Atrial fibrillation: review of current treatment strategies

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Abstract: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in modern clinical practice, with an estimated prevalence of 1.5–2%. The prevalence of AF is expected to double in the next decades, progressing with age and increasingly becoming a global medical challenge. The first-line treatment for AF is often medical treatment with either rate control or anti-arrhythmic agents for rhythm control, in addition to anti-coagulants such as warfarin for stroke prevention in patient at risk. Catheter ablation has emerged as an alternative for AF treatment, which involves myocardial tissue lesions to disrupt the underlying triggers and substrates for AF. Surgical approaches have also been developed for treatment of AF, particularly for patients requiring concomitant cardiac surgery or those refractory to medical and catheter ablation treatments. Since the introduction of the Cox-Maze III, this procedure has evolved into several modern variations, including the use of alternative energy sources (Cox-Maze IV) such as radiofrequency, cryo-energy and microwave, as well as minimally invasive thoracoscopic epicardial approaches. Another recently introduced technique is the hybrid ablation approach, where in a single setting both epicardial thoracoscopic ablation lesions and endocardial catheter ablation lesions are performed by the cardiothoracic surgeon and cardiologist. There remains controversy surrounding the optimal approach for AF ablation, energy sources, and lesion sets employed. The goal of this article is review the history, classifications, pathophysiology and current treatment options for AF.

Keywords: Atrial fibrillation (AF); ablation; surgery; Cox-Maze; Maze surgery; catheter ablation; radiofrequency; cryoablation; hybrid ablation

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Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia (1). With the ever-ageing population, the prevalence of AF is also increasing (2,3). In AF, the upper chambers of the heart do not function correctly as a result of abnormal electrical signalling (4). It can be characterised by rapid and irregular atrial depolarisations with a discrete lack of P waves on electrocardiograms. As a result, the blood in the atria remains static and can promote

blood clot formation and increase the risk of stroke (5). This can cause detrimental symptoms, impair functional status and reduce the quality of life (6,7). In recent times, advancements in medical technology have helped us gain a greater understanding of AF and the mechanisms of its onset. As a result, many novel pharmacological and non-pharmacological therapies have been developed that can control or potentially prevent AF. The goal of this article is review the history, classifications, pathophysiology and current treatment options for AF.

Prevalence and incidence

AF has been shown to be increasing in prevalence and incidence across the world (8-10). In fact, the prevalence of AF in the United States is predicted to jump from 2.3 million in 1996–1997 to 5.6 million by 2050 (11). Other reports estimate that the projected prevalence will be as high as 7.56 million by 2050 (12). Age, sex, race and geographical location play a role in determining the prevalence of AF. AF is uncommon in children and healthy young adults, with the prevalence of AF generally increasing with age (10,13). While the overall prevalence of AF is approximately 1%, for those over 75 years of age the prevalence increased significantly to 9% (11). In Sweden, the prevalence of AF in a 75- to 76-year-old population was also around 12% (14). In another European population, while the prevalence was 0.7% in those between 55 to 59 years of age, it drastically increased to 17.8% for those aged over 85 years (15). In every age group, the prevalence of AF in males was also higher than that of females (1.1% *vs.* 0.8 %) (11). Also, a study has found that the prevalence of AF was greater in white people over the age of 50, when compared to black people of similar age (15). The age-adjusted prevalence of AF was also the greatest in North America at around 770 to 775 cases per 100,000 population (8). The lowest rates were observed in Japan, South Korea and China, which ranged from 250 to 400 cases per 100,000 population (8).

Similar to the increasing prevalence of AF, the incidence of AF is estimated to double with each passing decade of adult life (16). Approximately, 3 people per 1,000 person-years between the ages of 55 and 64 develop AF every year (17). This significantly increases to 32 per 100 person-years between the ages of 85 and 94 years (17). At the age of 80 years, the lifetime risk of developing AF is quite substantial with a rate of approximately 22% (18). While males have greater risk of developing AF than females, the independent risk factor for death that the arrhythmia causes is lower in males (1.5 *vs.* 1.9 relative risk) (17).

Brief history

Medical practitioners have been interested in the heart and its pulse for many years. The symptoms of AF have been described in articles dating back almost 1,000 years, when Maimonides noted irregular human pulses that were likely AF (19,20). However AF was not fully described until 1874 when Vulpian termed irregular atrial electrical activity in canine hearts to be “*fresmissement fibrillaire*” (21).

