RF/ThermoCool catheter	89,5%	Mitral Isthmus line 15,7% Cavo Tricuspid Isthmus line 10,5%	7-day Holter Monitoring at 3 – 6 – 12 months ECGs and cardiologist examinations during symptoms	0	12 months	Normal Sinus Rhythm - Absence of AF, Afl, or AT lasting > 30 sec	12-month success rate in pt off AADs 12-month success in pt with AADs 12-month AF prevalence 12-month AADs prevalence 12-month OACs prevalence	Overall: 37% Overall: 63% 9% 15% 22% 15% 26% 38% 19% 35% 53%		
Pison et al. [69]	2012	Hybrid Ablation	26	Symptomatic Lone AF: Parox 58% Persist 44%	Bilateral/Right sided thoracoscopic epicardial approach6 Bipolar RF Isolator Pen and Coolrail (Atricure)	Antral PVI7 as pair Additional Left Atrial ablation lines Left Atrial Appendage Removal	100% 85%	77%	1 Pleural effusion (4%) 1 Chest pain (4%)	CONCOMITANT Lasso mapping catheter; RF/ThermoCool catheter Cryoenergy/ Cryo balloon catheter6	23%	Mitral Isthmus line 11,5% Cavo Tricuspid Isthmus line 8%	7-day or 24 h Holter Monitoring at 3 – 6 – 9 – 12 months	2	12 months	Normal Sinus Rhythm - Absence of AF, Afl, or AT lasting > 30 sec	12-month single procedure success rate off AADs 12-month overall success rate 12-month AADs prevalence 12-month OACs prevalence	79% 90% - Overall: 83% 93% 90% - Overall: 8,5% Overall: 21%		
Krul et al. [66]	2011	Thoracoscopic PVI + Electrophysiological confirmation of PVI	31	Symptomatic Lone AF: Parox 51,6% Persist 42% LSP 6,4%	Bilateral thoracoscopic epicardial approach Bipolar RF Isolator Transpolar Clamp and Cooltip ablation Pen (Atricure)	Antral PVI as pair Roof LA 8 line Inferior LA line Gangionated plexi ablation Left Atrial Appendage Removal	100% 39% 26% 97% 94%	100%	4	INTRA PROCEDURAL electrophysiological confirmation of PVI Standard decapolar electrophysiology catheter (C. R. Bard Inc, Murray Hill, NJ)	-	-	7-day Holter Monitoring at 3 – 6 – 9 – 12 months ECGs and cardiologist examinations during symptoms	0	12 monyhs	Normal Sinus Rhythm - Absence of AF, Afl, or AT lasting > 30 sec	12-month single procedure success rate off AADs 12-month OACs prevalence	92% 78% 100% Overall: 86% Overall: 48%		

Mahapatra et al. [70]	2011	Hybrid Ablation	15	Lone AF: Persist 60% LSP 40%	Bilateral thoracoscopic epicardial approach Bipolar RF Synergy Clamp and CoolRail (Atricure)	Atral PVI as pair Roof LA line	100%	N.R.	0	SEQUENTIAL 4 days after. 3D Mapping Nav X Intracardiac Echocardiography RF Irrigated tip catheter (Biosense) or 5 mm tip catheter (Boston)	53%	Superior Vena Cava isolation Cavo Tricuspid Isthmus line 30% 9 Mitral	7-day Holter Monitoring at 3 – 6 – 12 months 24-hour Holter Monitoring at 9 – 18 – 24 months ECGs and cardiologist examinations at 1 – 3 – 6 – 9 – 12 – 18 – 24 months	0	20 months	Normal Sinus Rhythm - Absence of AF, Afl, or AT lasting > 30 sec		Hybrid	Cath Alone	P val
						Legament of Marshal Ablation Left Atrial Appendage exclusion	100% 93%					Isthmus and Coronary Sinus line 100% + 20% CFAEs 13%				20-month success rate with AADs	93%	57%	0,01
		Catheter Alone Ablation	30	Lone AF: Persist 80% LSP 20%	-	-	-	-	1 Tamponade 2 Hematomas	-	PVs Antral Isolation 100% Roof line 100% Cavo Tricuspid Isthmus line 100% Mitral Isthmus line N.R.		3			20-month AADs prevalence	6,7%	36,7%	0,04

[1] Anti arrhythmic Drugs
[2] Oral Anti Coagulants
[3] In patients with severe chronic obstructive pulmonary disease,they performed thoracosopic epicardial isolation of the pulmonary veins(Pvs) only on the right, and the left Pvs were isolated using a cryothermal enery balloon catheter endocardially
[4] Pulmonary veins Isolation
[5] Left Atrium
[6]All Ptients received a first CTI line and MI line.Those patients in whom atrial fibrillation or atrial flutter were induced,underwent additional CTI or MI line.

availability of two separate teams (surgeons and electrophysiologists) during an overall time-consuming procedure.[72]

The lack of extensive clinical data with this novel hybrid approach has required all patients to undergo an EP evaluation postoperatively (both with the concomitant and the sequential approach), as to gather further insights about the effectiveness of the procedure. From an overview of all recently reported series,[31,64,66,68-70,73] around 40% of patients did not require any additional touch up at the time of the EP evaluation and have undergone "de facto" unnecessary EP procedures, and therefore having been potentially overtreated.[64] This consideration further supports the sequential strategy rather than the concomitant one, since patients could be evaluated first in terms of rhythm outcomes for 1-2 months and then potentially scheduled to undergo a second step.

