SURGICAL TREATMENT OF ATRIAL FIBRILLATION – AN UPDATED REVIEW

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Abstract

The first Cox-Maze procedure was performed in 1987, demonstrating the feasibility of a nonpharmacological treatment for AF. Since then, surgery for AF has changed over time, in parallel with technological advances, eventually leading to the Cox-Maze III procedure. Replacement of surgical incisions with linear ablation lines has transformed a cumbersome procedure into one accessible to most surgeons, while keeping the same success of conventional Cox-Maze procedure.

On the other hand, new ablation technologies paved the way for the development of minimally invasive surgery, which may potentially extend the scope of surgery to patients who would otherwise be deemed unsuitable. Nonetheless, literature on minimally invasive surgery is still scarce and randomised clinical trials currently under way are expected to shed light on the some controversial issues.

Moreover, successful treatment of AF will probably rely on close collaboration between surgery and electrophysiology. Indeed, the hybrid procedure, though still is in its very beginning, seems to combine the best of catheter and surgical ablation. However, further studies are warranted to determine the effectiveness of this promising strategy, especially in patients with persistent and LSP AF.

Better understanding of AF pathophysiology as well as more accurate preoperative localisation of AF triggers will bring about the possibility of tailoring specific lesion sets and ablation modalities to individual patients. This in turn will increase restoration and maintenance of SR, which entails significant improvements in long-term outcomes.

Key words

Atrial fibrillation; cardiothoracic surgery; ablation; minimally invasive surgery; electrophysiology

Introduction

Atrial fibrillation (AF) is a rhythm disturbance defined by irregular, rapid electrical and mechanical activation of atria, which causes unsynchronized atrial contraction and promotes thrombus formation. Heart rate can be dangerously fast and is highly variable due to uneven impulse conduction to the ventricles.

Clinically, AF can be divided into paroxysmal, persistent, and permanent.[1] Paroxysmal AF is defined as AF that is self-terminating, usually within 48h. Although AF paroxysms may continue for up to 7 days, after 48 hours the likelihood of spontaneous conversion is low. Persistent AF is present when an episode of AF lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion 48h after onset. Longstanding persistent (LSP) is defined as AF that has lasted for 1 year or more but a rhythm control strategy is still considered. Permanent AF exists when the arrhythmia is accepted by both the patient and physician, when cardioversion has failed or has been deemed inappropriate and thus rhythm control is no longer pursued. It is important to stress that the decision to label AF as permanent represents a therapeutic attitude rather than a pathophysiological entity. Indeed, it derives from a joint decision by patient and physician to cease further efforts to restore normal rhythmic activity at a certain moment, but it is not irreversible, which means that AF can be reclassified in case previous conditions change[1]. On the other hand, it is not rare for patients to present with episodes that fall into more than one of the aforementioned categories, in which case it is recommended to take into account the most frequent pattern of AF over the last 6 months before ablation.[1] Any of AF types can be asymptomatic, if diagnosed only by an accidental ECG or rhythm strip.

AF is the most common sustained cardiac rhythm disorder, and is increasing in both prevalence and incidence. Ageing of population and improved survival from acute heart diseases are fostering the health-care burden related to AF.[2] The lifetime risk for development of AF is about 25% for men and women aged over 40, remaining around 16% in the absence of concurrent cardiovascular disease.[3, 4]

The presence of AF independently increases morbidity and mortality due to stroke and thromboembolism, congestive heart failure (CHF), and impaired quality of life.[1, 5]

AF is often associated with a number of cardiac and non-cardiac risk factors including ischaemic heart disease, CHF, valvular heart disease, hypertension, diabetes, alcohol abuse, thyroid disorders and pulmonary disease.[6] Indeed, data from the Atherosclerosis Risk in Communities (ARIC) study showed that 56.5% of new-onset AF could be attributed to common cardiovascular risk factors, like hypertension, obesity, diabetes mellitus, and smoking.[7] Moreover, occurrence of AF depends on age, race, and gender, with prevalence increasing from only 0.1% before 55 years old to 9% after 80 years old.[2, 8]

AF is present in 3–6% of acute medical admissions, most commonly in association with coronary artery disease and CHF.[1] AF is often a postoperative complication, especially after cardiothoracic surgery[9], but it can also be isolated (lone AF), which is essentially a diagnosis of exclusion.[1]

The mechanisms underlying development of AF are heretofore only partially characterised and multiple factors have been put forward, such as activation of renin–angiotensin–aldosterone system, haemodynamic overload, inflammation and oxidative stress, structural and electrophysiological remodelling in atria, focal triggers, and atrial fibrosis and/or dilatation promoting re-entry.[10] In addition, the progression from paroxysmal to persistent AF, as well as, the factors responsible for the individual response to treatment are even further from being completely understood. In keeping with this, pharmaceutical armamentarium currently available aims at reducing recurrences, controlling symptoms and minimising thromboembolic risk. Even though medical management is indicated as first-line treatment[11], the advantage of rhythm versus rate control remains hotly debated[11] and efficacy and safety of anti-arrhythmic drugs (AAD) is a matter of concern.[12] In fact, most patients need a combination of AAD, paying the price of suffering more severe adverse side effects sometimes with rather modest gains regarding efficacy.[12-14]

Therefore, until novel therapies targeted to the pathogenic mechanisms responsible for initiation and perpetuation of AF become the mainstay, ablation of arrhythmic triggers, either through percutaneous or surgical approaches, draw advantage from the ability to abrogate the inherent issues of the sustained arrhythmia itself as well as its medical treatment.

Despite being strongly recommended upon failure of AAD, catheter ablation as first-line therapy may be considered in specific and well-defined clinical scenarios.[15] Indeed, the procedure is cumbersome and not exempt of complications, which means that carefully weighing risks and benefits at an individual basis is warranted before deciding for the intervention. If catheter ablation is contra-indicated or successively fails to control rhythm or symptoms, then stand-alone surgical treatment may be considered[1].

On the other hand, the frequency of AF as comorbidity in patients undergoing coronary artery bypass surgery and/or valve surgery[16, 17] is on the rise and it considerably boosts the mortality risk over the years after operation.[18] Besides improving long-term survival, surgical ablation of AF may additionally obviate the need of permanent anticoagulation.[15] This risk can be further decreased by intraoperative resection or exclusion of the left atrial appendage (LAA).[19]

All patients submitted to AF ablation should have an outpatient appointment 3 months after ablation and then every 6 months for at least 2 years, irrespective of being enrolled in a clinical trial. ECGs should be obtained at all follow-up visits, with stricter monitoring reserved for patients in whom AF detection can have a significant impact. Counselling patients to monitor pulse irregularity and ECG-recording using manually activated event recorders are effective for initial screening of asymptomatic AF episodes. Frequent asymptomatic recurrences of AF can be easily detected with 1 to 7 days Holter monitoring, whereas less frequent AF episodes may require auto-trigger event monitor, mobile cardiac outpatient telemetry system or implantable subcutaneous monitoring.[15]

Surgical treatment of AF

1. The best option (just) for some

Despite being fairly effective at resuming normal sinus rhythm (SR), surgical ablation in general and the Cox-Maze procedure in particular, should be restricted to specific sets of patients. In this regard, the Heart Rhythm Society/ European Heart Rhythm Association/ European Cardiac Arrhythmia Society (HRS/EHRA/ECA) expert consensus statement on catheter and surgical ablation of AF strictly define the indications for surgical treatment of AF (Table 1).[1] In short, surgery as a stand-alone procedure can be considered if catheter ablation is unsuccessful, contra-indicated or otherwise declined by the patient. On the other hand, surgical ablation should be offered to patients undergoing concurrent cardiac surgery, even before trying AAD.

Despite being separate pathophysiological entities, AF and atrial flutter are commonly seen together and radiofrequency (RF) ablation of the cavotricuspid isthmus has been successfully employed in patients with typical atrial flutter.[20] On the other hand, atrial flutter and other atrial tachyarrhythmias are common complications of AF ablation and should be considered treatment failures, with the potential of being successfully ablated.[15, 21]

2. From the "cut and sew" approach to sophisticated ablation techniques

The surgical treatment of AF dates back to the early 90s when the original Cox-Maze I procedure emerged with the intention of ablating all macro re-entrant circuits perpetuating AF. This rather invasive intervention involved cutting and sewing through multiple incisions in an attempt to destroy all macro re-entrant circuits in atrial myocardium. Besides restoring SR and atrioventricular synchrony, the intervention aimed at recovering appropriate electrical conduction and contractility to decrease thromboembolic risk. Nonetheless, by isolating the sinus node, standard atrial incisions interrupted its blood supply, which in turn resulted in significant chronotropic incompetency. Moreover, one of the lesions affected the Bachmann bundle, leading to a substantial (around 180 milliseconds) conduction delay between right and left atria and thus asynchronous heart beating.[22] Together these two important caveats undermined the potential success of the Cox-Maze I procedure. However, rather than stumbling blocks they were stepping stones for improvement. Following versions of this procedure moved the surgical incision to the back of the superior vena cava, close to the interatrial septum, thereby avoiding sinus node-dependent chronotropic dysfunction and conduction delay but without compromising the three-dimensional concept.[21,22] More recently, modern technological advances paved the way for replacement of surgical incisions by surgical ablation lines with specifically designed devices.[23, 24] The less-technically demanding though highly successful Cox-Maze III procedure met with great approval and significantly reduced cerebrovascular accidents[25] as well as pacemaker implantation.[26, 27] In fact, both the original procedure and its modern counterpart have consistently shown to result in very low morbidity and excellent long-term freedom from AF and thromboembolic accidents, when performed by experienced hands.[28-31]

3. The contemporary form of the Cox-Maze procedure

Increasingly better understanding of AF pathophysiology set the stage for crucial improvements in the electrophysiological concept underlying Cox-Maze procedure. The new modified intervention, known as Maze IV, replaced previous atrial incisions by accurate linear ablation lines, in accordance to modern knowledge of arrhythmic triggers and pathways (Figure 1). Hence, circular pulmonary vein (PV) isolation, the well-established trigger of AF, is now the key element of any ablation therapy, mainly for paroxysmal AF.[32] However, due to progressive electrical and structural remodelling, atrial myocardium ultimately becomes capable of initiating and sustaining arrhythmic activation independently of PVs. Therefore, more complex cases (e.g. persistent and long-standing persistent AF) require substrate modification, *i.e.*, complete isolation of the posterior atrial sleeve, also known as box lesion, and ablation of the left atrial isthmus toward the posterior mitral valve ring.[33, 34] This intervention can be further expanded to the right atrium and the left atrial appendage, thus mimicking the full lesion set of its predecessor Maze III.[35] Indeed, these procedures are not conspicuously different, neither regarding the design of the intervention itself nor the outcome.[36] Furthermore, replacing the original incision lesions with linear ablation lines proved to yield identical efficacy but with less time on the bypass machine (84% of patients in SR and off AAD at 24 months).[37]

Nowadays, the Cox-Maze IV procedure is usually performed on cardiopulmonary bypass (CPB), but the option between full sternotomy and minimally-invasive thoracotomy (mini-thoracotomy) depends on the concurrent cardiac intervention and surgical team skills. Indeed, the standard open-chest approach is likely the most appropriate in case of multivalvular and/or complex coronary artery bypass surgery, whereas minimally-invasive right mini-thoracotomy can be preferable for certain cases of atrial septum defect closure, and mitral or tricuspid valve surgery.[38, 39] In fact, minimally-invasive ablation techniques are garnering sympathy as they afford creation of effective transmural lesions with low endothelial damage and no significant risk added to the core cardiac procedure.[12, 14, 40, 41]

Off-CPB surgical-ablation is gathering increasing interest,[40] despite no apparent safety advantage over on-pump ablation (Figure 2).[42] In contrast with on-CPB procedures, in which biatrial lesions are usually performed, off-CBP techniques tend to confine the lesions to the LA, which can influence long-term success-rates.[42] However, if first attempts aimed at just isolating the PVs, LA-ablation and even additional right-atrial lesions proved to be possible.[43, 44] Being still in its very beginning, the effect of a surgical learning-curve should be considered when interpreting the results of off-CPB interventions. In conclusion, epicardial-ablation is reasonable for short-term paroxysmal-AF and small-LA and likely preferable for off-pump-CABG.[45]

4. Matching the best approach and lesion set

The progressive development of devices, mapping systems, and surgical ablation techniques has fostered the evolution of the Cox-Maze procedure. Technological advances should be funnelled into developing novel instruments capable of combining the efficacy of the full Cox-Maze procedure and the requirements of minimally-invasive surgery. Nonetheless, the enthusiasm always generated by such promising technological advances needs to be restrained by potential pitfalls yet to be revealed. Indeed, both the strengths and weaknesses of each technique and device should be taken into account when considering alternatives to conventional Cox-Maze procedure (Table 2).[12, 14, 40, 41]

Minimally-invasive surgery is generally preferred for treatment of lone AF, in which ablation tends to be performed on the epicardium. Indeed, this endoscopic intervention can use either a mono or bilateral thoracoscopic approach, depending on the requirements of the ablation procedure, and obviates the need of CPB. Therefore, it reduces operation time, fastens recovery and decreases hospital length of stay, without bringing any additional serious ablation-associated complication.[46] On the other hand, when endocardial ablation lines are to be performed, CPB can be connected to the groin vessels and cardioplegic arrest can be achieved through right atrial minithoracotomy.[12, 14, 40, 41]

The most widely employed approach for stand-alone AF is video-assisted bilateral mini-thoracotomy or thoracoscopic PV island creation and LAA excision/exclusion, often associated with evaluation and destruction of ganglionic plexus (GP).[47] It has the advantage of averting the cumbersome passage of the ablation device through the transverse and oblique sinuses, around the PVs, typical of unilateral thoracoscopy. The reported success ranges from 40 to 90% at a follow-up between 6 and 40 months, suggesting that selecting patients likely to get the greatest benefit is imperative.[43, 48, 49]

Contrary to AF ablation as an addition to an otherwise indicated cardiac procedure, in surgical ablation of lone-AF, invasiveness is the crux of the matter. Therefore, less-invasive techniques, such as unilateral approach, have been the focus of intense research. The monolateral approach, indeed, can potentially reduce post-operative bleeding, pain and pulmonary complications, resulting in faster recovery and early discharge.