Nothnagel later found that the irregularity of the pulse was a feature of the arrhythmia, which he termed “*delirium cordis*” (22). MacKenzie was able to record jugular and radial pulses in patients, also identifying an irregular pulse (23,24). He found that the electrical activity in the atrium disappeared during the periods of irregular pulse but returned when the pulse was normal again (23,24). The lost electric waves in the jugular venous pulse also correlated with the loss of atrial contraction that was observed in *delirium cordis*. In 1906 Einthoven published the first electrocardiogram that showed AF (25). The development of the electrocardiogram greatly helped clinicians explain the connection between the electrical and anatomical pathologies of AF, along with the irregular pulse observed in *delirium cordis* (26). Ultimately, with the advent of the electrocardiogram, the amount of research on AF has greatly increased and along with our understanding of the condition.

Types of AF

There are three primary forms of AF that have been categorized with regards to duration of episode. The first type is intermittent or paroxysmal AF, which occurs spontaneously and generally resolves by itself or with treatment within 7 days (27). It is characterised by episodes of irregular heart rhythm, which can occur with varying frequencies and periods of time before stopping. Persistent AF is sustained abnormal heart rhythm for more than 7 days even with treatment or direct current cardioversion (27). Despite this, persistent AF may eventually cease on its own or via treatment. Long standing persistent AF is defined as lasting longer than 12 months, with the term permanent AF used when all means of treatment to restore normal heart rhythm have failed (27). If the patient decides to undergo further treatment or if new therapies are available, the patients AF status can change (5).

It can sometimes be difficult to distinguish between paroxysmal and persistent AF as physicians often decide to terminate recent-onset AF via pharmacological or electrical means (3). This means that it is unknown whether the case of AF would have spontaneously converted, and as such an accurate classification can technically be very difficult (3). Over time, untreated paroxysmal and persistent AF may also become worse and result in permanent AF (28). There can also be new-onset AF in patients undergoing cardiac surgery, which significantly increases post-operative complication rates (29). Regardless of the type of AF, the

patients commonly have characteristic symptoms of AF such as palpitations and shortness of breath (3). Generally, palpitations are more common in paroxysmal AF, and shortness of breath in more chronic AF. AF can also have other non-specific symptoms such as fatigue (30). However, not all types of AF are symptomatic, with paroxysmal AF patients more frequently being asymptomatic (31).

AF has also been classified into valvular and non-valvular AF although the terms have not been defined consistently (5,32). However, in general a valvular AF is where the cause of AF is related to an implanted artificial heart valve or rheumatic heart disease (5). The proportion of patients with valvular AF has been reported to range from 4% to 30% of all patients with AF.

Pathophysiology

There are a variety of pathophysiological mechanisms by which AF is caused. These range from structural and electrical abnormalities, tissue remodelling and inflammation (27,33). When the atrial tissue has electrical or structural defects, the atrial contractions become irregular and there is uncoordinated flow of blood into the ventricles. As a result AF can cause large variations in blood pressure and cardiac output.

AF is thought to be caused by certain triggers, such as a single rapidly firing focus in the atria (34). This can subsequently cause fibrillatory conduction through the heart (34). Studies have shown that this rapid focus firing occurs most frequently in the pulmonary veins or at the base of pulmonary veins (35). In these locations, there is myocardial tissue that can instigate repetitive firing or in some cases, episodic re-entrant activation of the veins (36). While less common, rapid ectopic activity can also arise from the muscular sleeves of the superior vena cava, coronary sinus or ligament of Marshall (37-39). The exact mechanisms behind AF initiation due to rapid firing have not been fully elucidated but it may potentially involve enhanced automaticity, micro-reentry, or triggered activity (40). The focal rapid firing activity in the atria seems to be the cause of paroxysmal AF, and is the rationale behind pulmonary vein isolation as a treatment option. While triggers for persistent AF are commonly also located in the pulmonary veins, exclusive pulmonary vein isolation in persistent AF has a low success rate (41,42). Thus other triggers may be involved in longstanding AF although they are still not well elucidated (40).

The maintenance of arrhythmia in persistent AF can be facilitated via abnormalities to the atrial tissue substrate,

which can cause non-uniform or slowed conduction (43-45). As a result, multiple wavelets of excitation can propagate through the atrial myocardium and perpetuate the arrhythmia (45). The high failure rates of pulmonary vein isolation in patients with persistent AF is possibly due to the lack of treatment for the abnormal atrial substrate perpetuating AF (41,42). It has been proposed that there are 'driver domains' located in areas of the atrium that can act as unstable re-entry circuits (46). Re-entry within the atrial myocardium is potentially mediated by slower conduction and shorter refractory periods (45). Focal triggers may also still act in combination with re-entrant activity to maintain AF (40). This is supported by the finding that multiple persistent AF patients had 2 to 4 foci in each atrium from which the wave fronts emanated (40,47).

