Ablation treatment strategies for atrial fibrillation

Kevin Phan

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Authors’ contribution and declaration

The work in this thesis is the result of original research and has not been submitted for a higher degree at any other university or institution.

The author planned the research, designed the study protocol, collected data, performed the statistical analysis and interpretation of the data, wrote and revised the manuscripts for submission to peer-reviewed journals, and wrote and compiled the thesis. The work and publications presented in this thesis were carried out under the academic supervision of Professor Tristan D. Yan and co-supervision of Dr Caroline Medi.

The author wishes to acknowledge the support and contribution of the co-authors to each of the publications included in this thesis. Specific contributions of each co-author is listed in Appendix 1.

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Abstract

The present series of publications represent a comprehensive review of ablation techniques, energy sources, lesion sets, and hybrid approaches performed in the surgical management of atrial fibrillation. Endpoints examined include the srahort-term and medium-term success rate and complications of concomitant ablation with cardiac surgery in "*Surgical ablation for treatment of atrial fibrillation in cardiac surgery – a cumulative meta-analysis of randomized controlled trials"*(2014). Minimally invasive thoracoscopic epicardial ablation was compared with percutaneous catheter ablation in terms of success rates and complications in "*Thoracoscopic surgical ablation versus catheter ablation for atrial fibrillation*"(2016). Energy sources explored include radiofrequency ablation, cryoenergy, microwave and cut-and-sew techniques, as examined in "*Comparing energy sources for surgical ablation of atrial fibrillation – A Bayesian network meta-analysis of randomized controlled trials*"(2015). Biatrial versus left-atrial lesion sets were compared in "*Biatrial ablation versus left atrial concomitant surgical ablation for treatment of atrial fibrillation: a meta-analysis*"(2015). The role of obesity in postoperative atrial fibrillation was demonstrated in "*Obesity and postoperative atrial fibrillation in patients undergoing cardiac surgery: systematic review and meta-analysis*" (2016), and the impact of obesity on the outcomes of hybrid ablation procedure was investigated via a retrospective analysis of 3-year follow-up data in "*Effectiveness and safety of simultaneous hybrid thoracoscopic endocardial catheter ablation of atrial fibrillation in obese and non-obese patients*"(2016). Overall, this body of work includes

comprehensive and up-to-date clinical data on the surgical management of atrial fibrillation in the existing medical literature.

Chapter 1

Introduction

Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia[1]. With the ever-ageing populations, the prevalence of AF is expected to increase and progress with age, posing as a global medical challenge[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 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-pharmacologic therapies have been developed that can control or potentially prevent 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 also 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 was 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 patients 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 1000 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 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 1000 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 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 patients decide 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] (Figure 1). 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 the 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].

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Figure 1. The influence of trigger and substrate on atrial fibrillation. The importance of trigger and substrate is displayed in three common categories of AF, which is a progressive disorder. Paroxysmal AF is predominantly a trigger-based phenomenon, whereas permanent AF is substrate-dependent. Persistent AF is influenced by both the trigger and the substrate undergoing remodeling. Abbreviations: AF, atrial fibrillation; APBs, atrial premature beats. Figure and caption adapted from Wyse et al[32].

AF has also been classified into valvular and non-valvular AF although the terms have not been defined consistently[5, 33]. 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, 34]. 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[35]. This can subsequently cause fibrillatory conduction through the heart[35]. The mechanisms maintaining AF is known as the driver and take one of the following forms: (1) continued local ectopic firing, (2) a single localized reentry circuit, or (3) multiple functional circuits varying in time and space[3]. Studies have shown that rapid focus firing occurs most frequently in the pulmonary veins or at the base of pulmonary veins[36]. In these locations, there is myocardial tissue that can instigate repetitive firing or in some cases, episodic re-entrant activation of the veins[37]. While less common, rapid ectopic activity can also arise from the muscular sleeves of the superior vena cava, coronary sinus or ligament of Marshall[38-40]. 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[41]. 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, the success of exclusive pulmonary vein isolation in persistent AF has a low success rate[42, 43]. Thus other triggers may be involved in longstanding AF although they are still not well elucidated[41].