The first attempt to perform LA ablation through single right thoracotomy came from Solinas *et al.*, who employed a bipolar irrigated RF device for LA ablation during minimally-invasive mitral surgery.[50] The positive, though preliminary, results prompted the development of the unilateral approach. The unilateral approach had already been described but with CPB and cardioplegic arrest, which inherently increase invasiveness.[49, 50] In fact, this new procedure suffers from two important pitfalls, as it is performed only partially off-pump and during surgery of the mitral valve, when the LA is open. Subsequent studies lent further support to the effectiveness of minimally-invasive surgery through a small right thoracic cavity incision (approximately 4-6 cm), even in patients with LSP AF, with more than 85% of patients free from AF and AAD at 24 months.[46, 51, 52]

Most recently, Ad *et al.* presented a series of 104 patients with non-paroxysmal-AF, operated since 2005 for lone AF. They used a right anterolateral mini-thoracotomy to perform the complete Cox-Maze III lesion set in both atria, using argon-based cryothermal energy and CPB. The results were rather promising (Figure 3), with more than 90% of the patients in SR at 36-months (80% off-AAD), attesting the safety/effectiveness of the Cox-Maze procedure even for non-paroxysmal AF. Furthermore, morbidity was similar to percutaneous catheter-ablation and off-CPB minimally-invasive surgery. However, the learning curve associated with this innovative technique cannot be overlooked.[53]

Overall, the best lesion set and the best approach seem to be inversely related. Alternative sources of energy have tried to overcome this apparent dilemma. Lee *et al.* presented an outstanding method of performing the full lesion set of Cox-Maze procedure using a right mini-thoracotomy (5-6 cm) and a combination of RF and cryoablation, with CPB and cardioplegic arrest.[54] Short-term results reinforce that minimally-invasive surgery achieves a success rate comparable to the conventional Cox-Maze procedure but with lower morbidity (81% of patients were free from AF and off AAD at 12 months). In addition, Vanelli *et al.* have shown the efficacy of Epicor (St Jude Medical, Sunnyvale, CA, USA) low profile system, a device using high-intensity focused ultrasound (HIFU), for AF ablation also through right mini-thoracotomy.[55] The procedure consisted in creating an epicardial box lesion of the PVs and mitral isthmus under transoesophageal echocardiographic guidance. There were no postoperative complications, but 3 (out of 10) patients required postoperative cardioversion to resume SR. However, HIFU was unable to create a bi-atrial lesion set appropriate for patients with more severe and advanced states of AF, which underscores the importance of a thorough patient selection.

However, right-side thoracoscopic approach is flawed by the difficulty in removing the LAA. In this regard, Balkhy *et al.* published a case report describing a new device for LAA exclusion that was introduced into the standard right thoracoscopic microwave ablation system (Surg-ASSIST computer-mediated thoracoscopic stapling system)[56]. Larger trials are warranted to ascertain the safety and efficacy of this novel stapling system.

Besides the more common right-side approach, there is a case report of left-side video-assisted thoracoscopic drainage associated with epicardial RF isolation of the PVs in a 68-year old female suffering from lone permanent AF.[57] However, this approach was never replicated in the literature.

Robotically-assisted techniques have been also employed for microwave ablation (daVinci-system) concomitantly with MV-replacement using a right anterior mini-thoracotomy.[58] The promising results (80% and 73% of the patients in SR at 6-weeks and 6-months, respectively) support the feasibility of combined totally-endoscopic treatment of atrial-arrhythmias and mitral-insufficiency. Another robotically-assisted RF-ablation procedure (Hansen-Robotic-system) achieved a rate of arrhythmia-free survival of 76% after one intervention, being all the targets but the right inferior PV easily accessible.[59] The complications associated with the robotic system are similar to the manual approach, but if successfully managed no long-term morbidity ensues. Appropriate choice of ablation-catheter and titration of power, as well as, experienced operators with good anatomical knowledge are paramount to ensure safety and effectiveness.[59]

Complete robotic MV repair (daVinci telesurgical system) has also been combined with CryoMaze, including right and left atrial lesion sets. Indeed, cryoablation simultaneously with robotic MV repair achieved 96.5% freedom from AF off-AAD and warfarin, though significantly increasing operative times.[60] Taken together, all these studies suggest that as experience is gained and technology advances, robotically-assisted endoscopic surgery incorporating AF ablation may well become more accessible.

Despite the dearth of studies seeking the best surgical treatment of AF, none of them has yet been adopted as “gold-standard”.[61] Indeed, the ideal technique would be easy to perform, off-pump, unilateral, epicardial, and able to produce adequate transmural lesions and provide good clinical outcomes.

5. Seeking the best energy source and device

Today most AF surgical procedures seize the opportunity provided by an otherwise indicated cardiac surgery. Under these circumstances, invasiveness is no longer the cornerstone of treatment and hence several types of energy sources are currently available, such as unipolar or bipolar RF energy, cryoenergy with argon or nitrous oxide and HIFU, each with its inherent advantages and pitfalls.[62, 63] Overall, RF and HIFU tend to be used for epicardial interventions, while cryoablation is often preferred for endocardial procedures, for instance during the surgery of the mitral valve when the LA would be opened anyway.[12, 14, 40, 41]

The efficacy of microwave energy is bleak, with merely 42% (37 out of 88) of patients in SR at 12 months in the most recent study.[64] This unfocused heat energy is able to induce transmural endocardial lesion but not epicardial lesion on the beating heart. Similarly, HIFU energy can create transmural endocardial lesions only in the arrested heart and with a modest efficiency. Indeed, Klinkenberg *et al.*[51] performed PV isolation by minimally invasive epicardial off-pump monolateral right-sided video-assisted thoracic surgery using the UltraCinch with HIFU in 15 patients with stand-alone AF.[65] At a follow-up of 1.3±0.6 years, 4 (27%) patients were in SR after one epicardial PV isolation (2 were on AAD) and 6 (40%) patients were submitted to endocardial RF re-ablation, which was successful in 3 (20%) of them.

On the other hand, bipolar RF, which has already been shown to induce transmural linear lesions on the beating heart, is the most popular energy source.[66] Indeed, the reported success rate, in terms of freedom from AF and anti-arrhythmic medication, varied between 51% and 86% at 1 year, being slightly higher for paroxysmal (65-92%) than for persistent (67-80%) AF.[67, 68]

The myriad of devices currently available turned surgical treatment less invasive but also more confuse. The implications of employing the appropriate energy source, lesion set and surgical approach cannot be overlooked and should take into account not only the underlying type of AF but also the concomitant surgical procedure.

6. The main adverse events and complications

A recent review reported an overall mortality of 0.4%, which is comparable to percutaneous catheter ablation (0.7%).[1] However, as all surgical procedures it is not exempt of risks and post-operative complications remain a matter of concern. Among them, pulmonary problems, bleeding, and diaphragm/phrenic nerve dysfunction were the most frequent, being nowadays rare with the most used energy sources. The risk of phrenic nerve injury with wide area circumferential RF ablation can be reduced by modification of ablation lines close to right PVs/carina.[69]

Transient ischemic attack and stroke are also rare (0.5%) and less common than with catheter-based PV isolation.[1] Most complications are transient but 1.4% of patients may ultimately require pacemaker implantation.[70]

The clinical success of the ablation procedure depends on persistence of the transmurality of the lesions, which is likely the main limitation of the RF devices.[71, 72] Indeed, total recovery of conduction after irrigated bipolar RF ablation remains reasonably high and repeated multiple ablations, possibly complemented by block validation with electrophysiological testing,[73] might be required to ensure longstanding transmurality.[71]

A worldwide survey on catheter ablation of AF (including 20825 procedures and 16309 patients) reported a risk of serious complications of 4.5%, including stroke (0.23%), cardiac tamponade (1.3%), and PV stenosis (<0.29%).[74]

Moreover, patients undergoing minimally-invasive surgery may develop atrial tachycardia, probably because lesions fail to achieve conduction block.[71, 72] This problem can be minimized by confirming complete conduction block with electrophysiological testing.[75]

Overall, operative risk is low in terms of morbidity and mortality but depends on the pre-operative health condition of the patient. Furthermore, surgical complications are related to the procedural difficulty and learning curve of the surgery and thus tend to decrease over time.

7. A highly successful intervention

The Cox-Maze procedure has stood the test of time certainly due to its high success rate, which ranges between 75 and 95% after up to 15 years of follow-up, depending on the centre, type of intervention and patients.[36] However, there is always some risk of procedural failure and persistence of arrhythmia. The Heart Rhythm Society defines failure as any monitored atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) lasting more than 30 seconds, that is documented by an ECG or device recording system more than 3 months after the procedure.[15] In the early postoperative period, up to one-third of patients might have temporary atrial arrhythmia. These early arrhythmias should be addressed routinely with AAD and/or cardioversion, which generally resume SR.[1]

Moreover, the vast majority of patients (about 80%) submitted to Cox-Maze procedure will be kept in SR without taking any antiarrhythmic or anticoagulation drugs. For most of the remaining, even the ones refractory to medical therapy pre-operatively, a single AAD may be enough to achieve appropriate rhythm control.[76] Even though guidelines might consider SR on AAD as failure, under those circumstances patients at low to moderate risk of thromboembolic events might consider discontinuing anticoagulation, which decreases bleeding risk and boosts quality of life.[46, 77]

In addition, success rates depend on the type and aetiology of AF. Indeed, patients with stand-alone paroxysmal AF seem to take the greatest advantage of minimally-invasive AF ablation, with more than 90% in SR after 12 months. On the other hand, the figures are modestly worse when AF ablation is performed in conjunction with another cardiac surgery. For instance, among 216 patients submitted to AF ablation concomitantly to coronary artery bypass graft, the proportion of them in SR at 12 months was 75% for paroxysmal AF, but merely 55% for persistent AF (Figure 3). The lack of benefit of more extensive ablation procedures led the authors to recommend off-pump coronary bypass surgery using epicardial ablation either restricted to PV isolation for paroxysmal AF or expanded to encompass the full box lesion for persistent AF.[40]

Rheumatic-valve-disease remains a matter of concern in developing countries, but the effectiveness of the Cox-Maze-procedure seems to be lower in this context (46-70%).[78] There is evidence suggesting that concomitant bipolar RF ablation is safe and reasonably effective for treating AF in patients with rheumatic-heart-disease undergoing valve-surgery (66-79% in SR at 12-months).[79] Anatomical remodelling associated with progressive atrial fibrosis, as well as, inflammation can explain post-operative AF recurrence.[80] Indeed, SR restoration does not mean atrial-contraction recovery, particularly in patients with AF duration longer than 5-years, lending support to the concept of progressive inflammation-driven myocardial degeneration.[81] Echocardiographic studies suggest that, in patients with chronic-AF, SR recovery and maintenance results in “reverse” atrial remodelling and better atrial contractility, independently of pre-operative atrial size.[82] However, global and regional atrial function remains modestly impaired, either due to ablation-induced lesions or pre-existing atrial structural remodelling and both issues need to be considered when devising the post-operative anticoagulation regimen.[83, 84]

By its turn, AF cryoablation associated with minimally invasive mitral valve surgery through right lateral minithoracotomy improved survival, reaching a level identical to that of patients in SR. The ablation procedure consisted in PV isolation with additional isolation of the posterior atrial sleeve and lesion of the posterior mitral valve annulus and reached a success rate higher than 70%. Moreover, ablation of pre-existing AF afforded a survival benefit up to 5 years after surgery (Figure 3).[40] In the same line, the Cox-Maze IV procedure yielded identical results in patients with lone AF versus patients with concomitant mitral disease (77% success rate off AAD for the lone AF group) at 12-months, with lack of ablation of the posterior LA appearing as the single predictor of failure in either group.[85] Altogether, these results strongly advise performing AF ablation along with minimally invasive mitral valve surgery in patients with preoperative AF.

A recent report showed great benefits concerning return to SR and health-related quality of life physical functioning scores in patients with heart failure with low ejection fraction and AF.[86] The same group demonstrated that adding Cox-Maze procedure to coronary artery bypass grafting or aortic valve surgery in patients older than 75 or considered high-risk did not increase operative risk nor induce worse long-term outcome. Therefore, exclusion of those patients from surgical ablation procedures seems no longer justified.[87, 88]

A meta-analysis [61] conducted in 2006 including a total of 69 studies with 5885 patients demonstrated that patients undergoing surgical ablation did fare better in terms of freedom from AF than control patients (84.5±10.3 versus 30.8±19.6 after 12 months, p=0.001). In addition, biatrial surgical ablation was more effective in restoring SR than procedures restricted to the LA at all time points (88.9±8.2 versus 75.9±8.4 after 12 months; p=0.001). However, these results must be interpreted with caution as most of the studies were retrospective (75%), small (42%) and very few involved control groups (19%).

A subsequent meta-analysis[89] carried out in 2010 as part of the International Society for Minimally Invasive Cardiothoracic Surgery consensus statement, analysed the results of 10 randomised and 23 nonrandomised control studies on AF ablation during concomitant cardiac surgery (4647 patients). At discharge, the number of patients in SR was higher in the group submitted to AF ablation concomitantly with core cardiac surgery, both in randomised controlled trials (OR 10.1, 95% CI 4.5–22.5) and non-randomised studies (OR 7.15, 95% CI 3.42–14.95). This benefit for patients undergoing AF ablation persisted over a follow-up between 1 and 5 years, with 74.6% versus 18.4% in SR (OR 6.7, 95% CI 2.8–15.7 and OR 15.5, 95% CI 6.6–36.7 for randomised and non-randomised trials, respectively). Moreover, all-cause mortality at 30 days and at 1 year or more (up to 5 years) was similar irrespective of addition of AF ablation to standard surgical intervention (OR 1.21, 95% CI 0.59–2.51, at 1 to 5 years in randomised controlled trials). Even though stroke incidence was not significantly reduced, in meta-regression, the risk of stroke decreased significantly with longer follow-up. Not surprisingly, operation time was significantly increased with surgical AF ablation, but hospital length of stay did not differ between groups. The lack of consistency among reports concerning ablation technique hindered any sub-analysis to determine the best lesion set. In fact, the huge variety of lesion sets currently being employed as part of the Maze procedure has been a stumbling block to the comparison of outcomes among different studies.

The most recent systematic review on the topic of minimally-invasive surgery for lone AF included 23 observational studies reporting on RF ablation of AF.[70] Other energy sources, e.g. microwave and HIFU, were excluded due to their rather disappointing results. The global success rate at 12 months was 79% and 69% with and without anti-arrhythmic drugs, respectively (Figure 4). However, results at 6 months are slightly worse (64% off AAD and 75% on AAD), probably because they derive from the very first trials of minimally-invasive surgery and keeping patients on AAD for 6 months after intervention is not unusual. Despite the mixed population included in most studies, pooled data reinforce the highest efficacy of minimally-invasive surgery for paroxysmal AF, but also stress than even for persistent and LSP AF the intervention is beneficial in more than 50% of the cases. Unfortunately, invasive AF ablation fails to stop disease progression in some patients, with recurrence of arrhythmia eventually ensuing. Interestingly, about 26% of the patients had one or more previous catheter ablation, which can have either a positive or negative impact on the outcome of subsequent ablation surgery. On one hand, these patients may have incomplete lesions leading to atrial tachycardia, which are cumbersome to identify and hence to treat; on the other hand, pre-operative catheter ablation may have already partially eliminated AF triggers and re-entrant circuits.