It is believed that the advancement of paroxysmal to persistent AF is a result of structural and electrical changes in the atrium. Fibrosis is a structural change in the atria that has been shown to create abnormal AF substrates that can further prolong AF (48). Fibroblasts act by electrically coupling to cardiomyocytes before proliferating and promoting ectopic activity and/or re-entry (3). Along with that, AF inducibility is progressively increased with increasing levels of fibrosis in the heart (48). This can potentially induce the creation of re-entrant circuits that will further propagate AF (48). Electrophysiological changes can also occur within minutes of AF onset, shortening the refractory period, and increasing the likelihood of persistent AF (49). However, even after 14 days of persistent AF, restoration of normal sinus rhythm can cause an immediate reversal of electrophysiological remodelling (49). Defects of cardiac ion channel can also cause ectopic firing by hyperactivating intracellular ion channels (3). This sympathetic activation of the atrium can cause remodelling of the cardiac autonomic neural tissue to promote further persistence and recurrence of AF (50,51). All these changes have been shown to occur in the presence of AF, explaining the concept that "AF begets AF" (28,49). Therefore, extended periods of continuous AF detrimentally affect a patient's ability to restore and maintain normal sinus rhythm (45,52). Along with that there is also a reduced possibility of spontaneous AF termination (45,52).

The literature has identified a multitude of risk factors for AF (7). Firstly there is evidence that suggest there is a genetic risk factor for AF (53,54). The 2004 Framingham Heart Study found that if one of both parents had AF, the independent risk of AF in the offspring was significantly elevated (18). Obesity has also been shown to increase

the risk of AF, although the pathogenesis has not been fully elucidated (7). Each unit increase in body mass index has been shown to increase risk of AF by 4% (55). After adjusting for age, sex and independent BMI predicted progression to permanent AF; obesity was shown to catalyse the advancement of paroxysmal AF to permanent AF (56). Obesity has also been associated with a moderately higher risk of AF following cardiac surgery (57). Additionally, more than 70% of subjects with obstructive sleep apnoea (OSA) are overweight or obese (58,59). This further increases the risk of AF as OSA can independently increase the risk of AF through potential mechanisms that involve disturbances of autonomic tone, atrial stretch and hypoxia (60). Alcohol consumption (57), extreme endurance exercise and caffeine (61,62) have also been shown to increase the risk of developing AF.

Medical management of AF

Before the AF is to be treated, it is important that the clinical significance of the arrhythmia is identified. This can be done through a detailed history and physical examination (4). Along with that echocardiography and thyroid function tests can be conducted to evaluate cardiac and thyroid activity (4). This process must be completed to ensure that the treatment plan for a specific patient with AF does not have any potential side effects, which may be caused by other underlying heart conditions.

Early anti-arrhythmic drug therapies

For the majority of patients that do not require immediate cardioversion, anti-arrhythmic drug therapies can potentially be utilised. Digoxin can be used to slow ventricular heart rate but it has a very slow onset and is therefore not very effective in hyperadrenergic patients (1,63). Thus, intravenous administration of calcium-channel blockers, like diltiazem and verapamil, and beta-blockers like esmolol and metoprolol can be used (4). These drugs are more effective than digoxin as they elicit a quicker response irrespective of the patient's sympathetic tone (4). There is also synergism between these drugs and digoxin (64). Anti-arrhythmic drugs have been highly effective in converting AF to normal sinus rhythm if promptly administered following onset of AF and at an adequately high dosage (65). Constant electrocardiographic monitoring of the patient has been recommended for the first 48 to 72 hours following the initial anti-arrhythmic drug dose (4). While

anti-arrhythmic drugs treatment is effective for immediate treatment of new onset AF, many of these patients (67%) spontaneously convert to sinus rhythm within 24 hours of onset (66).

In patients with new onset AF, pharmacological interventions to control the heart rate and rhythm can be used as the first course of action. However, other methods of interventions are required if the patient is presented with other conditions such as unstable angina, acute myocardial infarction or any other abnormal ventricular response that are related to preexcitation syndrome (67). For example in Wolff-Parkinson-White syndrome, there is an accessory pathway between the atrium and ventricle that results in preexcitation. Many anti-arrhythmic pharmacological treatments should not be used as it can cause ventricular fibrillation and further morbidity (67). Thus cardioversion or catheter ablation is recommended for this rare presentation of AF (67).

