Historical Perspectives of the Evolution of Hybrid Atrial Fibrillation Ablation

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HYBRID AF ABLATION: PIONEERING A NEW FRONTIER

In the early 2000s, hybrid AF ablation emerged as a synergistic strategy to optimise the outcomes, combining minimally invasive surgical and catheter-based approaches to address complex AF cases. Hybrid AF ablation is a two-stage procedure that combines surgical epicardial ablation followed by catheter-based ablation of the endocardium.[1-3] Hybrid AF ablation also excludes the left atrial appendage (Figure 1.1). Although hybrid ablation can be performed via a thoracoscopic or subxiphoid approach, thoracoscopic access is necessary to complete epicardial PV and LOM isolation and LAA management. Currently, all methods utilise radiofrequency (RF) ablation, either uniparietal or biparietal, using unipolar or bipolar modality.[4, 5] However, biparietal bipolar RF ablation creates superior transmural and durable lesions compared to uniparietal

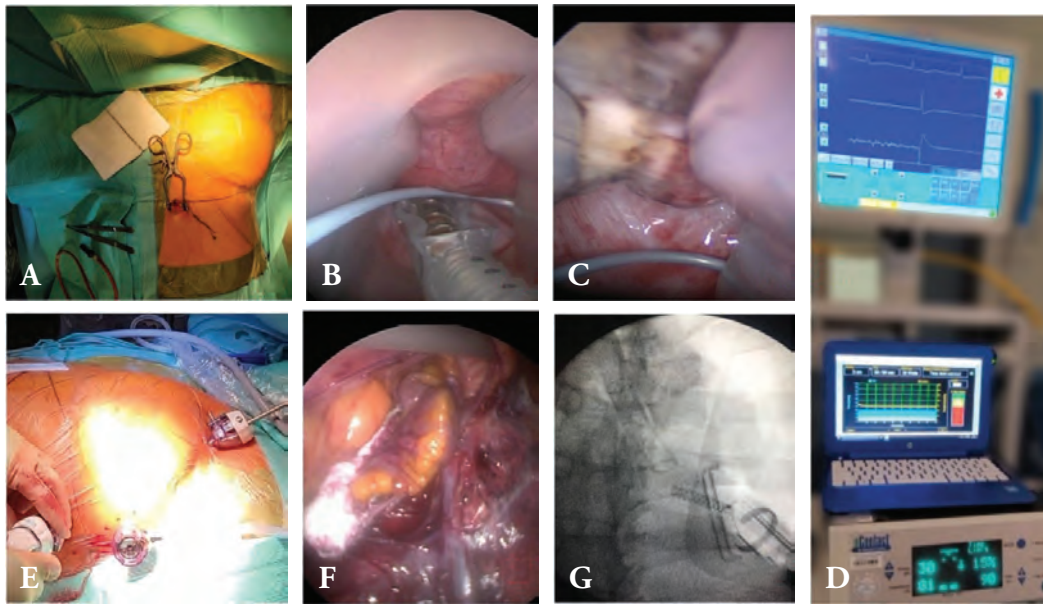

Figure 1.1 Convergent ablation with Left VATS Exclusion of the Left Atrial Appendage (LAA): A) subxiphoid incision for pericardioscope (5 mm) placement; B) ablation catheter (3 cm) to perform sequential superior and inferior transmural ablation across the back left atrium; C) ablation areas are macroscopically discoloured; D) monitoring electrograms during epicardial ablation; E) 3 left VATS ports: 5 mm port in the 2nd intercostal space (ICS), 5 mm port in the mid-axillary line at the 4th ICS, and 12 mm port in the 6th ICS in the posterior axillary); F) intraoperative deployment of AtriClip for exclusion of the base of the LA Appendage; G) real-time guidance with C-arm imaging to ensure precise application of the Atriclip device to the LAA.

bipolar and unipolar RF devices. In addition, devices utilise two energy sources: irrigated and non-irrigated RF energy, with irrigated energy enabling controlled heating by adding saline, whereas the latter solely heats affected tissue.[6-8]

COX MAZE SURGICAL ABLATION

Concomitant Surgical Ablation

Surgical ablation, particularly the Cox-maze procedure, has been associated with improved outcomes in persistent and longstanding persistent atrial fibrillation (AF).