8. Role of ganglionic plexus ablation

Animal studies have consistently shown that conversion of focal firing from PVs into AF is modulated by the autonomic nervous system.[90] This raised the possibility that GP destruction might influence the substrate for AF induction and perpetuation and hence reduce arrhythmic relapse. Moreover, epicardial fat pads where GP reside are easily accessed using a surgical approach. Therefore, GP ablation has been increasingly adopted as a routine part of minimally-invasive surgical protocols. GP localisation before ablation can be done visually or with high frequency stimulation and lack of vagal response to high frequency stimulation usually confirms adequate GP elimination.

Nonetheless, the rationale of GP ablation is being increasingly challenged. Evidence favouring GP ablation derived from catheter-based PV isolation, in which a vagal response during intervention was associated with lower AF recurrence.[91] On the contrary, recent systematic reviews point to the opposite effect, with patients submitted to GP ablation presenting higher AF relapse at 12 months.[92, 93] In fact, GP ablation in conjunction with PV isolation was associated with a lower success rate (63% versus 83% of patients in SR with and without GP ablation, respectively). These findings argue against performing GP ablation on the basis of reducing AF recurrence in the long-run, probably because autonomic ganglia tend to reconnect or regrow with time.[94] Nevertheless, the small number of studies and short follow-up available thus far preclude drawing definite conclusions regarding the role of GP and their destruction in the outcome of AF ablation.

9. Exclusion/excision of the LAA

Patients with AF are at least 5- to 7-fold more susceptible to cerebrovascular accidents.[12, 14, 40, 41] The balance between preventing thromboembolic events and bleeding complications is precarious before and after AF ablation. Based on well-defined risk scores (CHADS2 and more recently CHA2DS2Vasc), almost all cardiac surgical patients with AF will require long-term anticoagulation.

However, surgical ablation offers the possibility of excluding or excising the LAA[95], the main source of thromboembolic formations. Compelling evidence supports the benefit of adding prophylactic occlusion of the LAA to standard AF surgical treatment, especially in persistent AF where the ablation success rate is limited to 55-75%. This procedure actually improves patient's outcome, particularly in terms of decreasing risk of thromboembolic events after discontinuation of anticoagulant therapy, achieving an event rate comparable to ongoing permanent anticoagulation.[40, 96]

Therefore, these data are fuelling the controversy over management of anticoagulation after surgical ablation, as the widely used CHADS2 score seems to have no predictive power in determining who was at risk for stroke, predicting instead who would experience a major bleeding event.[77] Therefore, more research is urgently needed to improve management of anticoagulated patients, an issue made even more critical in face of the recent approval of novel anticoagulant drugs.[97]

Despite the fact that retaining the LAA better preserves atrial booster function[98], nowadays prophylactic occlusion of the LAA is considered by the guidelines. Several techniques have been described for LAA exclusion, including occlusion of the endocardial orifice between the LAA and the LA, resection of the appendage with subsequent double-row stitches, or epicardial ligation at its base while leaving the appendage *in situ*. The latter is possible not only by surgical purse-string sutures, but also endoloop systems, staplers or clips, which offer great advantage for videoscopic and minimally-invasive ablation procedures. In fact, there has been great interest in developing new endocardial and epicardial procedures for occlusion of the LAA, many of which tend to use staplers or, less frequently, endocardial sutures.[99] Different sizes of staplers and clips are available to account for the variability in terms of size and anatomy of the LAA. However, it is always important to bear in mind that the LAA can be very thin and thus easily damaged.[12, 14, 40, 41]

[1, 100] Nonetheless, the best approach remains hotly debated.[101] Excision/resection appeared to be more effective than exclusion by sutures or staplers regarding the presence of residual niches at the base of the LAA.[102] Nonetheless, the extent to which this can be transferred to current exclusion systems is not known and more recent data indeed suggest higher success with modern exclusion systems.[19] In any case, the optimal position and occlusion should be checked by intraoperative transoesophageal echocardiography.

Noteworthy, in a recent review of 28 studies (27 observational and 1 non-randomised prospective) regarding minimally-invasive surgery for treatment of lone AF, LAA removal seems to have no impact on the incidence of adverse cerebrovascular events, thus casting doubt on the absolute necessity of this procedure. Nonetheless, the small number of studies and the heterogeneity regarding anticoagulation management cannot be overlooked when interpreting this finding. There is a pressing need to clarify the role of LAA exclusion in minimally-invasive surgery, because that intervention is cumbersome and the main culprit of intraoperative bleeding.[93]

More recently, the multicentre PROTECT AF study (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation), conducted in 707 patients with nonvalvular AF and CHADS2 score ≥1, showed that percutaneous LAA closure with the Watchman system was non-inferior to oral anticoagulation with warfarin in terms of thromboembolic prevention (Figure 5).[103] However, procedure-related safety events were more common in the LAA closure arm, mainly pericardial tamponade and procedure-related stroke. The latter was indeed the culprit of lack of superiority over warfarin. Furthermore, patients-reported quality of life was also significantly better in the Watchman group after 12 months.[104] Probably the utmost finding was the efficacy of LAA closure for secondary stroke prevention, in which warfarin, even at high doses, is much less effective.[105] On-going clinical trials testing similar devices[106-108] will likely clarify some of the questions raised by this study.

The hybrid approach

With the astonishing development of new techniques and devices, multidisciplinary management of AF is becoming reality, with close collaboration between surgeons and electrophysiologists. The novel approach, usually known as “hybrid approach”, takes advantage of combining percutaneous endocardial catheter ablation with minimally invasive epicardial ablation in a stepwise fashion. The ultimate goal is to minimise the drawbacks of each technique and synergistically combine their advantages. The combination of endocardial and epicardial linear lesions has the potential to improve the creation of transmural lesions. The surgical procedure is performed off-pump and using a totally thoracoscopic approach. Once it is finished, the electrophysiologist based on mapping systems can seal gaps, connect lesions that are not transmural and induce additional lesions.

Moreover, performing the full set of lesions required to completely eliminate arrhythmic substrate in persistent and long-standing persistent AF on the beating heart is far from being easy. The connection to the mitral annulus is more difficult than all other lesions that can be induced through the transverse sinus. Indeed, the poor visualisation behind the left atrium (LA) on the beating heart increases the risk of inadvertently damaging the circumflex coronary artery. In addition, the accuracy of the coronary sinus as epicardial landmark for the mitral annulus is questionable. In this regard, the “Dallas lesion” has been introduced by Edgerton *et al.* and consisted in making a line connecting to the anterior annulus at the junction of the left and noncoronary cusps of the aortic root. However, the abundant fatty tissue around the dome of the LA and the superior vena cava rendered RF unable to penetrate deep enough to induce transmural lesions. The hybrid approach has the potential for solving this problem by making use of mapping conduction block. Indeed, conduction block confirmation, using either an epicardial or endovascular approach, has recently attested the feasibility and better outcome achieved with electrophysiological measurements during minimally-invasive surgery.[73, 109]

On the other hand, the hybrid approach averts some of the hazards typically faced by electrophysiologist. Indeed, the risk of cardiac tamponade during transseptal puncture is no longer an issue, since the pericardium is open; collateral phrenic nerve or oesophageal injury can be prevented by surgical protection; the risk of cardiac emboli often associated with endocardial lesions is reduced, as most of the lesions are induced epicardially; and stenosis of PVs is almost impossible to ensue since the surgical ablation device is placed on the antrum of the LA and left as a radiopaque marker.

However, the hybrid approach has its own shortcomings: (1) the risks of measuring a temporary block as well as bleeding of surgical dissected areas are increased by patient’s heparinisation after transseptal puncture; and (2) the intervention is time-consuming and significantly longer than sole surgical ablation.

Pak *et al.* were the first to combine percutaneous epicardial catheter ablation with endocardial ablation for treating complex cases of AF, thereby ushering in the “hybrid approach”. Following in their tracks, Krul *et al.* [109] reported a single-procedure success rate of 86% with thoracoscopic PV isolation and ganglionic plexus ablation guided by peri-procedural electrophysiological testing. On the other hand, Mahapatra *et al.* [110] slightly adapted the original hybrid procedure, with surgical epicardial and catheter endocardial ablation being carried out in two sequential steps (during the same hospitalisation). At a follow-up of 20.7±4.5 months, the novel approach seems to be clearly superior for patients with persistent and long-standing persistent AF when compared to catheter ablation alone (86.7% versus 53.3% of patients free of any atrial arrhythmia and off AAD, respectively; p=0.04). De Roy *et al.* also performed the hybrid procedure in two stages, with either endocardial catheter isolation of PVs followed by epicardial approach (29% in SR at a follow-up of 25.7±12 months) or first the epicardial procedure and subsequently percutaneous completion of PVs isolation (55% in SR at a follow-up of 33.4±12 months).[48] More recently, the same group published the results of single-step procedure, with epicardial followed by endocardial catheter RF ablation, with a success rate of 93% and 90% at 1-year follow-up for paroxysmal and persistent AF, respectively.[111]

Nevertheless, this promising approach is just taking its first steps and therefore adjustments and improvements are to be expected in the near future. Comparative studies currently underway will surely help defining its role in AF management.

Percutaneous catheter ablation versus surgical ablation

The widespread popularity of catheter-based techniques made them the most often used nonpharmacological approach to treat AF.[41] Percutaneous catheter-based interventions are increasingly being used for rhythm control, and several types of energy and catheters are now available for AF ablation, under accurate guidance of sophisticated mapping systems.[112, 113]

The reported success rate of PV isolation ranges between 60 and 85%, doing particularly well in patients with paroxysmal short-lasting episodes of AF. [74, 114, 115] Nonetheless, apprroximately 80% of patients have at least partial recovery of PV conduction at 4 months after ablation when unipolar RF energy is used (Circ 2003;108:1599). Consequently, about one-third of patients require a second intervention, which entails an increment of 6% in procedural-related complications [74, 116] There is also substantial evidence supporting that catheter ablation is not as effective in patients with AF other than paroxysmal or with larger LA.[117] Minimally invasive surgical RF ablation is also more effective for paroxysmal AF.[45, 109, 118, 119] However, these patients, like the ones with persistent AF[45, 118, 119], seem to do fare better with minimally-invasive surgery than catheter ablation. The same may not be true regarding LSP AF.[118]

A recent report released by the American Heart Association showed that the success of percutaneous catheter ablation for AF has been hampered by many post-procedural complications, the most common of which were vascular events, such as haemorrhage and stroke.[41] Indeed, the rate of complications was found to be particularly high in female and older patients and mainly in those with multiple hospitalisations for AF in the year before ablation. The readmission rates for AF at 1 and 2 years were 22% and 30%, respectively, pointing to the limited success of catheter ablation in the long run.[41] Those findings were corroborated by another study that reported arrhythmia-free survival rates after single catheter-based intervention of 40%, 37%, and 29% at 1, 2, and 5 years, respectively.[112] The majority of recurrences took place in the first 6 months after intervention, being valvular heart disease and non-ischaemic dilated cardiomyopathy independent predictors of recurrence.[112] Moreover, arrhythmia-free survival steadily declined at an annual recurrence rate of 8.9% following last ablation attempt (Figure 6).[112] In contrast, consistent data support the high efficiency of Cox-Maze procedure even in the presence of multiple predictors for failure.[29, 30, 36, 37, 85]

The FAST study (Atrial Fibrillation Catheter Ablation versus Surgical Ablation Treatment) enrolled patients with paroxysmal and persistent AF for at least 12 months that was refractory to or intolerant of at least 1 AAD, the majority with failed prior catheter ablation (Figure 6). They were randomized to receive either percutaneous catheter ablation (PV isolation with optionally additional lines; n=63) or surgical ablation (PV isolation with bipolar RF, ganglionic plexus ablation, and LAA excision; n=61). Despite doing significantly better in terms of freedom from atrial arrhythmias without medication at 12 months (36.5% versus 65.6%; p=0.0022), surgical ablation was associated with significantly more adverse events than catheter ablation (34.4 versus 15.9; p=0.027). However, most of them were procedural complications, such as pneumothorax, major bleeding and pacemaker implantation; and had no actual impact on final outcome.[120] Therefore, surgical treatment should be considered as secondary treatment for symptomatic patients after unsuccessful percutaneous catheter ablation or as first line therapy in more severe settings of AF. The choice of surgical ablation should also take into account that limited ablation and off-pump approaches proved to be less effective in patients with more complex AF.[49, 87, 88, 121]

Two other randomised clinical trials are being carried out right now, both in patients suffering from paroxysmal AF. The SCALAF success trial compares the efficacy of surgical and catheter-based circumferential ablation of PVs ostia. The FAST II trial addresses the effectiveness of minimally invasive thoracoscopic RF ablation versus percutaneous catheter-based technique in patients refractory to at least one antiarrhythmic drug. Hopefully, these trials will provide deeper insight on AF pathophysiology and elucidate some of the issues still glooming AF management.

Future perspectives

Surgical treatment of AF has been continuously evolving and further improvements are to expect. Great endeavour is being funnelled into two broad areas, namely (1) better understanding the underlying mechanisms of AF and (2) developing less invasive techniques without compromising safety and efficacy.

Ideally, the mechanism of AF should be defined before planning surgery. Technological advances ushered in several sophisticated, high-density and/or three-dimensional (3D) mapping systems, which performed much better than the conventional 12-lead ECG, in terms of revealing the mechanisms, electrophysiologic characteristics and localization of atrial arrhythmias. Indeed, a recently developed 252-lead, surface ECG-based non-invasive epicardial mapping system showed an overall accuracy of 92% when compared to invasive electrophysiology. Global atrial activation patterns of sustained as well as transient atrial arrhythmias were ascertained in a single beat/cycle and non-invasively. This promising system might improve ablation planning and thereby save procedure time, fluoroscopic exposure and/or global efficacy of the ablation procedure.[122] On the other hand, electrocardiogram imaging is a technology that allows reconstruction of atrial electrograms with anatomical information provided by computed tomography/magnetic resonance scan obtained simultaneously with ECG recording.[123-125] Despite being very useful to localise arrhythmic triggers and circuits, these mapping systems are still not widely available in most centres for routine clinical care.