Early anticoagulant therapy

If the onset of AF cannot be accurately determined then anticoagulant therapy is necessary before attempting cardioversion. Anticoagulant therapy is essential as patients with AF are more susceptible to blood clots in the atria, which can lead to stroke (5,68). For those with AF that do not receive anticoagulation therapy, the risk of clot formation is as high as 23.5% in patients aged between 80 and 89 years (69). The choice of anticoagulant medication should take into account the patient's comorbidities, potential drug interactions and the patient's ability to strictly adhere to the medication schedule (5). A strict adherence to the schedule is essential as a missed dose can significantly increase the risk of a thrombotic event (27).

For patients with valvular AF, warfarin is the recommended drug to be used in anticoagulation therapy (27,70). For those with lone AF and no valve replacements, oral anticoagulants can be used (27). The type of medication recommended is dependent upon the patient's CHA₂DS₂-VASc score, which is a clinical predictor that estimates the risk of stroke in AF patients. For patients with a CHA₂DS₂-VASc score of 2 or greater, it is recommended that they use warfarin or inhibitor of factor Xa such as rivaroxaban, dabigatran or apixaban (27). If the CHA₂DS₂-VASc score is 1, antithrombotic therapy may not be necessary but the physician may still consider using an oral anticoagulant or aspirin (27,68). A patient with a CHA₂DS₂-VASc score of 0 requires no anticoagulation therapy (5,27). For

patients requiring a treatment that involves interruption of anticoagulation, heparin in unfractionated or low molecular weight form can be used (27). While direct Xa inhibitors such as apixaban have been shown to cause fewer strokes and bleeding events than warfarin, they do not have any reversal agents (5). This is not the case with warfarin as vitamin K can be used to reverse its effects (5). However since warfarin still requires significant monitoring and long duration of onset, new oral anticoagulants (NOACs) have been introduced as alternatives (71). These NOACs, such as dabigatran and rivaroxaban act via direct inhibition of factor Xa or thrombin and have less drug interactions than warfarin (29,71,72). Studies have also demonstrated similar efficacy profiles for rivaroxaban, dabigatran and warfarin in patients undergoing catheter ablation (29,72). Ultimately, assessing the risk of stroke is essential for determining the treatment that will be most effective in improving outcomes and quality of life of patients with AF.

Cardioversion

Synchronised current cardioversion depolarises the cardiac cells simultaneously in an attempt to restore normal sinus rhythm (5). The electric current is delivered during the QRS complex to avoid any discharge during the repolarisation of the ventricles (5). Traditionally the shock waves were monophasic, but new defibrillators use a biphasic waveform, which requires less energy and fails less (73). Cardioversion is generally not attempted within early onset of AF unless the patient has other heart conditions like preexcitation (4). More commonly, cardioversion is attempted if the AF has lasted longer than 7 days, as the probability of it spontaneously converting to normal rhythm after then is very low (66). For the patients that require cardioversion, adequate anticoagulation therapy must be administered immediately (5,27,67).

In many cases, electrical cardioversion is coupled with the administration of an anti-arrhythmic drug. The combination of the electrical shock with an intravenous drug like ibutilide increases the chance of restoring and maintaining the sinus rhythm (74). However it is important that the selected drug is appropriate for the individual patients as ibutilide for example can cause tachycardia in patients with low ventricle function (75). If recurrence of AF occurs within 3 months of the intervention, it may be necessary for a repeated current cardioversion in combination with another drug or an increased dosage of the drug used in the initial cardioversion procedure (4,76). However, if the recurring AF

has minimal symptoms, anti-arrhythmic drugs and long term anticoagulation can be used alternatively (4).

Catheter-based management

Catheter ablation for the treatment of AF is increasingly used as an alternative to medical management, or when medical management has been ineffective or not tolerated (77). It is an effective treatment option in certain patients that have persistent AF and systolic dysfunction (4). As a result drugs are ineffective or have detrimental inotropic effects (4). In AF catheter ablation, energy is delivered to the myocardium to destroy areas of the heart resulting in electrically isolate small areas of tissue where abnormal electrical signals originate. Following the procedure a permanent pacemaker must be implanted to maintain the heart rate (4). While ablation does not eliminate the AF per se, it can limit the ventricular rate in a similar fashion to rate control drugs for AF. It facilitates this by eliminating triggers and altering electrophysiological connections in the heart (78).

Lesions

Lesions targeted in AF ablation include muscle sleeves of the pulmonary veins (PVs) or less commonly at other atrial sites including the superior vena cava, coronary sinus, LA posterior wall, interatrial septum, and the vein of Marshall (42).