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[44-46]. As a result, multiple wavelets of excitation can propagate through the atrial myocardium and perpetuate the arrhythmia[46]. 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[42, 43]. It has been proposed that there are ‘driver domains’ located in areas of the atrium that can act as unstable re-entry circuits[47] (Figure 2). Re-entry within the atrial myocardium is potentially mediated by slower conduction and shorter refractory periods[46]. Focal triggers may also still act in combination with re-entrant activity to maintain AF[41]. 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[41, 48].

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Figure 2. Structure and mechanisms of atrial fibrillation. (A) Schematic drawing of the left and right atria as viewed from the posterior. The extension of muscular fibers onto the PVs can be appreciated. Shown in yellow are the four major LA autonomic ganglionic plexi and axons. Shown in blue is the coronary sinus which is enveloped by muscular fibers which have connections to the atria. Also shown in blue is the vein and ligament of Marshall. (B) Large and small reentrant wavelets that play a role in initiating and sustaining AF. (C) Common locations of PV (red) and also the common sites of origin of non PV triggers (shown in green). (D) Composite of the anatomic and arrhythmic mechanisms of AF. Focal triggers leading to initiation of reentry (rotors). Eventually, atrial remodeling leads to additional focal triggers and perpetuation of reentry. Figure and caption adapted from Calkins et al[49].

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[50]. Fibroblasts act by electrically coupling to cardiomyocytes before proliferating and promoting ectopic activity and/or re-entry[3]. Along with that the AF inducibility is progressively increased with increasing levels of fibrosis in the heart[50]. This can potentially induce the creation of re-entrant circuit that will further propagate AF[50]. Electrophysiology changes can also occur within minutes of AF onset, shortening the refractory period, and increasing the likelihood of persistent AF[51]. However, even after 14 days of persistent AF, restoration of normal sinus rhythm can cause an immediate reversal of electrophysiological remodelling[51]. 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[52, 53]. All these changes have been shown to occur in the presence of AF, explaining the concept that “AF begets AF”[28, 51]. Therefore, extended periods of continuous AF detrimentally affects a patient ability to restore and maintain normal sinus rhythm[46, 54]. Along with that there is also a reduced possibility of spontaneous AF termination[46, 54].

The literature has identified a multitude of risk factors for AF[7]. Firstly there is evidence that suggest there is a genetic risk factor of AF[55, 56]. 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]. Alcohol consumption[57], extreme endurance exercise and caffeine[58, 59] have also been shown to increase the risk of developing AF. Of increasing importance and emphasis in the literature is the role of obesity and 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%[60]. 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[61]. Obesity has also been associated with a moderately higher risk of AF following cardiac surgery (postoperative AF)[57]. There have been various proposed underlying mechanisms, including the association between obesity and ventricular dysfunction, metabolic correlates, inflammation, sympathetic activity, and fatty infiltration of the atria[62-65] (Figure 3). To further support the notion of the importance of obesity in the pathophysiology of AF, there is increasing evidence demonstrating the positive influence of weight reduction in obese AF patients[66, 67]. Currently, it is not clear whether the outcomes of catheter or surgical ablation in obese versus non-obese AF patients have any different efficacy rates or morbidity outcomes. Additionally, more than 70% of subjects with obstructive sleep apnoea (OSA) are overweight or obese[68, 69]. 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[70].

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Figure 3. Flow chart demonstrating the intermediate mechanisms linking obesity to atrial fibrillation. Adapted from Magnani et al[65].

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 very 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 been used to slow ventricular heart rate but it has a very slow onset and is therefore not very effective in hyperadrenergic patients[1, 71]. Thus, intravenous administration of calcium-channel blockers, like diltiasem 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[72]. 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[73]. 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[74].