Novel approaches for minimally invasive surgery are also on the pipeline, such as the subxiphoid approach, which has already been shown promising for coronary bypass surgery and implantation of cardioverter defibrillators.[126-128]

Conclusion

Over the last two decades, medical, catheter-based and surgical management of atrial fibrillation have achieved remarkable improvements. The development of novel ablation techniques, energy sources and minimally invasive approaches revolutionized surgical therapy of atrial fibrillation. Today atrial fibrillation ablation concomitantly to an otherwise indicated cardiac surgery improves patients' prognosis without adding significant operative risk. As more is learned about the underlying mechanisms and with better preoperative assessment, including electrophysiological mapping systems, it probably will become possible to tailor specific lesion sets and ablation modalities to individual patients. Close collaboration between electrophysiology and surgery is ushering in a new era of atrial fibrillation management.

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Table 1: Consensus indications for catheter and surgical ablation of AF*

	Class and level of evidence
Indications for concomitant surgical ablation of AF	
Symptomatic AF refractory or intolerant to at least one class 1 or 3 antiarrhythmic medication	
Surgical ablation is reasonable for patients undergoing surgery for other indications irrespective of AF type	IIa C
Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a class 1 or 3 antiarrhythmic agent	
Paroxysmal/Persistent: surgical ablation is reasonable for patients undergoing surgery for other indications	IIa C
LSP: surgical ablation may be considered for patients undergoing surgery for other indications	IIb C
Indications for stand-alone surgical ablation of AF	
Symptomatic AF refractory or intolerant to at least one class 1 or 3 antiarrhythmic medications	
Stand-alone surgical ablation may be considered for patients who have failed one or more attempts at catheter ablation or prefer primary surgical approach, irrespective of AF type	IIb C
Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a class 1 or 3 antiarrhythmic agent	
Stand-alone surgical ablation is not recommended irrespective of AF type	III C

* Adapted from the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation [15]

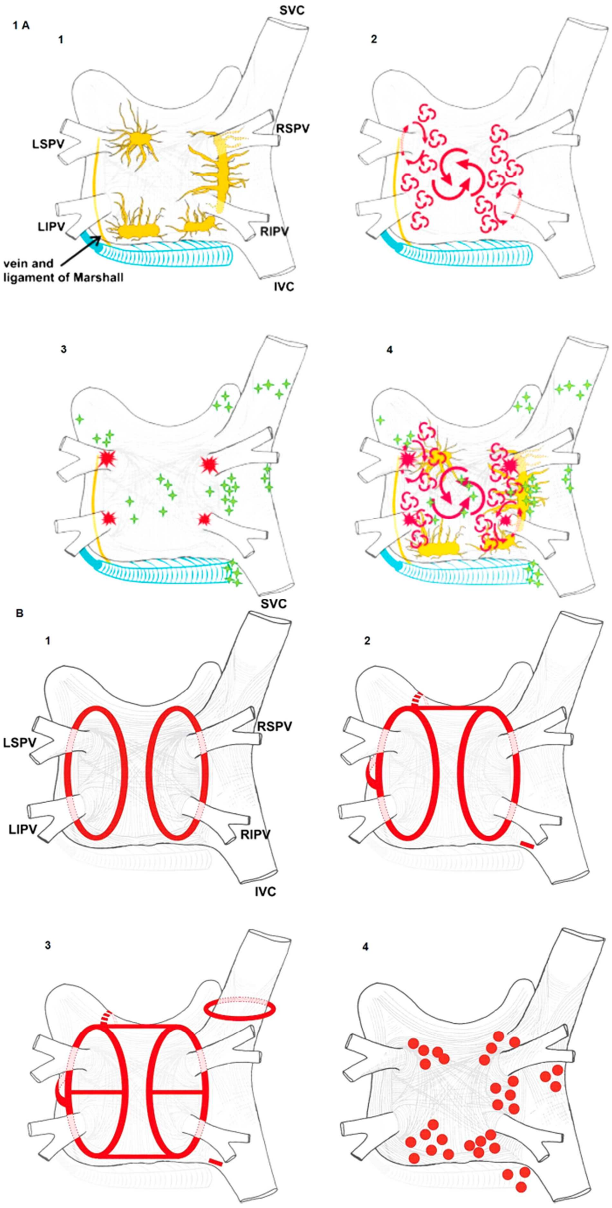
AF, atrial fibrillation.

Table 2: Comparison of different techniques available as modern alternatives to the conventional Cox-Maze procedure			
Technique	Advantages	Disadvantages	Comments
Radiofrequency ablation	Creation of precise and transmural lesions by measurement of tissue resistance; Avoidance of collateral damage; Easily used during epicardial application.[129, 130]	Potential risk of thrombogenicity of ablation lesion lines; Demanding performance of a full epicardial/endocardial box lesion.[131]	RF energy has been extensively used since many years in the electrophysiological laboratory and operating theatre.[132] Alternating current generates electromagnetic energy of frequencies between 350 and 1000 kHz.
Cryoablation	Preservation of the fibrous skeleton of the heart; Improved safety margin for ablation near the coronary arteries or atrioventricular node; Low incidence of thrombus formation.[12, 14, 40, 41]	Relatively time-consuming (2 to 5 minutes required per lesion); Higher recurrence rate in comparison with RF energy; Lesions on the beating heart might be ineffective; Increased risk of oesophageal lesions.[133]	Cryoablation is, next to RF ablation, the most common method of generating linear, continuous, and transmural lesions. Application of cold by fast-expanding N_2O (Boyle's law) or by Argon or Helium (max. -160◦C) leads to a three-step tissue injury (freeze and thaw, inflammation, and fibrosis).
Microwave	Deeper tissue penetration than RF ablation, thus enhancing the likelihood of a transmural lesion; Avoidance of endocardial surface charring, which may reduce the risk of thromboembolism.[134, 135]		In spite of its theoretical advantages, microwave energy failed to get into widespread use.

Laser energy	Generation of precise, focused, and well-demarcated lesions.	Requirement of a nearly perpendicular delivery angle for efficient energy delivery; Increased risk of atrial thrombus formation.[136]	
High-energy focused ultrasound	Tissue penetration independently of the surrounding fatty tissue; Fast creation of deep lesions (within less than 2 sec); Production of effective box lesions without electrical gaps; Adaption to tissue thickness; Reduced risk of thrombus formation, as the endothelium is relatively spared.[137, 138]		Ultrasound allows for the development of heat by oscillation of aqueous tissue.

Figures

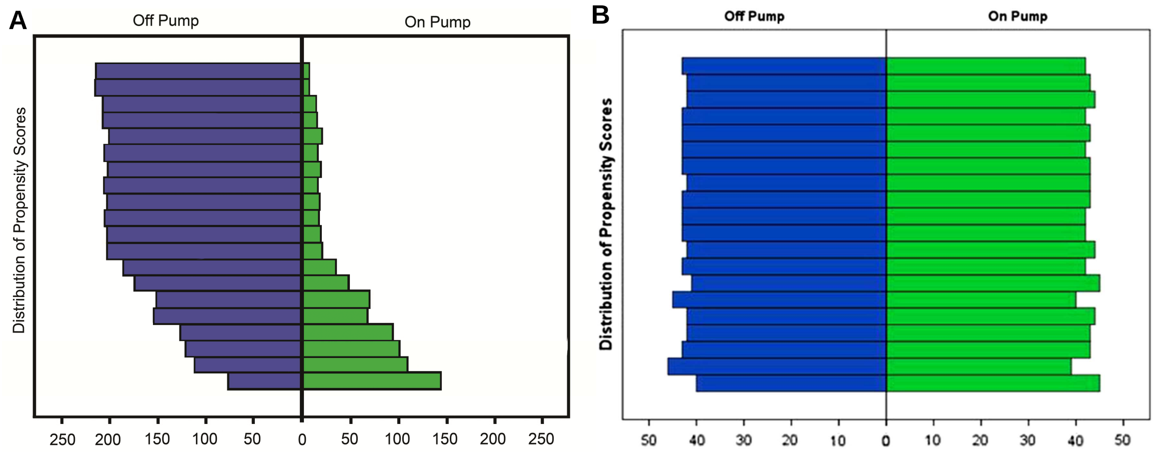
Figure 1:



(A) Structural basis of AF. (1) The posterior view of both atria shows the extension of muscular fibres onto the pulmonary veins (PVs). The five major left atrial autonomic ganglionic plexi (GP) are depicted in yellow. The coronary sinus (in blue) is enveloped by muscular fibers that connect to the atria. Also in blue are the vein and ligament of Marshall, which travels from the coronary sinus to the region between the left superior PV and the LAA. (2) Large and small re-entrant wavelets responsible for initiation and perpetuation of AF. (3) Common location of PV (red) and non-PV triggers (green). (4) The anatomic scaffold of arrhythmic activity in AF.

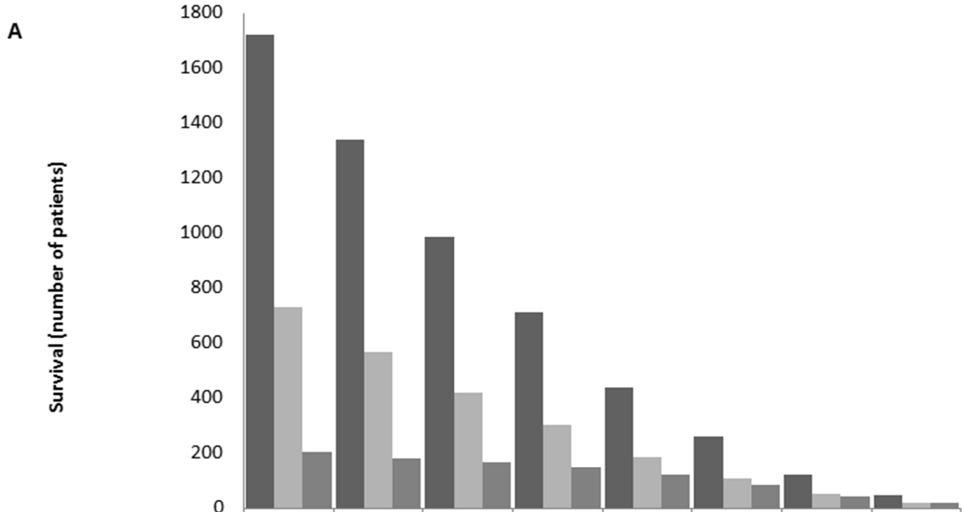
(B) Lesion sets often employed in AF ablation. (1) Circumferential ablation lesions are created around the right and left PVs to isolate electrically the PV musculature. (2) The most usual ablation-lines include a “roof line” connecting the lesions encircling the left and/or right PVs, a “mitral isthmus” line connecting the mitral valve and the lesion encircling the left PVs at the level of the left inferior PV, and an anterior line connecting either the “roof line” or the left or right circumferential lesion to the mitral annulus anteriorly. A linear lesion at the cavotricuspid isthmus is commonly employed in patients who have experienced cavotricuspid isthmus-dependent atrial flutter clinically or have it induced during electrophysiologic testing. (3) Additional ablation-lines between the superior and inferior PVs result in a figure of eight lesion set and a posterior inferior line affords electrical isolation of the posterior left atrial wall. Electrical isolation of the superior vena cava with an encircling lesion is performed in case of focal firing from the vein. (4) Some of the most common sites of ablation lesions when complex fractionated electrograms are targeted (these sites are also close to the autonomic GP). Modified from Calkins et al [15].

Figure 2:

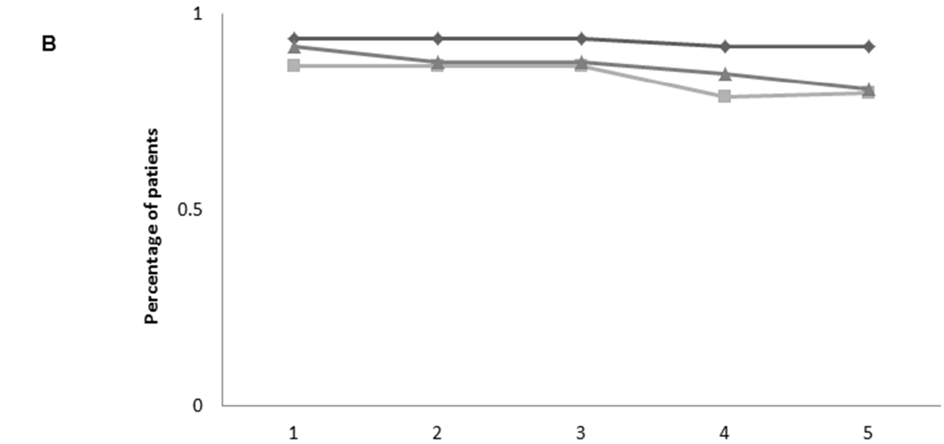


Distribution of percentile scores before (A) and after (B) propensy-matching, taking into account that the outcomes of the patients undergoing on-pump procedures were influenced by the fact that they had more comorbidities. The safety of on-pump and off-pump procedures seems to be comparable, with a modest benefit for the latter in terms of duration of ventilation, reoperation for bleeding and length of stay. Data from the North-American adult cardiac surgery database (1708 patients). Modified from Ad et al [42].

Figure 3:



	1	2	3	4	5	6	7	8
AF without cryoablation	1723	1340	986	715	439	259	123	47
AF with cryoablation	732	568	418	303	186	110	52	20
Sinus rhythm	207	183	170	149	122	84	42	17

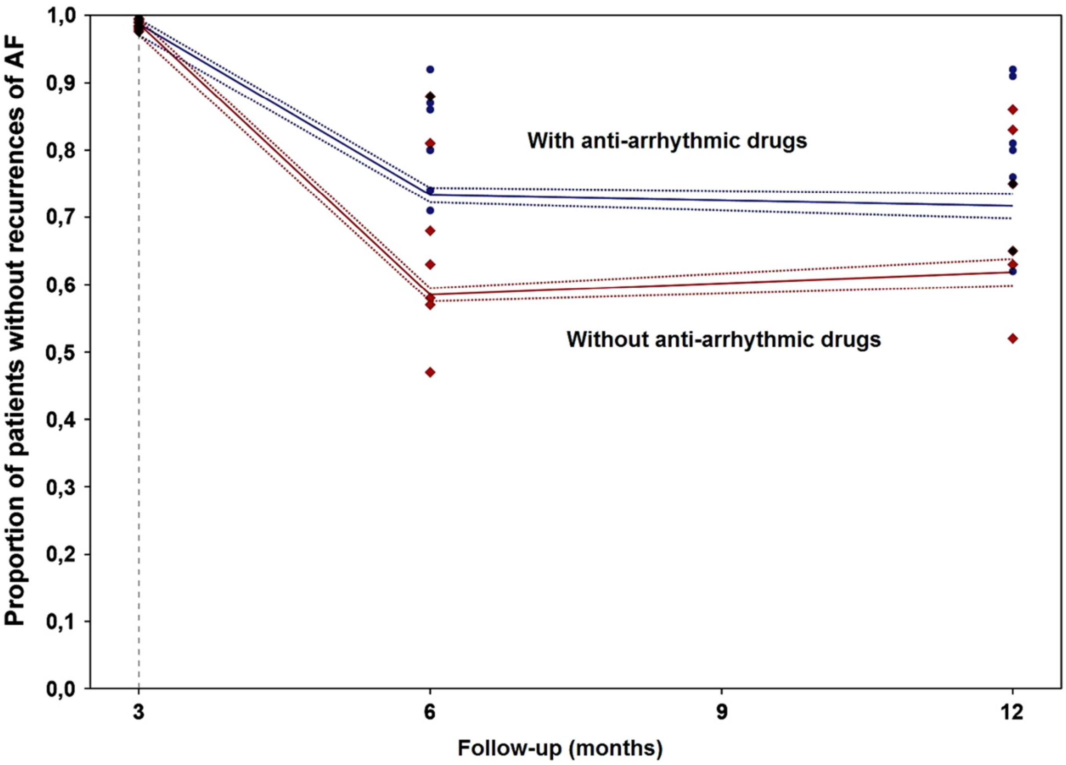


	1	2	3	4	5
Overall AF freedom	94%	94%	94%	92%	92%
AF freedom off-AAD	87%	87%	87%	79%	80%
Survival	91.8%	87.8%	87.8%	84.9%	80.9%

(A) Cumulative survival of patients in sinus rhythm and atrial fibrillation with and without cryoablation after mitral valve surgery. Ablation of atrial fibrillation concurrently with mitral valve surgery boosted survival up to 5 years after surgery. Modified from Haensig et al [40].