Energy sources

The two US Food and Drug Administration-approved options for catheter ablation include radiofrequency energy, which heats the target site(s), and cryoablation, which cools the site(s). Cryoablation can be performed using either a focal catheter (as in radiofrequency ablation) or with a balloon catheter. Studies to compare the efficacy and safety of radiofrequency *vs.* cryoablation/cryoballoon demonstrate noninferiority (79), with equivalent 1-year freedom from AF, but shorter fluoroscopy times (80) and greater reproducibility with cryoballoon ablation (81). Also, a meta-analysis of only randomized data revealed no significant differences between radiofrequency and cryoballoon ablation (82). However there was a consistent reduction in procedure duration for phased duty-cycle radiofrequency ablation (82). In regards to cryoablation *vs.* cryoballoon, it has been suggested that cryoballoon allows for the creation of contiguous lesions, resulting in significantly higher durability than focal cryoablation (83).

Outcomes

Several randomized controlled trials (RCTs) have demonstrated superior results for restoration of normal sinus rhythm with catheter ablation compared with antiarrhythmic drug therapy, despite some patients requiring multiple ablation procedures (84-88). When catheter ablation is used in combination with antiarrhythmic drug therapy, the success rate of achieving normal sinus rhythm was 71% [95% confidence interval (CI), 65–77%], which is superior to antiarrhythmic drug therapy alone at 57% (95% CI, 50–64%) (88). Catheter ablation also produces an AF recurrence rate of 20%, which is superior to the 75% found in those taking antiarrhythmic drug therapy alone (89). A recent systematic review comparing catheter *vs.* surgical ablation for AF demonstrates higher freedom from AF with surgical ablation (90) though complications, including tamponade and pacemaker implantation rates were higher in those that underwent surgical ablation. Overall radiofrequency catheter ablation is a treatment method that has been shown to increase a patient's quality of life and also improves ventricle function in a large portion of patients (91,92). For patients with abnormal firing from a focal source, focal radiofrequency ablation can be used (2,35). However identification of the exact location of abnormal firing can be difficult (2).

Surgical management

The field of AF is evolving rapidly with emergence of percutaneous and surgical interventional therapies as safe alternatives to restoring normal sinus rhythm. The Cox-Maze III procedure remains the gold standard treatment for patients with AF, though remains technically demanding. Introduction of new ablation technologies has made the procedure much easier and safer to perform and is now more widely embraced. Minimally invasive modifications and the advent of hybrid ablation, combining percutaneous and surgical intervention, have offered an important step towards developing a stand-alone procedure for the cure of AF with potentially decreased morbidity. This section of the review focuses on the history of past surgical treatments, current surgical options and the future direction of surgical therapy.

Indications

The 2012 HRS/EHRA/ECAS Expert Consensus Statement

on Catheter and Surgical Ablation of Atrial Fibrillation recommends that: (I) it is appropriate to consider all patients with symptomatic AF undergoing other cardiac surgery for AF ablation and (II) stand-alone AF surgery should be considered for symptomatic AF patients who prefer a surgical approach, who have failed one or more attempts at catheter ablation or who are not candidates for catheter ablation (77). These are class IIa and class IIb level of evidence C, respectively.

History

Cox-Maze I

Starting in the 1980s, unsuccessful attempts at surgically treating AF included left atrial isolation (93), corridor operation (94), and atrial transection (95). Cardiac surgeon Dr. James Cox, in collaboration with cardiologist Dr. John Boineau and physiologist Richard Schuessler, pioneered the first effective surgical treatment for AF in 1987: Cox-Maze I (95) which was further refined to the Cox-Maze IV procedure today. The Cox-Maze I relied on a premature pulmonary vein trigger to propagate to the left atrium and induce macro-reentrant circuits resulting in AF. Though, AF begets AF due to atrial electrical remodeling (96), thus a therapy focused on pulmonary vein isolation alone was insufficient to treat long-standing persistent AF. Following several iterations, the Cox-Maze I was refined to the Cox-Maze IV procedure today with key components of the initial Cox-Maze I procedure including the isolation of the pulmonary veins maintained.