The Cox-maze procedure was initially a cut-and-sew method involving a series of incisions and sutures with the aim of preventing macro re-entry circuits and creating a maze of transmural conduction blocks. In 1987, the first Cox maze procedure was performed, and subsequently, 32 patients underwent the original Cox-maze I procedure.[9, 10] Observations found that some patients could not generate appropriate sinus tachycardia during exercise and experienced occasional left atrial dysfunction, which led to modifications of the technique. The Cox-maze II involves a revised pattern of incisions than Cox-maze I, where incisions through the sinoatrial node were skipped, and the left atrial dome incision was moved posteriorly to permit better intra-atrial conduction. The Cox-maze II is a more complex surgery involving the superior vena cava (SVC) with pericardial patch repair of the incision into the SVC orifice. The Cox-maze II procedure was initially performed on 15 patients and the findings were then published.[10] Both Cox-maze I and II techniques resulted in delayed interatrial conduction. To address this problem, the Cox-maze III lesion pattern was developed, in which the left atrial dome lesion was moved further posteriorly, behind the SVC, allowing for easier exposure of the left atrium and simplifying the procedure.

The progression from the Cox-maze I to the Cox-maze III procedure provided better protection for the sinoatrial node and improved interatrial conduction compared to previous versions. A single centre experience of 198 patients and observed long-term outcomes for the Cox-maze III procedure were highly favourable, with an estimated 92% of patients who underwent the operation as a standalone procedure remained free from AF at 14 years, while 97% of those with a concomitant procedure were free from AF at ten years.[11] Despite its effectiveness, the Cox-maze III was not widely adopted due to its technical complexity and significant morbidity, particularly left atrial dysfunction and the need for implantation of a pacemaker. By 2002, the Cox-maze IV emerged, which utilises minimally invasive techniques and advanced technologies like radiofrequency and cryoablation, reducing operative time and complication rates, and improving patient outcomes.

Linear AF ablation using various energy sources was evaluated as an alternative to traditional cut-and-sew techniques for creating transmural lesions to block abnormal conduction. Ablation with RF and cryothermal energy devices presented a viable alternative method. Gaynor *et al.* reported the first prospective results of the Cox-maze IV procedure, which primarily replaced incisions with RF and cryothermal ablations, retaining only one left atrial and two right atrial incisions.[12] Early results indicated a high level of clinical success, with 91% of patients being free from atrial fibrillation at six months and no operative mortality. Comparisons between the cut-and-sew maze technique and the Cox-maze IV procedure, which used RF energy

augmented by cryoablation, showed similar long-term rhythm outcomes, mortality rates, and the need for pacemaker intervention.[13] However, using dedicated surgical ablation devices for Cox-maze IV significantly reduced the technical complexity and duration of the procedure, facilitating broader adoption. Experimental data from studies conducted on nine explanted human hearts that were rejected for transplantation found that 100% transmurality could be achieved by two applications of bipolar RF energy ablation.[14]

Since the initial report of Cox-maze IV procedures, an investigational device exemption clinical trial and a post-approval study have demonstrated better safety and efficacy of the procedures utilising bipolar RF and cryoablation techniques.[15-18] These studies also confirmed the long-term success of such ablation when performed alongside cardiac surgery procedures. A critical factor in the outcomes of surgical ablation is the lesion set used. The true Cox-maze IV lesion set (Figure 1.2) is biatrial, with left atrial lesions focused on isolating all four pulmonary vein (PV) antrums, connected by roof and floor lines, and including lesions to the left atrial appendage (LAA) and the mitral valve annulus.[15] Right atrial lesions involve the superior vena