University of Brescia clinical experience

To date, we focused our clinical activity mostly on the hybrid approach of patients with persistent or long-standing persistent AF, as previously reported.[31,62,64]

Thirty-six consecutive patients meeting study re quirements were prospectively enrolled. Qualifying patients were symptomatic for persistent (8 patients, 22%) and long-standing persistent (28 patients, 78%) lone AF, refractory to anti arrhythmic drug therapy. In the study population, the mean left atrial dimension was 50.5 ± 8 mm, and the mean AF duration was 82.7 months (range of 7 - 240 months).[64] Additional data are summarized in Table 1.

As outlined above, the surgical ablation is performed first with a continuous lesion encircling "en bloc" the origin of all PVs and the posterior aspect of the left atrium being delivered ("box" lesion set). Immediately before the surgical procedure, a 6F decapolar electrode catheter (P-SUPRA CS; Webster, Diamond Bar, CA USA) is positioned in the coronary sinus.[31,64]

The chest trauma from the surgical approach is minimal since only three 1cm ports are utilized allowing for a full endoscopic procedure. The ablation device used[31,64] is a temperature controlled monopolar radiofrequency probe with suction adherence and internal cooling (Cobra Adhere XL; Estech, San Ramon, Calif). It is of utmost importance to deliver multiple ablations on the epicardial surface to achieve an effective isolation. Moreover, an extensive overlapping is performed at the level of the Waterston groove to ensure the closure of the box lesion.

A tetrapolar catheter (AVAIL electrophysiology catheter, Josephson Curve, type A; Webster, Diamond Bar, CA USA) is introduced trough a port and advanced on the epicardial surface:[31,64] in particular, once positioned within the box lesion (at the level of the right pulmonary veins and the posterior aspect of the left atrium) bidirectional conduction block is tested. First, the tetrapolar catheter is used as a pacing probe, with the catheter in the coronary sinus sensing potential captures (exit block). Then, the entrance block was assessed by pacing from the catheter in the coronary sinus and sensing with the tetrapolar catheter positioned on the posterior wall of the epicardium within the box.[31,64]

The choice to isolate the entire posterior left atrium is based upon previously reported evidence[71,72,74] that the creation of a box lesion instead of a single connecting lesion between the right and left pulmonary vein isolations resulted in a significant decrease in the incidence of early postoperative atrial tachyarrhythmia (up to 48% decrease). Another explanation for the decreased incidence of atrial arrhythmias in the box lesion group is the reduction of the critical mass available for the circulating wavelets responsible for sustaining AF, as reported by Byrd GD et al.[75] Finally, the box lesion yields another potential advantage compared to the single connecting lines since the latter could represent a source of macro reentrant circuits thereby promoting the onset early atrial tachyarrhythmias.[71]

Nevertheless, the posterior wall accounts for about a third of the total left atrial mass: therefore, it has been previously argued that a wide isolation of the posterior left atrium could negatively influence the left atrial function, promoting thrombus formation and finally increasing the risk of stroke[71] However, other studies (by means of magnetic resonance imaging), depicted that the posterior portion of the left atrium can provide a minor contribution to the overall atrial function, thereby the creation of box lesion set does not jeopardize the recovery of atrial function in presence of sinus rhythm restoration.[76]

A continuous rhythm monitoring device (REVEAL XT, Medtronic) is implanted in all patients at the end of surgical procedure,[64,71] thereby providing an unique set of data compared to other series which rely only on 24-hour Holter monitoring.[66,68-70,77-80]

About 1 month following the surgical procedure, all patients underwent an EP evaluation: gaps in the surgical box lesion were identified in 10-15% of cases, while in about 20% of patients complex fractionated atrial electrograms (CFAEs) were targeted; of note, no lesion to the mitral isthmus was performed. As previously outlined, in about 40% of cases no additional ablations were required, and we believe this approach could in fact allow for more tailored treatments for these patients, especially in order to avoid unnecessary overtreatment.[31,64]

Excellent durable clinical outcomes have been obtained, as confirmed by continuous rhythm monitoring: at a mean follow up of 30 months, 90% of patients are in sinus rhythm, 77% of whom off antiarrhythmic drugs and 88% free of warfarin.[31,64] We defined success as the absence of AF episodes with a duration longer than 5 minutes or an overall monthly burden of AF less than 0.5% of the time. The decision to use this cut off followed the observation that episodes, documented by the loop recorder as AF, lasting less than 5 minutes were actually episodes of repetitive supraventricular extrasystoles. Moreover, success rate was based upon a single EP procedure after the surgical ablation.

We are currently evaluating the outcomes of this novel approach also as principal investigators of multicenter, prospective trial, i.e. the Hybrid Staged Operating Room and Interventional Catheter Ablation for Atrial Fibrillation (HISTORIC-AF).[81]

Conclusions:

Over the recent years, the development of minimally invasive surgical techniques and the collaboration between the electrophysiologist and the cardiac surgeon allowed for the development of novel hybrid strategy which could merge both approaches, with the aim of increasing the safety and efficacy of each procedure. The hybrid approach combines the expertise of cardiac surgery with the electrophysiology skills, thereby improving outcomes while reducing complication rates. Larger data are warranted in order to conclusively validate this intriguing therapeutical option, which allows for a true tailored approach to stand-alone atrial fibrillation.

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