Cox-Maze III

The Cox-Maze I was modified into the Cox-Maze III procedure, also known as the 'cut and sew' Maze, which remains the gold standard procedure for the surgical management of AF (97). It involves making multiple incisions in the atria to create a series of scars to force the electrical impulse from the sinus node to the AV node. This fixes the refractory period between areas of scar and prevents macro-reentry circuits required to sustain AF. The procedure also includes en bloc isolation of the pulmonary veins and posterior left atrium along with excision of the left atrial appendage. Despite the technically demanding procedure, increased myocardial ischemic time, bleeding and operative mortality of 1.5–3%, long-term results at 5 years were excellent, demonstrating 96.6–99% of patients free of AF (98). Though, this rate of freedom from AF may be overinflated due to the inability to detect

paroxysmal asymptomatic episodes with single ECGs and absence of symptoms alone, reflecting the evolvement of AF monitoring over the decades. Postoperative challenges of the Cox-Maze III stem from questionable atrial function following the procedure, with a frequent need for a postoperative pacemaker and fluid retention due to decreased atrial natriuretic factor (99).

Cox-Maze IV

Despite excellent outcomes, the Cox-Maze III did not gain widespread acceptance for the treatment of lone AF due to its complexity and technical demand. Development of technologies to create scars without cutting of tissue brought renewed interest in the Maze procedure. This led to simplification of the Cox-Maze III to the Cox-Maze IV technique (100,101). This method utilizes new ablation technologies to replace the “cut-and-sew” technique (101) and utilize heating or freezing to create scars while leaving the structure intact. Success of the procedure depends on the creation of a transmural, full thickness lesion leaving no gap of viable conduction tissue, with efficacy varying by technology.

Cox-Maze IV omits the atrial septal lesion, which was used in the previous Cox-Maze III version to expose the left atrium, and performing an independent isolation of the pulmonary veins by a connecting lesion. Several studies report success rates of the Cox-Maze IV using alternative technologies to be comparable to the classic ‘cut and sew’ Maze, while having significantly shorter cross clamp times (101-103). In patients with stand-alone AF, the type of AF, duration of AF, the left and right atrial sizes are important predictors of ablation procedural success (104).

In contrast the need for sternotomy, as in prior versions of the Cox-Maze, Cox-Maze IV can be done through a less invasive right mini thoracotomy (RMT). Contraindications to a RMT include a previous right thoracotomy, severe atherosclerotic disease of the aorta, iliac or femoral vessels and severely decreased left ventricular ejection fraction (<20%).

AF surgical ablation can also be performed with concomitant cardiac surgical intervention. Several randomized controlled trials examining surgical ablation with concomitant mitral valve surgery (105-107), CABG or aortic valve surgery (108) have demonstrated significantly increased the odds of freedom from AF. A meta-analysis suggests that at 12 months of cardiac surgery, odds of freedom from AF can be over 5-fold and did not result in increased hospital length of stay, perioperative complications or mortality (109-111). The most common

energy source for this purpose is cryoablation, yielding excellent results with an 88.5% rate of freedom from AF after 1 year (112). There is variability in the literature as to the success rate of concomitant AF ablation, ranging from 57% to 88% which likely stems from the different ablation lesion sets, type of energy source used, and the patient's AF subtype.

Energy sources

The modern cardiac surgeon is equipped with a variety of energy sources and lesion sets to choose from (113).

Types of lesions

Three broad lesion sets in the surgical treatment of AF include (I) pulmonary vein isolation; (II) left atrial lesion set; and (III) biatrial lesion set with the luxury of tailoring lesion sets required to the patient. Patients with new-onset paroxysmal AF can achieve AF ablation with pulmonary vein isolation lesion, whereas those with recent onset paroxysmal AF or those undergoing non-right heart surgery can achieve ablation with a left atrial lesion. Patients with longstanding symptomatic AF or AF in young patients undergoing right heart surgery are likely to benefit from biatrial lesions—which are the most effective (114,115).

Types of energy sources

Compared to the cut-and-sew Cox-Maze procedure, alternative energy sources reduce surgical time, technical challenges, lessen bleeding and facilitate a minimally invasive approach.

Technologies that create transmural lesions investigated include unipolar radiofrequency ablation (dry and irrigated), bipolar radiofrequency ablation (dry and irrigated), microwave, high intensity focused ultrasonography, cryoablation and more (116,117). Each will be discussed along with their advantages and disadvantages. Though, general limitations of these alternative energy sources compared with the traditional cut-and-sew technique include the uncertainty of creating transmural lesions.

Unipolar radiofrequency ablation

Unipolar radiofrequency ablation has a variety of probes available resulting in the creation of scar tissue with heat and is often irrigated to provide a more even distribution of heat and prevent charring (118). Though compared to other

energy sources, they are less efficient, more thrombogenic and can, in rare cases, result in development of an atrioesophageal fistula as the energy is in one direction. Unipolar suction-assisted radiofrequency is a method to stick the probe evenly to the surface of the atrium for a more reliable transmural lesion (119), though clinical experience is limited with this technique.