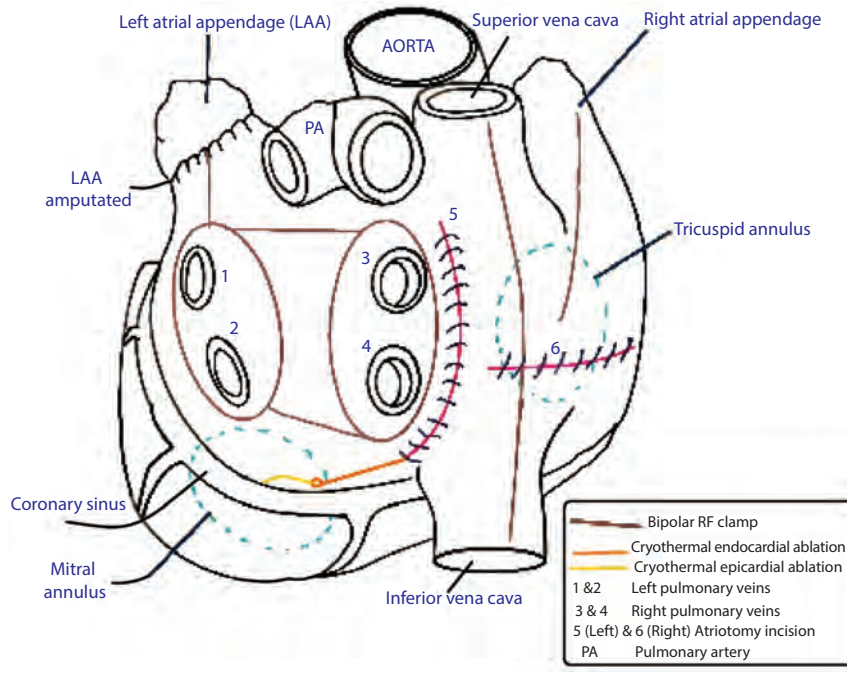

Figure 1.2 The Cox-maze IV lesion set[15] illustrates the position of the bipolar RF Clamp, surgical incision, and cryothermal (epicardial and endocardial) ablation.

cava (SVC), inferior vena cava (IVC), lines from the right atrial appendage to the free wall and tricuspid valve annulus, and a connection from the tricuspid valve annulus to the atriotomy. Further, the left atrial appendage is also managed, either by surgical excision or deploying closure devices like AtriClip, or excluded by applying suture ligations or surgical staplers, depending on the specific clinical scenario, such as the patient's anatomy, and the surgeon's preference. Most of the lesions are ablated using RF energy, with cryoablation applied to the tricuspid and mitral valves to prevent valvular stenosis. Ablation can instead be performed using only cryoablation, in which case the Cox-maze III lesion set is used. Several observational studies have compared cryothermal ablation with sole RF ablation and RF combined with cryoablation. Vural *et al.* reported identical findings in sinus rhythm maintenance at 12 months between ablation performed with cryothermal energy alone compared to RF energy alone.[19] However, these lesion sets created with cryothermal, or RF energy alone were incomplete Cox-maze IV lesion sets and lacked a coronary sinus lesion. Additionally, RF-only ablation has limitations in fully addressing the mitral and tricuspid annular pathways. Cryothermal energy is preferred as it appears to preserve the collagen matrix and avoid valvular stenosis.

Ad and coworkers compared the outcomes of concomitant cryothermal ablation with or without the addition of RF energy in patients undergoing Cox-maze III or IV procedures.[20] Despite antiarrhythmic drugs (AADs), sinus rhythm restoration was statistically similar between the cryothermal and RF plus cryoablation groups. However, sinus rhythm restoration was higher without AADs with cryothermal ablation at 6-, 36-, and 60 months post-procedure, with fewer cardioversions and catheter ablations during the 60-month follow-up. The embolic stroke rate was significantly lower with cryothermal-only ablation.