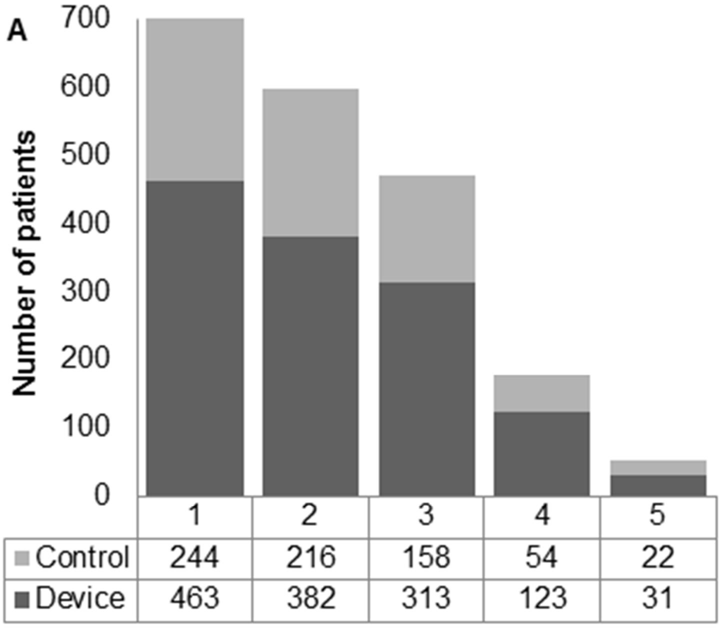
(B) Proportion of patients in SR overall and off-anti-arrhythmic drugs 6, 12, 24 and 36 months after surgery. Cumulative arrhythmia-free survival for 5 years after AF ablation. Modified from Ad et al[53].

Figure 4:



Pooled results of a meta-analysis including 23 observational studies on radiofrequency ablation for atrial fibrillation. Other energy sources, e.g. microwave and HIFU, were excluded due to their disappointing results. The overall freedom from atrial fibrillation for minimally-invasive surgery after 12 months, was 79% and 69% on- and off-AAD, respectively. The results at 6 months are slightly worse (64% off-AAD and 75% on-AAD), probably because they derive from the very first trials of minimally-invasive surgery and keeping patients on AAD for 6 months after intervention is not unusual. The blue line represents the overall results with anti-arrhythmic drugs. The blue dotted line is the confidence interval of the overall results. Blue circles represent the different studies and their outcome. Red lines and diamonds represent results without anti-arrhythmic drugs. Modified from Krul et al [70].

Figure 5:


A
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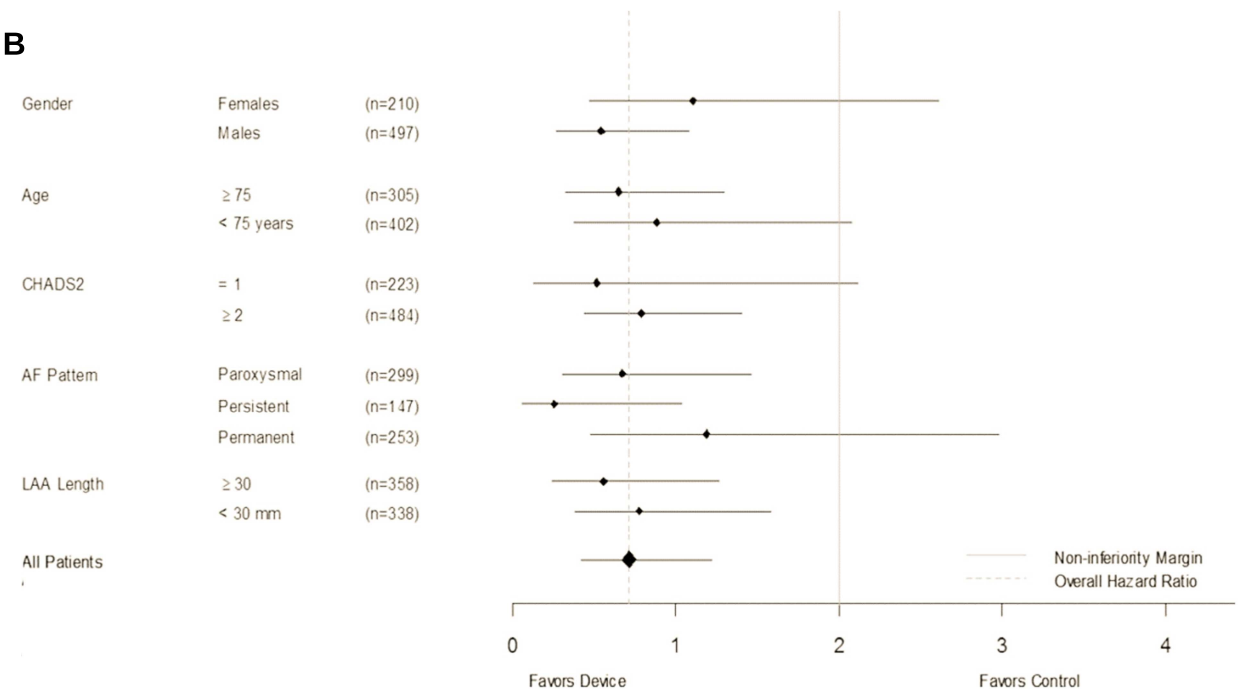
B
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Males
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Age
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< 75 years
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CHADS2
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(n=484)
AF Pattern
Paroxysmal
(n=299)
Persistent
(n=147)
Permanent
(n=253)
LAA Length
≥ 30
(n=358)
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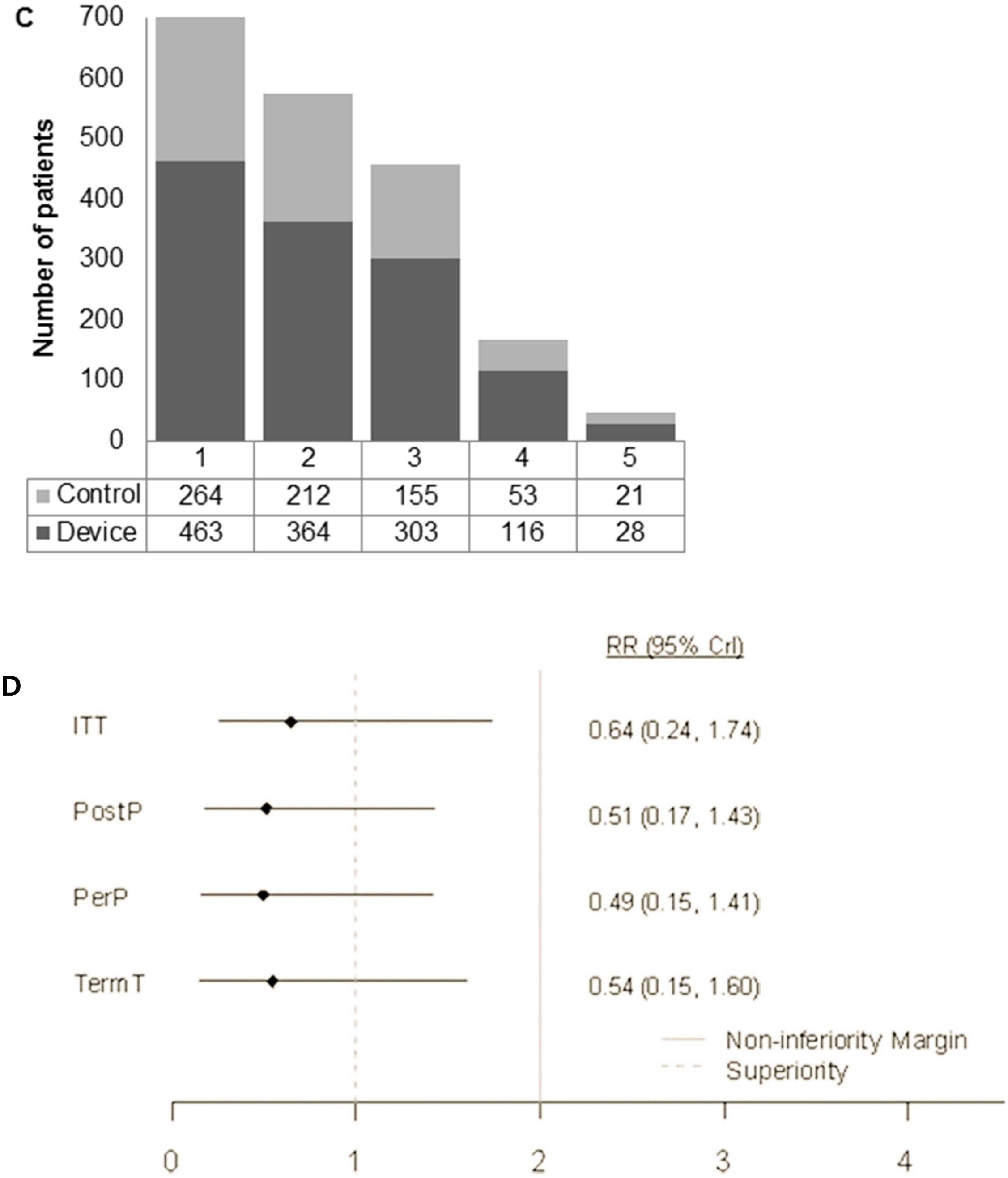


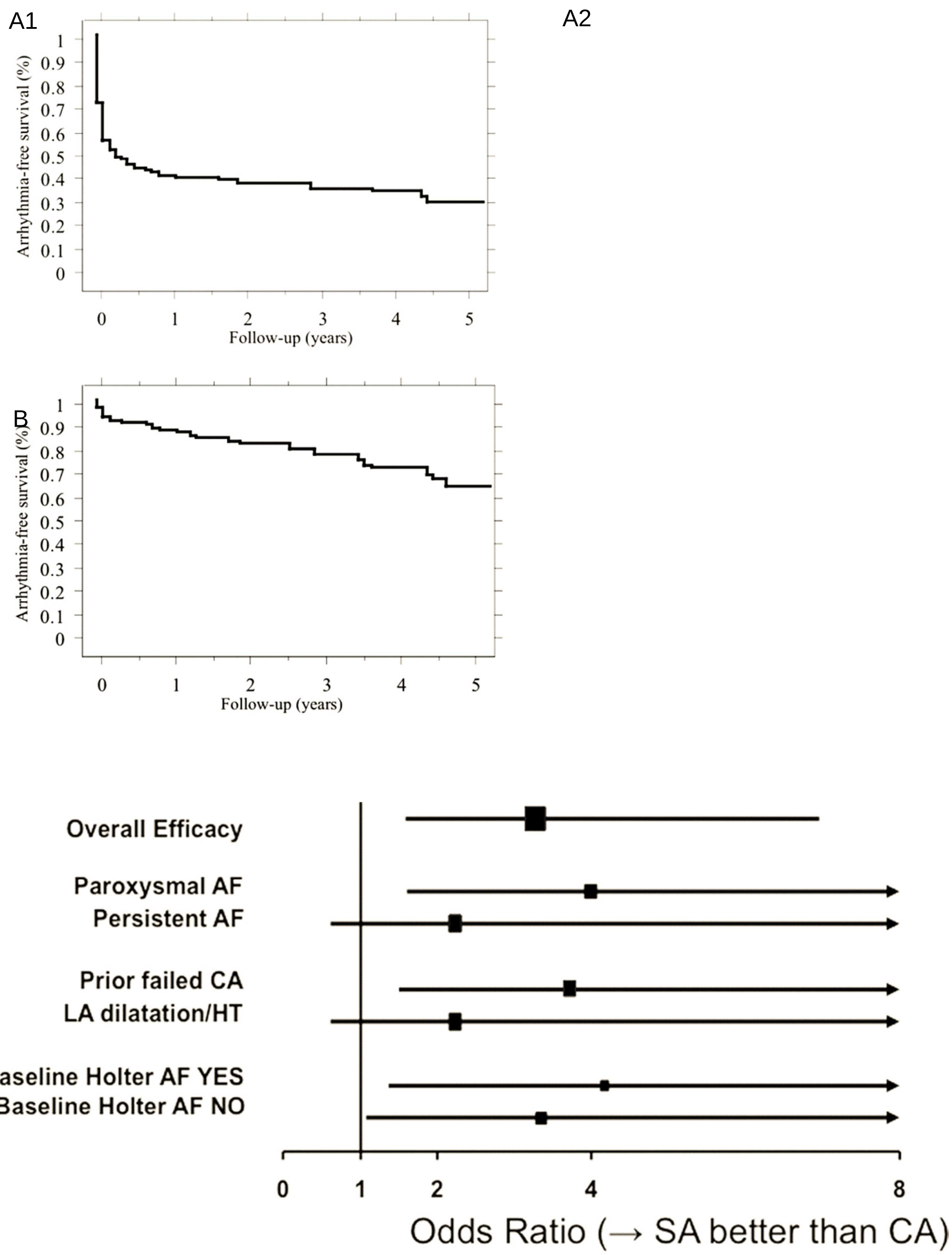
(A) Kaplan-Meier curves for the composite primary efficacy end point of stroke, systemic embolism, and cardiovascular death (incident probabilities for the intention-to-treat analysis are shown with time calculated as days since randomisation).