Bipolar radiofrequency ablation

Bipolar radiofrequency ablation is a safe and more efficient method of achieving transmural lesions than unipolar radiofrequency ablation. This method is performed by clamping atrial tissue and heating it between two electrodes until irreversible protein denaturation occurs. Its jaw-clamp structured device has the distinct advantage of allowing for real-time assessment of transmural lesions by measurement of impedance as atrial tissue is clamped and ablated. Its use has been reported in the off-pump technique (99). Furthermore, as the radiofrequency energy stays between the two electrodes, in contrast from the unipolar method, it does not cause collateral damage to surrounding tissues. Though, similar to the unipolar method, it can also be thrombogenic, is not optimal for lesions around valves which would require an endocardial approach and can, in rare cases, result in pulmonary vein stenosis. When compared with unipolar radiofrequency ablation, bipolar ablation has better success at achieving transmural lesions with shorter procedural time (120).

Microwave ablation

Microwave ablation has a lower risk of thromboembolism compared to radiofrequency ablation though may risk the development of an incomplete transmural lesion and perforation at higher energy levels (121,122). As well, bipolar radiofrequency ablation is regarded as superior to microwave ablation in achieving transmural lesions (123).

High intensity focused ultrasonography

High intensity focused ultrasonography is a quick method that results in creation of satisfactory transmural lesions though is limited to epicardial method of ablation, with risk of collateral tissue damage. It also has a fixed depth of penetration making it problematic in situations of anatomical variability of atrial wall thickness (121,122).

Cryoablation

Cryoablation freezes the tissue, which dies and results in a scar. It has been established as a safe method resulting

in smooth well-demarcated transmural lesions with a low risk of bleed or perforation and less endocardial thrombus formation. It is limited to the use of rigid probes and can, in rare cases, result in coronary artery stenosis. Cryoablation requires an arrested emptied heart and is thus limited to use in the endocardial approach as the warm blood of a beating heart would act as a heat sink making it difficult to achieve transmural lesion from the epicardial surface of a full heart (99). It is the most often used method of AF ablation in concomitant cardiac surgical procedures, with excellent results of an 88.5% rate of freedom from AF after 1 year (112).

Left atrial appendage occlusion

During surgical ablation, concomitant left atrial appendage occlusion (LAAO) has emerged as a potential method of improving operative outcomes (124,125). While there are currently limited studies in the literature investigating this, a recent meta-analysis found that LAAO can significantly reduce the incidence of stroke and incidence of all-cause post-operative mortality (126). However, routine LAAO remains controversial and long-term studies are currently underway to address this technique.

Minimally invasive surgical ablation

Despite the efficacy achieved with traditional sternotomy for lone AF ablation, it has not achieved widespread application due to reluctance and perception as an invasive technique. Thus with the advent of new technology, three main minimally invasive approaches have been attempted including the (I) beating heart right-sided thoracoscopic pulmonary vein isolation with multiple technologies; (II) beating heart bilateral thoracotomy with bipolar radiofrequency ablation; and (III) arrested heart right-sided thoracotomy.

Beating heart right-sided thoracoscopic approach

A unilateral rightsided port approach with two or three ports has been described with microwave energy ablation resulting in short hospital length of stay (1–4 days) (122,127,128). A single-sided approach restricts the user to only monopolar devices and bi-directional conduction block will not be obtained. As well, the main limitation to this approach is the inability to remove the left atrial appendage which may be the Achilles' heel to long-term treatment of AF resulting in need for adjunctive postoperative catheter-based interventions (122).

Beating heart bilateral thoracotomy approach

This approach consists of bilateral ports and a video-assisted thoracoscope to create pulmonary vein isolation lesions, usually with ganglionic plexus ablation, division of ligament of Marshall and left atrial appendage excision. The most commonly described energy source used for this technique is bipolar radiofrequency ablation with dry or irrigated radiofrequency (129). Reported outcomes demonstrate 75–90% freedom from AF (130) with overall procedural success rate, as defined as the completion of the procedure without conversion to sternotomy or cardiopulmonary bypass, as 99.5% (130). The successful ablation of AF with this method appears to vary by AF subtype with 96% in persistent, 93% in paroxysmal and 71% in long-standing persistent AF (131).