Given the efficacy, without increasing operative mortality or morbidity, concomitant surgical ablation with mitral valve surgeries has received a class 1A recommendation and a class 1B recommendation for non-mitral valve surgeries from the Society of Thoracic Surgeons (STS).[21] The European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS) guidelines assign a class 2a (level A) recommendation to concomitant surgical ablation with cardiac surgery.[2] Despite reported positive long-term outcomes and consensus recommendations, concomitant Cox-maze IV procedures are not universally performed in patients with preoperative atrial fibrillation (AF) undergoing planned cardiac surgery. An analysis of the STS database from 2011 to 2014 revealed that 48% of AF patients who underwent non-emergency cardiac operations also received concomitant AF ablation.[21] After propensity matching, patients who underwent surgical ablation experienced improved 30-day mortality and stroke rates. However, lower rates of concomitant surgical ablation have been observed

in non-mitral valve surgeries despite evidence indicating similar safety and effectiveness compared to concomitant ablation during mitral valve surgeries.[22, 23]

STANDALONE SURGICAL ABLATION

Not all patients with atrial fibrillation (AF) require primary cardiac surgery procedures such as coronary artery bypass grafting or valve repair. Studies have reported long-term outcomes of standalone Cox-maze procedures conducted via sternotomy or right thoracotomy, often supported by cardiopulmonary bypass.[24, 25] Ad *et al.* analysed the STS database spanning 2012 to 2016, noting a 7% increase in standalone AF ablation procedures during this period.[25] However, most standalone surgical ablation procedures recorded between 2014 and 2017 were performed without cardiopulmonary bypass. Off-pump surgical ablation, conducted on the beating heart, avoids atriotomies and endocardial lesions.

THORACOSCOPIC ABLATION

Various approaches to surgical ablation, including video-assisted and totally thoracoscopic methods, have been detailed elsewhere.[26, 27] Epicardial RF ablation focuses on the left atrium, targeting isolation of the pulmonary veins (PVs) and creating additional lesions such as roof and floor lines, the region of the ganglionated plexi, and closure of the left atrial appendage (LAA). The totally thoracoscopic Maze (TT Maze) procedure involves bilateral port access to isolate PVs, create a box lesion and trigonum line, and close the LAA.[28] On the other hand, the Wolf mini-maze procedure incorporates video-assisted thoracoscopic PV isolation, ganglionated plexi ablation, and LAA closure.[29] While these terms are sometimes used interchangeably, a key distinction lies in the mini-maze procedure employing 5-6 cm bilateral incisions for working ports, whereas the TT maze procedure uses smaller bilateral working ports.[29] Notably, the epicardial approaches do not typically include lesions at the tricuspid and mitral valve annulus, which are standard in the Cox-maze IV procedure using cryoablation.

Comparative effectiveness studies have demonstrated that epicardial surgical video-assisted thoracoscopic ablation is more effective than endocardial catheter ablation in randomised trials despite encountering higher procedural complications.[30] However, reported success rates generally favour complete on-pump Cox-maze IV surgical ablation over epicardial-only surgical ablation (93% *versus* 80% with antiarrhythmic agents and 87% *versus* 72% without antiarrhythmic agents).[31] This discrepancy may stem from

the limitations of epicardial-only lesions confined to the left atrium, making it challenging to achieve transmural ablation solely from the epicardial surface.

HYBRID EPICARDIAL–ENDOCARDIAL ABLATION STRATEGIES

Hybrid epicardial-endocardial ablation (HEEA) is a comprehensive, minimally invasive approach combining epicardial and endocardial ablation techniques.[3, 32-34] HEEA strategies have shown promise in managing complex arrhythmias like atrial fibrillation (AF) involving a multidisciplinary approach, utilising techniques like epicardial access via minimally invasive surgical procedures, thoracoscopic ablation, and endocardial mapping for precise transmural lesion creation.[5, 33-37] The hybrid approach has demonstrated safety, feasibility, and efficacy in treating patients with persistent forms of AF achieving stable sinus rhythm and reducing the burden of atrial arrhythmias. Hybrid ablation can target and eliminate the sources of erratic electrical signals from both the inside and outside of the heart and may improve the success rate of restoring and maintaining normal sinus rhythm.[32, 38-40]