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[75]. 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[75]. Thus cardioversion or catheter ablation is recommended for this rare presentation of AF[75].

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, 76]. 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[77]. The choice of anticoagulant medication should take into occur the patient’s comorbidities, potential drug interactions and the patients 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, 78]. 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 CHA_2DS_2-VASc score, which is a clinical predictor that estimates the risk of stroke in AF patients. For patients with a CHA_2DS_2-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 CHA_2DS_2-VASc score is 1, antithrombotic therapy may not be necessary but the physician may still consider using an oral anticoagulant or aspirin[27, 76]. A patient with a CHA_2DS_2-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 have 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[79]. These NOACs, such as dabigatran and rivaroxaban act via direct inhibition of factor Xa or thrombin and have less drug interactions than warfarin[29, 79, 80]. Studies have also demonstrated similar efficacy profiles for rivaroxaban, dabigatran and warfarin in patients undergoing catheter ablation[29, 80].

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[81]. 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[74]. For the patients that require cardioversion, adequate anticoagulation therapy must be administered immediately[5, 27, 75].

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[82]. 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[83]. 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, 84]. 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[85]. 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, if can limit the ventricular rate in a similar fashion to rate control drugs for AF. It facilities this by eliminating triggers and altering electrophysiological connections in the heart[86].

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 [43]. A variety of catheter ablation lesion strategies is demonstrated in Figure 4.

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Figure 4. Schematic of common lesion sets employed in AF ablation. (A) Circumferential ablation lesions, which are created in a circumferential fashion around the right and the left PVs. (B) Some of the most common sites of linear ablation lesions. These include a “roof line” connecting the lesions encircling the left and and/or right PVs, a “mitral isthmus” line connecting the mitral valve and the lesion encircling the left PVs at the level of the left inferior PV, and an anterior linear lesion connecting either the “roof line” or the left or right circumferential lesion to the mitral annulus anteriorly. Also shown is a linear lesion created at the cavotricuspid isthmus. (C) Similar to B but also shows the addition of additional linear ablation lesions between the superior and inferior PVs resulting in a figure of 8 lesion set. Also shown is an encircling lesion of the superior vena cava directed at electrical isolation of the superior vena cava. (D) Some of the most common sites of ablation lesions when complex fractionated electrograms are targeted. Figure and caption adapted from Calkins et al[49].

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) (Figure 5). 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 [87], with equivalent 1-year freedom from AF, shorter fluoroscopy times [88] and more reproducible[89]. In fact, a meta-analysis of only randomized data revealed no significant differences between radiofrequency and cryoballoon ablation[90]. However there was a consistent reduction in procedure duration for phased duty-cycle radiofrequency ablation[90]. In regards to cryoablation vs. cryoballoon, it has been suggested that cryoballoon allows for creation for contiguous lesions resulting in significantly higher durability than focal cryoablation [91].

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Figure 5. Catheter ablation techniques. (A) shows the cryoballoon system, a single-step approach in which a balloon delivers subzero temperatures to the pulmonary-vein antra. (B) shows the radiofrequency catheter ablation system, which uses heat-energy transfer to tissue and delivers a series of point-by-point connected lesions with assistance from a three-dimensional navigational system. Figure and caption adapted from Kuck et al[92].

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 [93-97]. 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%) [97]. Catheter ablation also demonstrates superiority in regards to recurrence of AF of 20% as compared to 75% in those taking antiarrhythmic drug therapy alone [98]. Recent evidence comparing catheter vs. surgical ablation for AF demonstrates higher freedom from AF with surgical ablation [99] 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[100, 101]. For patients in with abnormal firing from a focal source, focal radiofrequency ablation can be used[2, 36]. However identification of the exact location of abnormal firing can be difficult[2].

Surgical Management

The field of atrial fibrillation 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 atrial fibrillation 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: (1) it is appropriate to consider all patients with symptomatic AF undergoing other cardiac surgery for AF ablation and (2) 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 [85]. These are class IIa and class IIb level of evidence C, respectively.