Arrested heart right-sided thoracotomy approach

With cryoablation, this method has been reported in patients with lone AF to achieve a freedom from AF approaching 90% at 6 months (132). This method has the benefit of achieving a full Maze lesion and is a promising technique for the treatment of lone AF.

Complications

A randomized controlled trial comparing minimally invasive surgical ablation vs catheter ablation (133) demonstrates superior freedom from AF at 12 months with surgical ablation though at the cost of a higher rate of adverse events (23% *vs.* 3% in the catheter ablation group; $P < 0.001$) (90,134,135). Adverse events included need for pacemakers (5%), hemothorax (3%), phrenic nerve injury (3%), transient ischemic attack (1%) and pulmonary embolism (1%) (131). Outcomes from the Society of Thoracic Surgeons (STS) database [2005–2010] comparing minimally invasive surgical ablation *vs.* sternotomy for lone AF demonstrated an acceptable complication rate of 0.7% for mortality or stroke, 1% for need of pacemaker and a median length of hospital stay of 4 days (136). The main technical challenge with minimally invasive approaches is difficult access to the posterior left atrium and left atrial appendage. Refinements in ablation technology, lesion assessment, exposure and manipulation are needed to facilitate the widespread application or minimally invasive surgical ablation.

Hybrid ablation

The ideal ablation strategy would (I) result in a durable

lesion; (II) offer the ability to tailor the ablation approach to the patient; (III) always generate transmuralities when required; and (IV) be minimally invasive (137).

Though epicardial surgical ablation results in superior transmuralities and durability compared to catheter ablation (120), it is regarded as an invasive procedure. Minimally invasive surgical ablations are less invasive than surgical ablation; however beating heart ablation does not consistently create lesions that extend to the mitral or tricuspid annulus. These leave an opportunity for iatrogenic circuits with predisposition to atrial flutter (138–140).

With the advent of hybrid procedures for AF ablation, the strengths of surgical and minimally invasive epicardial ablation can be combined with the strengths of catheter based endocardial ablation in a single step procedure to minimize their individual weaknesses. Hybrid (epicardial and endocardial) ablation can be done in a simultaneous or staged manner (141), where simultaneous ablation can limit the potential for unstable iatrogenic flutters which complicate epicardial only ablation. In contrast, staged ablation may allow for maturation of epicardial lesions for evaluation of gaps in ablation lines. Hybrid ablation offers detailed three-dimensional electroanatomical mapping systems and multipolar catheters to ensure adequacy of pulmonary vein isolation, block across lines of ablation as well as targeted ablation for remnant arrhythmias from an incomplete transmural epicardial lesion (142,143). This approach also gives access to areas of the atria not easily accessed epicardially such as the cavotricuspid isthmus, mitral isthmus and interatrial septum. Recent studies and systematic literature review (139) conclude that hybrid treatment of lone AF appears to be a safe technique with satisfactory 1-year results and an antiarrhythmic drug-free success rate that is higher than in isolated procedures.

Hybrid AF ablation requires a multidisciplinary approach to care of the patient with AF with close collaboration between surgeons, electrophysiologists and cardiologists. Changes to the delivery of patient care that would need to be made include the establishment of an arrhythmia team that would be involved in the preoperative decision making to provide a patient-tailored rather than procedure-based approach to deliver complication-free and high efficacy outcomes. Other considerations of changes to the delivery of patient care that would be required include: the location of the ablation procedure (hybrid surgical suite *vs.* staged operating room *vs.* electrophysiology laboratory), personnel involved and postoperative care team (99).

Hybrid AF ablation demonstrates potential benefit

though there remains many unanswered questions that need to be addressed. These include cost effectiveness of the procedure, whether lesions in addition to the standard pulmonary vein isolation and left atrial ablation add benefit, the ideal timing for the procedure, single step *vs.* staged procedure and the patient population that hybrid AF ablation is most likely to confer benefit. A randomized controlled trial comparing hybrid AF ablation to other ablation methods is warranted to clarify the role of hybrid procedures in AF ablation.

Conclusions

In the past few decades, research into AF has increased tremendously. With it, our understanding of AF pathophysiology and treatment options has improved as well. Drugs targeting specific ion channels are approaching the early stages of clinical investigation. There are also new and exciting areas of AF research such as gene therapy, cell therapy and microRNAs and their function on tissue remodelling. With our ageing population and ever increasing prevalence of AF, optimized treatment plans for individuals with AF are essential. However, while advances in technologies have helped elucidated many aspects of AF, many mysteries still remain. With continued research and into AF, we can expect more effective drug therapies and ablation techniques to be developed in the near future.

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Footnote

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