Physicians can adapt a tailored and individualised treatment approach based on the patient's specific anatomy, underlying cardiac conditions, and previous treatment history, potentially optimising outcomes.[2, 34-36] Compared to traditional surgical techniques, this can lead to shorter hospital stays, faster recovery times, and reduced post-operative complications. Although initial studies have shown promising outcomes for hybrid ablation, long-term data on its efficacy and safety are still limited. Further, hybrid ablation may be associated with higher costs than traditional ablation techniques due to the need for specialised equipment, multidisciplinary care, and longer procedural times. Despite limitations, hybrid epicardial-endocardial ablation is a potentially effective treatment for challenging arrhythmias, especially drug-resistant, long-standing persistent AF, emphasising the importance of multidisciplinary collaboration for successful outcomes.[34, 37-41]

HYBRID THORACOSCOPIC ABLATION

Mahapatra *et al.*[42] first introduced the thoracoscopic hybrid ablation approach in 2011, utilising different RF devices to isolate the posterior wall and pulmonary veins (PVs) through epicardial lesions. Subsequent endocardial ablation is also performed to address any identified gaps via electrophysiological mapping. A recent randomised

controlled trial known as the CEASE-AF study[43] comparing hybrid thoracoscopic ablation to endocardial catheter ablation showed that the hybrid technique is more effective in preventing arrhythmia recurrence (71.6% *vs.* 39.2%, respectively) at 12 months follow-up. Additionally, a randomised trial, the HARTCAP-AF trial[44] indicated that 89% of patients who underwent hybrid ablation were free from atrial arrhythmias without antiarrhythmic drugs at 12 months compared to 41% with endocardial catheter ablation. Albeit uncommon, hybrid thoracoscopic ablation led to bleeding requiring blood transfusion, cardiac tamponade, conversion to median sternotomy, in-hospital mortality, implantation of a pacemaker, pneumothorax, phrenic nerve injury, and insignificant pulmonary vein stenosis. However, other complications such as bleeding requiring reoperation, groin haematoma requiring therapy, pulmonary vein stenosis requiring stenting, and transient ischaemic attack or stroke were statistically similar compared to catheter ablation.[40-46] Furthermore, safety considerations for thoracoscopic hybrid ablation include the potential for prolonged unilateral lung ventilation and common complications such as pleuropericarditis.[45]

HYBRID CONVERGENT ABLATION

Kiser *et al.*[47] first introduced the hybrid Convergent procedure that was published in 2010, in which cardiac surgeons performed endoscopic epicardial ablations and an electrophysiologist performed electroanatomical mapping and catheter ablation to finalise pulmonary vein isolation (PVI) and fill any gaps left by the epicardial lesions. Convergent hybrid ablation reduces surgical invasiveness and complexity by employing a vacuum-assisted, unipolar radiofrequency ablation device to create two rows of parallel lesions between the left and right pulmonary veins on the posterior wall of the LA. The CONVERGE (Convergence of Epicardial and Endocardial Ablation for the Treatment of Symptomatic Persistent AF) randomised trial by DeLurgio *et al.*[48] demonstrated that Convergent hybrid AF ablation provides better freedom of AF recurrence compared to catheter ablation without antiarrhythmic drugs (53.5% *vs.* 32.0%, respectively). However, the overall arrhythmia-free survival at one year appeared to be comparatively lower than the CEASE-AF and HARTCAP-AF trials.[43, 44]

While hybrid Convergent ablation offers several advantages, including high success rates and reduced risk of complications, it also presents challenges such as procedural complexity and cost considerations.[1, 2] Continued research and clinical experience will further define the role of hybrid Convergent AF ablation in managing AF and refine its indications and outcomes. One such aspect is single-stage Convergent AF ablation