(B) Primary efficacy results by patient subgroup. The hazard ratios and 95% confidence intervals are shown for the primary efficacy end point of stroke, systemic embolism, and cardiovascular death for all patients and for several patient subgroups. Results are from Cox proportional hazards models, with each subgroup examined in a separate model. The number of randomized patients with data available for the subgroup variable is shown. For left atrial appendage (LAA) length, 30 mm represents the median value. AF stands for atrial fibrillation; and CHADS2 is a thromboembolic risk score considering the following factors: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

(C) Kaplan-Meier curves for the primary safety end point, which included serious adverse events related to excessive major bleeding (e.g., intracranial or gastrointestinal bleeding) or procedure-related complications (e.g., serious pericardial effusion, device embolization, and procedure-related stroke). The incident probabilities for the intention-to-treat analysis are shown with time calculated as days since randomisation.

(D) Primary efficacy results for the secondary prevention group. The rate ratios (RR) and 95% credible intervals (CrI) are shown for the primary efficacy end point for all 4 analyses: intention-to-treat (ITT), post-procedure (PostP), per-protocol (PerP), and terminal therapy (TermT). The number of randomised patients with data available for each analysis is shown. Modified from Reddy et al [103].

Figure 6:



(A) Kaplan-Meier event-free survival curve after a single (1) or since the last (2) catheter ablation attempt. Of note, arrhythmia-free survival rates after single catheter-based intervention decreased from 40% at 1 year to 29% at 5 years. The majority of recurrences took place in the first 6 months after intervention, being valvular heart disease and non-ischaemic dilated cardiomyopathy independent predictors of recurrence. Moreover, arrhythmia-free survival steadily declined at an annual recurrence rate of 8.9% since last ablation attempt. Modified from Weerasooriya et al [112].

(B) The FAST study (Atrial Fibrillation Catheter Ablation versus Surgical-ablation Treatment) enrolled patients with paroxysmal and persistent AF for at least 12 months that was refractory to or intolerant of at least 1 AAD, the majority with failed prior catheter ablation. They were randomised to receive either percutaneous-catheter ablation (PV isolation with optionally additional lines; n=63) or surgical-ablation (PV isolation with bipolar RF, GP ablation, and LAA excision; n=61). Despite doing significantly better in terms of freedom from atrial arrhythmias without medication at 12 months (36.5% versus 65.6%; p=0.0022), surgical-ablation was associated with significantly more adverse events than catheter ablation (34.4 versus 15.9; p=0.027). However, most of them were procedural complications, such as pneumothorax, major bleeding and pacemaker implantation; and had no actual impact on final outcome. The forest plot of subgroup analysis reinforces the efficacy of surgical-ablation (SA) versus catheter ablation (CA) even for more complex cases. AF indicates atrial fibrillation; LA, left atrium; and HT, hypertension. Modified from Boersma et al [120].

RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION DURING CONCOMITANT CARDIAC SURGERY

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Abstract

Background: We present the experience of our centre with radiofrequency (RF) atrial fibrillation (AF) ablation concomitantly with an otherwise indicated cardiac surgery.

Methods: Between 2005 and 2012, 170 patients were submitted to AF ablation with uni/bipolar-RF devices, depending on the requirements of the concurrent surgical procedure. They were followed for 3-months after surgery and then as appropriate for the structural cardiac disease. In 2013, patients still alive underwent rhythm monitoring with ECG and 24-hour tape for those in sinus rhythm (SR).

Results: The mean age was 65 years old and 42% of the patients were male. Prevalence of paroxysmal AF was 7%. The most common comorbidities were hypertension and diabetes mellitus and ~80% of the patients were in NYHA class II/III. 75% of the patients were on anticoagulation therapy, particularly in case of non-paroxysmal AF, and 11% of them had history of cerebrovascular events. Pre-operative echocardiographic examination showed that most patients had preserved ejection fraction and dilated left atria (diameter 53.2±7.5 mm).

The most common indication for cardiac surgery was valve disease, especially mitral valve disease. The prevalence of rheumatic disease was ~40%. Unipolar RF was more often used in case of atrioventricular valve repair/replacement, whereas bipolar RF tended to be preferred for aortic valve and coronary surgery. Prophylactic closure of the left auricle was performed in more than 75% of the patients. Pulmonary-vein isolation was performed in all patients, followed by other left atrial ablation lines. The right atrial isthmus was ablated in less than 10% of the patients. 80% of the patients received post-operative intravenous amiodarone and 66% had at least one AF relapse. Overall, surgical complications were rare, being the most frequent pacemaker implantation (15%) and infection, and there were no significant differences between unipolar and bipolar RF. Direct current cardioversion (DCC) was attempted in 23% of the patients before discharge. The median length of stay was 9 days (p25-p75:7-14). 69% of the patients were in SR at discharge, with 90% on anticoagulation, 69% on amiodarone and 37% on beta-blockers. Anticoagulation was more common in patients with nonparoxysmal AF and when unipolar RF was used. In-hospital mortality was less than 3% (5 patients). Follow-up at 3 months was complete for all the patients, being 50% in SR. 92%

of the patients were on oral anticoagulation and 75% of the patients were on antiarrhythmic drugs. DCC was successful in 8/12 patients. In the multivariate analysis, being in SR at discharge was the single independent predictor of maintaining SR at 3 months. In 2013, 145 patients were still alive (all-cause mortality 15%) and follow-up was complete for 138 (95.2%). At a median follow-up of 31 months (469 patients*year), 40% of the patients were in SR, being 45% of them on antiarrhythmic drugs, 80% on anticoagulation and 53% on beta-blockers. There were no significant differences between uni- and bipolar RF devices.

Conclusion: AF ablation with RF devices fares reasonably well even in an elderly population, with longstanding AF associated with severe heart disease, dilated left atria, and commonly rheumatic disease.

Key words: Atrial fibrillation; cardiac surgery; radiofrequency ablation

Introduction

Atrial fibrillation (AF) is the most common of all clinically sustained heart arrhythmias, affecting 1-2% of the population. Both ageing of the population[1, 2] and increased survival from acute cardiovascular events are fostering AF burden worldwide.[1-5]

AF often concurs with several cardiovascular risk factors and diseases [6-8] and it is associated with a high morbidity and mortality as well as a significant consumption of health care resources.[9, 10]

The pathogenesis of AF as well as the progression from paroxysmal to persistent AF are hitherto only partially understood and thus the therapeutic armamentarium currently available is limited and modestly efficacious. Medical treatment aims at controlling symptoms, reducing recurrences and decreasing thromboembolic risk. However, the advantage of rhythm versus rate control is far from being settled and the efficacy and safety of both antiarrhythmic and anticoagulation drugs remains a matter of concern.[11] Therefore, until novel therapies targeted to the pathogenic mechanisms responsible for initiation and perpetuation of AF become the mainstay, ablation of arrhythmic triggers, either through percutaneous or surgical approaches, draw advantage from the ability to abrogate the inherent issues of the sustained arrhythmia itself as well as its cumbersome medical treatment.

On the other hand, the number of patients with AF referred for coronary artery bypass graft (CABG) and/or valve surgery[12, 13] is on the rise and it considerably boosts the mortality risk over the years after operation.[14] Besides improving long-term survival, surgical ablation of AF may additionally obviate the need of lifelong anticoagulation.[15] This risk can be further decreased by intraoperative resection or exclusion of the left atrial appendage (LAA).[16]

Since the first Cox-Maze procedure in 1987, surgical treatment of AF has changed in parallel with the technological advances, including novel energy delivery devices. Replacement of surgical incisions with linear ablation lines has transformed a cumbersome procedure into one accessible to most surgeons, while keeping the same success of conventional Cox-Maze procedure.

Nonetheless, compelling evidence on the benefit of adjuvant surgical ablation versus established antiarrhythmic therapy, as well as comparing different lesion sets and energy sources is still scarce. Indeed, methodological limitations, such as variable AF definition, heterogeneity of lesion sets and unstandardized follow-up, have been precluding pooling data and comparing results from different studies. These caveats prevent drawing definite conclusions concerning efficacy and safety and thus surgical ablation is recommended for patients refractory or unsuitable for percutaneous ablation or in the setting of an otherwise indicated cardiac surgery, provided that the risk of the concurrent procedure remains low and there is a reasonable chance of success.[15] Accordingly, surgical ablation of AF in patients undergoing cardiac surgery receives only a recommendation class IIa or IIb, depending on the presence or absence of AF symptoms, respectively.

Moreover, the factors responsible for the individual response to treatment are far from being completely understood. Therefore, there is a pressing need to develop accurate models of predicting which patients would benefit more from surgical therapy and which would require more comprehensive ablation strategies.

In this article, we present the experience of our centre with uni- and bipolar radiofrequency (RF) ablation in 170 patients undergoing concomitant cardiac surgery. We intend (i) to assess the efficacy and safety of RF ablation of AF in patients undergoing concomitant cardiac surgery and (ii) to identify the main predictive factors of success or failure following AF ablation at 3-months.

Methods

Study design

This is an observational hospital-based retrospective cohort study, conducted at the Department of Cardiothoracic Surgery, Centro Hospitalar São João, EPE, Porto, Portugal.

Patients

Overall, 170 patients admitted to the Department of Cardiothoracic Surgery either for myocardial revascularization or valve repair/replacement with known AF, defined in accordance to the guidelines[15], were submitted to concurrent AF ablation between 2005 and 2012.

Data regarding demographics, cardiovascular risk factors and AF characteristics were recorded for all the patients. Electrocardiography (ECG), transthoracic echocardiographic examinations and laboratory tests were routinely performed before surgery.

Surgical technique

All patients underwent median sternotomy. Ablation technique comprised two main clinical situations. One mainly related with paroxysmal AF, where the procedure was limited to encircling left and right pulmonary veins (PV) through epicardial bipolar irrigated RF energy (Cardioblate LP from Medtronic), sometimes combined with ablation of the LAA (Figure 1). This strategy was mainly performed in those patients not requiring left atrium opening and in the beating heart and often off-cardiopulmonary bypass.

In all other clinical scenarios, a combined cut-and-sew with endocardial unipolar irrigated RF device (Cardioblate from Medtronic) was used under extracorporeal circulation and cardioplegic arrest. It comprehended the following ablation lines: right oblique atrial incision (from right oracle to inferior vena cava), interatrialseptotomy vertical incision (from the inferior vena cava to left atrial roof). RF energy completed the lesion subset: left and right PVs isolation; box lesion, through connection of cranial and caudal extremities of PV encircling lines; LAA; and left isthmus line, connecting de caudal left PVs encircling line with the mitral annulus (Figure 2).

During the study time frame some of the initial patients with persistent and longstanding AF had exclusive PV isolation and others didn’t have the caudal box line.

The line of the right atrial isthmus was done mostly in the beginning. It was partially abandoned because of significant atrioventricular conduction block. Recently, only patients with atrial flutter had this line done.

Definitions

AF was defined as paroxysmal, persistent/longstanding persistent and permanent according to recent guidelines.[15] Data provided by the referring doctor was used to classify patients’ AF. AF recurrence was considered any atrial arrhythmia lasting more than 30 seconds detected on ECG or 24-hour Holter monitoring 3 months after surgical ablation.[17]

Postoperative management and follow-up

After surgery, patients were managed according to the standard recommendations for their concurrent heart disease in our hospital. In the case of postoperative arrhythmias, amiodarone was the first-line treatment unless specifically contraindicated. Other drugs were used as required by the underlying heart disease and surgery. Direct current cardioversion (DCC) was attempted when deemed suitable. Drug prescription at discharge took into account not only the primary heart disease but also the heart rhythm on the last ECG. In-hospital deaths during the early postoperative period (7 days) were excluded for the analysis of the heart rhythm at discharge.

Patients were followed according to the protocol routinely used in our institution for their primary heart disease. All of them had an appointment within 3 months after surgery but subsequent outpatient appointments were booked as deemed appropriate by the Cardiologist or Cardiothoracic surgeon taking into account the patients' evolution. ECG and 24-hour Holter monitoring were requested at the first appointment after surgery and at variable time points afterwards. Therefore, we used the data obtained at 3 months to analyse the short-term results of the RF ablation procedure.

Between April and August 2013, all the patients still alive were invited to come to the clinics in order to check their heart rhythm. Rhythm monitoring was done using 12-lead ECG and, in case the patient was in sinus rhythm (SR), 24-hour tape. The follow-up period varied between 6 and 94 months, with a median of 31 months (469 patients*year). The 26 patients who died in the meanwhile were excluded for the analysis at this time point.

Data analysis

Categorical variables were presented as counts and percentages, and quantitative variables as means and standard deviation (SD) or medians and interquartile ranges (IQR – 25^{th} percentile-75^{th} percentile) as appropriate depending on the empirical distribution of the variables.

Subgroups of patients were compared by using chi-square test or Fisher's exact test for categorical variables and T-test and Mann-Whitney rank-sum tests for symmetrical and asymmetrical quantitative variables, respectively. The normality of the distribution of quantitative variables was assessed by the Kolmogorov-Smirnov test.

In order to have a more thorough understanding of the factors associated with the presence of AF recurrence (non-sinus rhythm) at 3 months after surgery, univariate and multivariate logistic regression models were used. Potentially relevant variables were selected from the database from pre-operative, surgical and post-operative variables. These variables were included in the univariate model. All the variables with a p-value lower than 0.1 were considered for inclusion in the multivariate model to increase the sensitivity of the analysis. We tried three different models, each one adjusting for pre-operative, surgical and post-operative variables. Adjustment for age and sex were additionally included in all models. Thus, the final multivariate model included adjustment for sex, age and all variables with crude association measures with p-values ≤ 0.1 in the univariate analysis. Goodness-of-fit and discriminative/predictive power for the multivariate logistic regression models were assessed based on the Hosmer-Lemeshow statistic and test and the analysis of the area under the ROC curve. Influence of outlier data values on model fit was estimated using leverage statistics (Cook's influence statistics with a cut-off of 1 as screening criteria), and collinearity was assessed by evaluation of the coefficients correlation matrix. Results were presented as odds ratios (OR) for each category, as compared with a predefined reference category, and their respective 95% confidence intervals.

All tests were two-sided, and p values less than 0.05 were considered as indicating significant differences. Analysis was carried out using the statistical software SPSS 20.0 for Windows.

Ethical considerations

The study was carried out according to the principles of the Declaration of Helsinki and approved by the hospital ethics committee.

Results

From admission to discharge (Tables 1, 2 and 3)

The mean age was 65 years old and 72 (42.2%) of the patients were male. The majority of them had permanent or persistent/longstanding persistent AF, being paroxysmal AF much less frequent (7.0%). The most common comorbidities were hypertension and diabetes mellitus. Almost all the patients were in NYHA class II or III. Most of the patients were overweight, with a mean BMI of 27 kg/m^2. More than 75% of the patients were on anticoagulation therapy, particularly in case of non-paroxysmal AF, and the prevalence of previous cerebrovascular events was 11%. Pre-operative echocardiographic examination showed that most patients had preserved LVEF and dilated LA (diameter 53.2±7.5 mm). Patients with paroxysmal AF as well as patients submitted to bipolar RF ablation had significantly smaller LA (46.7±5.9 mm versus 51.1±6.4 mm, p=0.030 for paroxysmal and non-paroxysmal AF, respectively; and 47.7±5.9 mm versus 52.3±6.2 mm, p<0.001for unipolar and bipolar RF, respectively).

The most common indication for cardiac surgery was valve disease, especially mitral valve disease. Almost half of the patients had also aortic and/or tricuspid valve disease. More than one-fourth had coronary artery disease. Therefore, valve surgery was much more frequent (mitral 58%, aortic 44% and tricuspid 54%) than CABG (22%), and bipolar RF was used in about 30% of the cases. Unipolar RF was more often used in case of atrioventricular valve repair/replacement, whereas bipolar RF tended to be preferred for aortic valve surgery and CABG. Prophylactic closure of the LAA was performed in more than three-fourths of the patients, being higher than 90% when unipolar RF was employed. PV isolation was performed in all the patients and the remaining left atrial ablation lines were usually done. On the contrary, the right atrial isthmus was ablated in less than 10% of the patients. The cardiopulmonary bypass time and the aortic clamping time were similar irrespective of the type of RF employed.

About 80% of the patients received post-operative intravenous amiodarone and AF episodes were reported in 66% of them. Overall, surgical complications were rather uncommon, being the most frequent pacemaker implantation and infection (of any site), and there were no significant differences between unipolar and bipolar RF. DCC was attempted in 23% of the patients before discharge and only in patients with nonparoxysmal AF. The median length of stay was 9 days (p25-p75: 7-14). Nearly 69% of the patients were in SR at discharge, with 90% on anticoagulation, 69% on amiodarone and 37% on beta-blockers. Anticoagulation was more common in patients with nonparoxysmal AF and when unipolar RF was used. In-hospital mortality was less than 3% (5 patients).

Follow-up at 3 months (Table 4)

Follow-up at 3 months was complete for all the patients, being almost half of them in SR (49%). Noteworthy, patients submitted to unipolar and bipolar RF ablation fared equally well in terms of maintenance of SR at 3 months. Nearly 92% of the patients were on oral anticoagulation, being the proportion lower when bipolar RF was employed. On the contrary, these same patients tended to take more often beta-blockers. About three-fourths of the patients were on anti-arrhythmic drugs, 70% on amiodarone and 5% on digoxin. DCC was attempted in 12 patients (7.6%), being successful in 2/3 of them (n=8). In the univariate analysis (Table 5), the variables significantly associated with an increased risk of arrhythmia relapse at 3 months were tricuspid disease (OR 2.644, 95%CI 1.381-5.062; p=0.003) and recurrence of AF in the immediate post-operative period (OR 2.009, 95%CI 1.022-3.948; p=0.043). On the contrary, being in SR at discharge (OR 0.275, 95%CI 0.128-0.591; p=0.001) as well as being discharged on amiodarone (OR 0.436, 95%CI 0.213-0.890; p=0.023) were significantly associated with remaining in SR at 3 months. However, in the multivariate analysis, being in SR at discharge was the single independent predictor of maintaining SR at 3 months (OR 0.353, 95%CI 0.136-0.919; p=0.033) (Table 6).

Follow-up in 2013 (Table 4)

In 2013, 145 patients were still alive (all-cause mortality 26 patients, 15.2%) and follow-up was complete for 138 (95.2%) of them. At a median follow-up of 31 months (p25-p75: 20.8-50.8), which meant 469 patients*year, 40% of the patients were in SR, being 34% of them on amiodarone and 12% on digoxin. More than 80% were on oral anticoagulation and 53% on beta-blockers.

Discussion

We present the experience of our centre in AF ablation concomitantly with an otherwise indicated cardiac surgery for valve or coronary artery disease. In our series, 170 patients were submitted to RF ablation, according to the needs of the scheduled concurrent intervention and attempting to be time efficient and minimally invasive. The bipolar device was employed epicardially when left atriotomy was not required, affording only isolation of PVs and sometimes the LAA, without any additional lesions to the mitral annulus or connecting the two PV islands.

Even though SR maintenance is better when the connecting lesion is performed, evidence suggesting the superiority of bipolar over unipolar RF is heretofore limited and we found no association between the type of energy and SR at 3 months. Despite being more efficacious in terms of transmurality, the limited lesion set performed in our centre with bipolar RF devices is likely not enough to abrogate the arrhythmia in cases other than paroxysmal AF. We might therefore speculate that the lower efficiency of the unipolar RF might well be counterbalanced by the higher number of lesions induced, i.e., the more comprehensive ablation concept. In fact, the substrate of complex and longstanding AF requires ablation of the full lesion set of the conventional Cox-Maze procedure to be successful. In the same line, addition of right atrial isthmus line brought not advantage to maintenance of SR at 3 months, which is in keeping with previous reports.[18-20] Indeed, ablation of the right atrial isthmus was performed in less than 10% of the patients, as this line was initially done as part of the standard lesion set in the arrested heart. However, it was sooner abandoned due to the high rate of AV block requiring pacemaker implantation after surgery. This line is particularly relevant to avert atrial flutter and may be more safely performed in the beating heart using a percutaneous endovascular approach. Therefore, catheter-based ablation of the RA isthmus would be a reasonable alternative to patients with atrial flutter of RA origin after AF ablation. Indeed, “hybrid interventions” that combine the best of the surgical and catheter-based approaches are the most promising alternatives for the future treatment of AF.

Bipolar RF was preferentially used in patients undergoing off-pump CABG, which may well explain the lower cardiopulmonary bypass time. In the same line, these patients were more often prescribed beta-blockers, which are recommended after acute myocardial infarction, and less frequently anticoagulation, which is mandatory after valve replacement with a mechanical prosthesis but not after coronary revascularisation.

In comparison with similar studies, the success of our intervention at discharge and at 3 months is modestly lower.[21-26] Several reasons can be put forward to explain this apparently worse outcome. In one hand, our patients presented with multiple risk factors for failure, namely they were older than most populations included in other studies, had longer duration of AF and severe underlying cardiac structural disease with associated heart failure. Therefore, they tended to have very dilated left atria, in which the longstanding arrhythmia is strongly supported by electrical and myocardial remodelling. Indeed, the ''AF begets AF'' phenomenon, which describes the tendency of AF to self-perpetuate, means that the longer the duration of AF, the more stable it becomes and the more difficult it is to resume SR.

The vast majority of our patients had permanent AF, which means that both patient and physician accepted the arrhythmia and thus rhythm-control was no longer pursued. AF ablation in this setting, despite being more demanding and more likely to fail, represented an unexpected chance of abrogating the arrhythmia and its cumbersome medical treatment. In line with this, *Benussi et al.* had already found that patients with permanent AF had a lower success rate than those with persistent AF.[25]

In addition, logistic regression analysis has consubstantiated that permanent AF ($p<0.0001$), a longer preoperative AF duration ($p=0.005$) and larger preoperative left atrial size ($p=0.018$) are the single predictive factors of postoperative AF recurrence.[22, 23, 27] However, in our multivariate model, being in SR at discharge was the single independent predictor of maintaining SR 3 months after surgery ($p=0.033$). This is in keeping with the notion that outcomes at 3 months are closely related to results at discharge and thus longer follow-up is advisable to appropriately address recovery of stable SR. Nonetheless, it is also worth mentioning that the proportion of patients in SR at 3 months and in 2013 was quite similar (49% and 40%, respectively), which means that resumption of SR tended to be maintained over time.

On the other hand, rheumatic valve disease was present in almost 40% of the patients, and in this setting AF ablation is well-known to be less successful.[28] Furthermore, in this group of patients resuming SR does not necessarily mean recovery of appropriate atrial contraction.[29] In fact, there was a trend towards lower recovery of SR at discharge and at 3 months for patients with rheumatic disease but the difference failed to reach statistical significance (60.9% versus 72.9% at discharge and 46.8% versus 51.2% at 3 months for patients with and without rheumatic disease, respectively). These figures are similar, or slightly better, than the previously reported for patients with rheumatic valve disease undergoing left atrial maze (52.5% and 55.0% of the patients in SR at discharge and 6 months, respectively).[30]

Benussi et al. reported very high rates of SR recovery (79%, 87% and 89% at 3, 6 and 12 months, respectively), but the poor follow-up rates precluded drawing reliable conclusions from these results.[23]

Heart failure symptoms were also very common in our series and *Onorati et al.* showed lower success rates in this setting (SR prevalence of 74% and 64% at 6 and 12 months, respectively). They further showed that recovery of SR was associated with improving heart failure[24], but unfortunately we do not have data on the functional class of the patients after surgery. In keeping with this, concomitant AF ablation even in high-risk patients seems to add no further operative risk and may well improve clinical outcomes.[31]

A prospective study of bipolar RF ablation in patients with permanent or persistent AF found a rate of SR of 64% (95% CI 75–93) at discharge, which is identical to our results.[25]

In addition, the learning curve associated with this procedure should not be overlooked when interpreting the results, particularly for the first patients. This is particularly relevant in our series, as the ablation procedure was done by several surgeons, each one with his own learning curve.

We would like to highlight that the overall SR restoration rate of 50% at 3 months is an encouraging result in a heterogeneous patient population with prolonged AF evolution and serious underlying heart disease. The percentage of patients in SR off-AAD was 25%, as we tended to keep the patients on

AAD for the first 3 months after surgery to prevent recurrences in the short post-operative period. Indeed, the inflammatory response elicited by the proper surgical intervention might have contributed to the lower success found within this short time frame. Indeed, *Gillinov et al.* suggested that the prevalence of AF peaks early after surgical intervention (2 weeks) and then decreases to 16% at 1 year.[27]

The very long-term outcomes (more than 5 years) of surgical AF ablation are still not known. In 2013, we looked back to all the patients submitted to AF ablation thus far and the rate of SR was 40%, with a median follow-up of 31 months (p25-p75: 20.8-50.8), corresponding to 469 patient*years. There was a trend towards higher success for patients with paroxysmal AF, but it failed to reach statistical significance, probably because of the small number of patients in this category (p=0.082). We hypothesise that patients who remain in SR at 3 months tend to keep in the long term. We would like to note that the overall SR restoration rate of 40% at late follow-up is an encouraging result in a heterogeneous patient population with long preoperative AF duration and severe underlying heart disease. It is also worth mentioning that the proportion of patients on amiodarone decreased in contrast with an increase in the prescription of digoxin. This could be attributable to the adverse side effects of amiodarone in the long term and to the fact that amiodarone was routinely given for 3 to 6 months after surgery.

Study limitations

Being an observational retrospective study, there was not standardised heart rhythm-monitoring in place during follow-up and hence it is possible that asymptomatic self-terminating AF episodes may have occurred during hospital stay or between outpatient appointments without being recorded. The patients did not undergo rigorous follow-up by present standards, although all of them had 24-hour Holter monitoring in addition to the 12-lead ECG to document their rhythm.

Conclusion

Concomitant AF ablation with either endocardial monopolar or epicardial bipolar RF confers satisfactory recovery of SR, with minimal intraoperative and early postoperative complications. Moreover, maintenance of SR seems to be fairly stable even at a long follow-up. Therefore, these data reinforce the evidence available thus far on the benefit of systematically adding ablation procedures to the standard cardiac surgery in patients suffering from AF. Indeed, this study suggest that RF ablation is still reasonably efficacious in an elderly population, with longstanding AF associated with severe heart disease, dilated left atria, and common rheumatic disease.

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Figures

Figure 1

Lesions usually performed with epicardial bipolar radiofrequency devices. In our centre, isolation of the pulmonary veins (PV) and ablation of the left atrial appendage (LAA) were routinely done. IVC inferior vena cava, SVC superior vena cava.

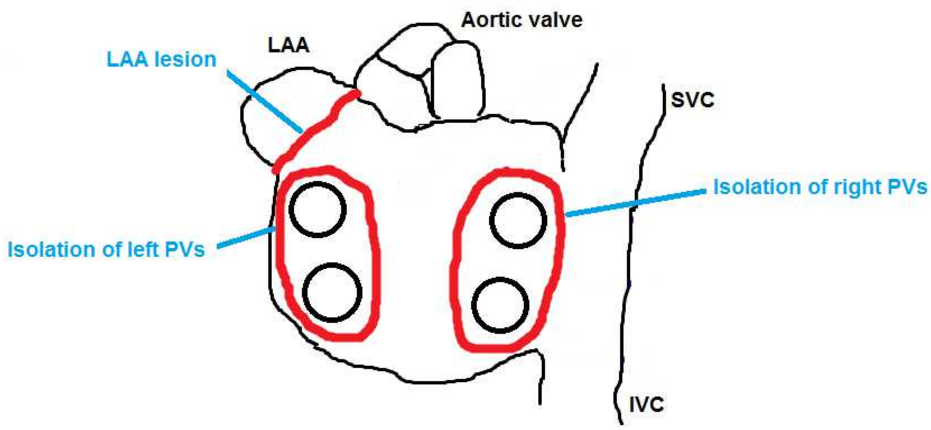
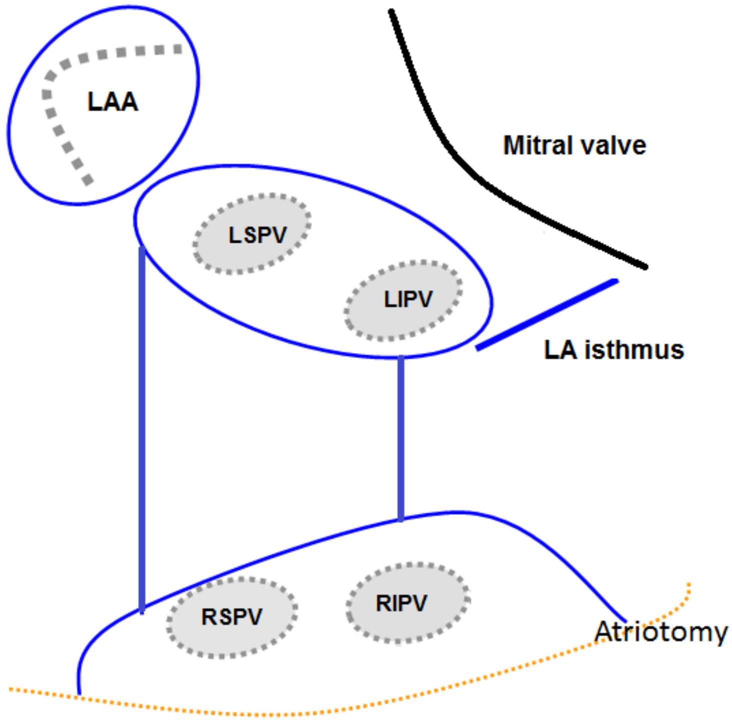


Figure 2

Lesions usually performed with endocardial unipolar radiofrequency devices. See section on *Surgical technique* for an appropriate explanation of the procedure. LA left atrial, LIPV left inferior pulmonary vein, LSPV left superior pulmonary vein, RIPV right inferior pulmonary vein, RSPV right superior pulmonary vein



Tables

Table 1: Pre-operative, surgical and post-operative characteristics of the patients.

Pre-operative data		All (n=170)	Paroxysmal AF (n=12)	Non-paroxysmal AF (n=158)	p-value	Unipolar RF (n=117)	Bipolar RF (n=53)	p-value
Age (years), mean (SD)		65 (11)	65 (11)	65 (11)	0.897	63 (11)	69 (10)	<0.001
Sex (male, %)		71 (41.8)	3 (25.0)	68 (43.0)	0.222	43 (36.8)	28 (52.8)	0.049
AF type	Paroxysmal	12 (7.1)				5 (4.3)	7 (13.2)	
	Persistent/LSP	45 (26.5)				33 (28.2)	12 (22.6)	
	Permanent	113 (66.5)				79 (67.5)	34 (64.2)	
Hypertension		85 (50.0)	9 (75.0)	76 (48.1)	0.072	51 (43.6)	34 (64.2)	0.013
Diabetes		37 (21.8)	4 (33.3)	33 (20.9)	0.314	25 (21.4)	12 (22.6)	0.852
Stroke/TIA		19 (11.2)	1 (8.3)	18 (11.4)	0.746	9 (7.7)	10 (18.9)	0.032
NYHA class	I	2 (1.2)	0 (0.0)	2 (1.3)		2 (1.7)	0 (0.0)	
	II	71 (42.0)	1 (8.3)	70 (44.6)		53 (45.7)	18 (34.0)	
	III	70 (41.4)	7 (58.3)	63 (40.1)		49 (42.2)	21 (39.6)	
	IV	7 (4.1)	1 (8.3)	6 (3.8)		5 (4.3)	2 (3.8)	
BMI (kg/m^2), mean (SD)		27.3 (4.2)	26.3 (3.5)	27.4 (4.3)	0.362	26.8 (4.4)	28.5 (3.7)	0.013
Anticoagulation therapy		129 (75.9)	4 (33.3)	125 (79.1)	<0.001	97 (82.9)	32 (60.4)	0.001

LVEF (>50%)	139 (83.2)	10 (83.3)	129 (83.2)	0.992	97 (85.1)	42 (79.2)	0.347
LA diameter (mm), mean (SD)	50.8 (6.5)	46.7 (5.9)	51.1 (6.4)	0.030	52.3 (6.2)	47.7 (5.9)	<0.001
LVED diameter (mm), mean (SD)	53.2 (7.5)	53.5 (12.6)	53.2 (7.1)	0.933	54.0 (7.8)	51.5 (6.7)	0.056
Mitral valve disease	116 (68.2)	7 (58.3)	109 (69.0)	0.445	101 (86.3)	15 (28.3)	<0.001
Aortic valve disease	80 (47.41)	5 (41.7)	75 (47.5)	0.698	47 (40.2)	33 (62.3)	0.008
Tricuspid valve disease	86 (50.6)	4 (33.3)	82 (51.9)	0.215	77 (65.8)	9 (17.0)	<0.001
Rheumatic disease	64 (37.6)	3 (25.0)	61 (38.4)	0.348	57 (48.7)	7 (13.2)	<0.001
Coronary artery disease	45 (26.5)	3 (25.0)	42 (26.6)	0.905	21 (17.9)	24 (45.3)	<0.001
Congenital cardiac malformation	8 (4.7)	1 (8.3)	7 (4.4)	0.538	6 (5.1)	2 (3.8)	0.699

All categorical variables are presented as n (%). p-value for differences between paroxysmal and non-paroxysmal AF as well as between uni- and bipolar RF energy. AF, atrial fibrillation; BMI, body mass index; LSP, longstanding persistent; LVED, left ventricle end diastolic; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RF, radiofrequency; SD, standard deviation; TIA, transient ischaemic attack.

Table 2: Types of cardiac surgery and ablation lines performed in the study population.

Surgery	All (n=170)	Paroxysmal AF (n=12)	Non-paroxysmal AF (n=158)	p-value	Unipolar RF (n=117)	Bipolar RF (n=53)	p-value
Mitral valve repair	61 (35.9)	5 (41.7)	56 (35.4)	0.665	58 (49.6)	3 (5.7)	<0.001
Mitral valve replacement	38 (22.4)	1 (8.3)	37 (23.4)	0.227	33 (28.2)	5 (9.4)	0.007
Tricuspid valve repair	92 (54.1)	4 (33.3)	88 (55.7)	0.134	84 (71.8)	8 (15.1)	<0.001
Aortic valve replacement	75 (44.1)	3 (25.0)	72 (45.6)	0.167	46 (39.3)	29 (54.7)	0.061
CABG	38 (22.4)	3 (25.0)	35 (22.2)	0.819	17 (14.5)	21 (39.6)	<0.001
Closure of LAA	129 (75.9)	8 (66.7)	121 (76.6)	0.439	108 (92.3)	21 (39.6)	<0.001
Bipolar energy	53 (31.2)	7 (58.3)	46 (29.1)	0.035			
PV isolation	170 (100.0)	12 (100.0)	158 (100.0)	1.000	117 (100.0)	53 (100.0)	1.000
Base line	97 (57.1)	4 (33.3)	93 (58.9)	0.085	97 (82.9)	0 (0.0)	<0.001
Roof line	113 (66.5)	5 (41.7)	108 (68.4)	0.059	113 (96.6)	0 (0.0)	<0.001
LAA line	107 (62.9)	4 (33.3)	103 (65.2)	0.028	98 (83.1)	9 (17.0)	<0.001
LA isthmus line	114 (67.1)	6 (50.0)	108 (68.4)	0.192	113 (96.6)	1 (1.9)	<0.001
RA isthmus line	15 (8.8)	1 (8.3)	14 (8.9)	0.950	14 (12.0)	1 (1.9)	0.032
CPB time (min), median (p25-p75)	153 (115-199)	156 (148-235)	151 (114-199)	0.458	157 (121-201)	147 (107-189)	0.060
AC time (min), median (p25-p75)	101 (73-135)	104 (89-163)	101 (72-135)	0.397	111 (81-139)	87 (65-105)	0.097

All categorical variables are presented as n (%). p-value for differences between paroxysmal and non-paroxysmal AF as well as between uni- and bipolar RF energy. AC, aortic clamp; AF, atrial fibrillation; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; LA, left atrium; LAA, left atrial appendage; PV, pulmonary veins; RA, right atrium; RF, radiofrequency; SD, standard deviation.

Table 3: Post-operative management and complications, length of stay, rhythm and medication at discharge and in-hospital mortality.

Post-operative data	All (n=170)	Paroxysmal AF (n=12)	Non-paroxysmal AF (n=158)	p-value	Unipolar RF (n=117)	Bipolar RF (n=53)	p-value
Amiodarone	136 (80.5)	7 (58.3)	129 (82.2)	0.045	94 (80.3)	42 (80.8)	0.948
Any episode of AF	113 (66.5)	7 (58.3)	106 (67.1)	0.536	78 (66.7)	35 (66.0)	0.936
Bleeding	1 (0.6)	0 (0.0)	1 (0.6)	1.000	0 (0.0)	1 (1.9)	0.312
Infection	16 (9.4)	2 (16.7)	14 (8.9)	0.362	11 (9.4)	5 (9.4)	0.995
Haemodynamic instability	9 (5.3)	1 (8.3)	8 (5.1)	0.626	4 (3.4)	5 (9.4)	0.105
Stroke/TIA	1 (0.6)	1 (8.3)	0 (0.0)	0.071	0 (0.0)	1 (1.9)	0.312
AV blockade	12 (7.1)	2 (16.7)	10 (6.3)	0.178	10 (8.5)	2 (3.8)	0.260
Pacemaker implantation	25 (14.7)	2 (16.7)	23 (14.6)	0.842	21 (17.5)	4 (7.5)	0.076
DCC	40 (23.5)	0 (0.0)	40 (25.3)	0.046	27 (23.1)	13 (24.5)	0.836
Cardiac troponin (µg/L), median (p25-p75)	14.8 (6.2-24.0)	22.2 (7.6-26.0)	14.6 (6.2-23.8)	0.854	17.6 (10.0-25.0)	5.8 (3.1-12.6)	0.371
Length of stay (days), median (p25-p75)	9 (7-14)	11 (8-23)	9 (7-14)	0.606	8 (7-14)	9 (7-15)	0.229
Sinus rhythm	116 (68.2)	8 (66.7)	108 (68.4)	0.892	80 (68.4)	36 (67.9)	0.959
Anticoagulation	153 (91.1)	8 (72.7)	145 (92.4)	0.037	110 (94.8)	43 (82.7)	0.039
Amiodarone	116 (69.0)	5 (45.5)	111 (70.7)	0.077	79 (68.1)	37 (71.2)	0.879
Beta-blocker	62 (36.9)	3 (27.3)	59 (37.6)	0.478	36 (31.0)	26 (50.0)	0.014

In-hospital mortality	5 (2.9)	2 (16.7)	3 (1.9)	0.040	3 (2.6)	2 (3.8)	0.646

All categorical variables are presented as n (%). p-value for differences between paroxysmal and non-paroxysmal AF as well as between uni- and bipolar RF energy. AF, atrial fibrillation; AV, atrioventricular; DCC, direct current cardioversion; RF, radiofrequency; SD, standard deviation; TIA, transient ischaemic attack.

Table 4: Follow-up data at 3 months and in 2013 (469 patients*year)

Follow-up (3 months)	All (n=170)	Paroxysmal AF (n=12)	Non-paroxysmal AF (n=158)	p-value	Unipolar RF (n=117)	Bipolar RF (n=53)	p-value
Sinus rhythm	76 (49.0)	6 (66.7)	70 (47.9)	0.321	54 (48.6)	22 (50.0)	0.879
DCC	12 (7.7)	1 (11.1)	11 (7.5)	0.692	8 (7.2)	4 (8.9)	0.721
Anticoagulation	137 (92.6)	7 (77.8)	130 (93.5)	0.081	99 (97.1)	38 (82.6)	0.002
Amiodarone	103 (69.6)	5 (55.6)	98 (70.5)	0.345	70 (68.6)	33 (71.7)	0.703
Digoxin	8 (5.4)	2 (22.2)	6 (4.3)	0.021	5 (4.9)	3 (6.5)	0.687
Beta-blocker	66 (44.6)	2 (22.2)	64 (46.0)	0.299	40 (39.2)	26 (56.5)	0.050
Follow-up (2013, 469 patients*year)							
All-cause mortality	26 (15.2)	7 (58.3)	19 (11.9)	<0.001	17 (14.4)	9 (17.0)	0.665
SR	55 (39.9)	4 (80.0)	51 (38.3)	0.082	39 (40.6)	16 (38.1)	0.780
Anticoagulation	108 (82.4)	4 (80.0)	104 (82.5)	1.000	78 (85.7)	30 (75.0)	0.138
Amiodarone	44 (33.6)	1 (20.0)	43 (34.1)	0.663	34 (37.4)	10 (25.0)	0.168
Digoxin	15 (11.5)	1 (20.0)	14 (11.1)	0.461	9 (9.9)	6 (15.0)	0.398
Beta-blocker	70 (53.4)	1 (20.0)	69 (54.8)	0.183	48 (52.7)	22 (55.0)	0.812

All categorical variables are presented as n (%). p-value for differences between paroxysmal and non-paroxysmal AF as well as between uni- and bipolar RF energy.AF, atrial fibrillation; DCC, direct current cardioversion; RF, radiofrequency; SD, standard deviation.

Table 5

Univariate logistic regression analysis – factors associated with the presence of AF recurrence (non-sinus rhythm) at 3 months after surgery

Variables	OR	95% CI	p
Age	0.998	0.970-1.026	0.875
Sex (male versus female)	0.693	0.363-1.322	0.266
Paroxysmal AF (versus non-paroxysmal AF)	0.461	0.111-1.912	0.286
Left atrium diameter ≥50 mm	1.977	0.984-3.972	0.056
Left ventricle end-diastolic diameter	1.006	0.992-1.020	0.388
Left ventricle ejection fraction>50%	0.587	0.247-1.391	0.226
Rheumatic disease	1.163	0.611-2.213	0.646
Mitral disease	1.056	0.525-2.122	0.879
Tricuspid disease	2.644	1.381-5.062	0.003
Aortic valve disease	1.204	0.640-2.265	0.564
Coronary artery disease	0.469	0.212-1.038	0.062
Unipolar radiofrequency (versus bipolar)	1.056	0.525-2.122	0.879
Base line	1.472	0.774-2.798	0.238
Roofline	0.945	0.478-1.868	0.872
Leftauricleline	1.056	0.545-2.045	0.872
Leftisthmusline	0.890	0.448-1.766	0.739
Rightisthmusline	0.900	0.310-2.617	0.847
Postop episodes of atrial fibrillation	2.009	1.022-3.948	0.043
Amiodarone iv postop	0.948	0.423-2.128	0.898

Cardioversion before discharge	1.775	0.846-3.723	0.129
Length of stay	1.015	0.985-1.045	0.341
Sinus rhythm at discharge	0.275	0.128-0.591	0.001
Amiodarone at discharge	0.436	0.213-0.890	0.023

Table 6

Multivariate logistic regression analysis – factors associated with the presence of AF recurrence (non-sinus rhythm) at 3 months after surgery

Variables	OR	95% CI	P
Age	1.019	0.984-1.056	0.295
Sex (male vs female)	1.707	0.800-3.644	0.167
Left atrium diameter ≥50 mm	1.862	0.830-4.175	0.131
Tricuspid disease	1.498	0.689-3.255	0.307
Coronary artery disease	0.482	0.180-1.290	0.146
Postop episodes of atrial fibrillation	1.247	0.549-2.832	0.598
Sinus rhythm at discharge	0.353	0.136-0.919	0.033
Amiodarone at discharge	0.715	0.297-1.722	0.454

Hosmer and Lemeshow test (X^2=2.218; p=0.974)

ROC curve analysis: AUC=0.717; 95%CI [0.632 – 0.802]

AUC – Area under the ROC curve; 95%CI – 95% confidence intervals; X^2 – Hosmer and Lemeshow chi-square statistic.