Development

Cox-Maze I

Starting in the 1980s, unsuccessful attempts at surgically treating AF included left atrial isolation [102], corridor operation [103], and atrial transection [104]. 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 [104] 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. As AF begets AF due to atrial electrical remodeling *[105],* thus a therapy focused on pulmonary vein isolation alone was insufficient to treat long-standing persistent AF. Thus, 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 [106]. 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 (Figure 6). 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 [107]. 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 [108].

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Figure 6. Schematic three-dimensional view of the heart, depicting the incisions of the Cox-Maze III procedure. Adapted from Calkins et al[109].

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 [110, 111]. This method utilizes new ablation technologies to replace the “cut-and-sew” technique [111] 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. Figure 7 demonstrates example lesions produced using a bipolar radiofrequency clamp.

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 [111-113]. 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 [114].

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Figure 7. Ablation lesions for Cox-Maze IV procedure made using a radiofrequency bipolar clamp, rather than “cut-and-sew” incisions of the Cox-Maze III procedure. (A) Right-sided pulmonary vein isolation, (B) ablation of the inferior vena cava [1], superior vena cava [2], and right atrial free wall [3] directed towards the atrioventricular groove near the acute margin of the heart. Figure adapted from Robertson et al[115].

In contrast to 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 [116-118], CABG or aortic valve surgery [119] have demonstrated significantly increased the odds of freedom from AF. A meta-analyses 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[120-122]. 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 [123]. There is variability in the literature as to the success rate 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[124].

Types of Lesions

Three broad lesion sets in the surgical treatment of AF include (1) pulmonary vein isolation; (2) left atrial lesion set; and (3) 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[125, 126].

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 [127, 128]. 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 [129]. 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 [130], 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 that 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 impedence as atrial tissue is clamped and ablated. Its use has been reported in the off-pump technique [108]. 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 transmurality with shorter procedural time [131].

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 [132, 133]. As well, bipolar radiofrequency ablation is regarded as superior to microwave ablation in achieving transmurality [134].

High intensity focused ultrasonography

High intensity focused ultrasonography is a quick method resulting 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 [132, 133].

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. Though 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 [108]. 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 [123].

Left atrial appendage occlusion

During surgical ablation, concomitant left atrial appendage occlusion (LAAO) has emerged as a potential method of improving operative outcomes[135, 136]. 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[137]. 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 (1) beating heart right-sided thoracoscopic pulmonary vein isolation with multiple technologies; (2) beating heart bilateral thoracotomy with bipolar radiofrequency ablation; and (3) arrested heart right-sided thoracotomy.

Beating heart right-sided thoracoscopic approach

A unilateral right-sided port approach with two or three ports has been described with microwave energy ablation resulting in short hospital length of stay (1-4 days) [133, 138, 139]. 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 [133].

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 [140]. Reported outcomes demonstrate 75%-90% freedom from AF [141] with overall procedural success rate, as defined as the completion of the procedure without conversion to sternotomy or cardiopulmonary bypass, as 99.5% [141]. 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 [142].

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 [143]. 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 [144] 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; $P < 0.001$)[99, 145, 146]. Adverse events included need for pacemakers (5%), hemothorax (3%), phrenic nerve injury (3%), transient ischemic attack (1%) and pulmonary embolism (1%)[142]. 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 [147]. 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 transmurality when required; and (IV) be minimally invasive [148].

Though epicardial surgical ablation results in superior transmurality and durability compared to catheter ablation [131], 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 latrogenic circuits with predisposition to atrial flutter [149-151].

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 [152]. Where simultaneous ablation limits the potential for unstable iatrogenic flutters which can complicate epicardial only ablation. In contrast, staged ablation may allow for maturation of epicardial lesions for evaluation of gaps in ablation lines. Hybrid ablation offer 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[153] [154]. 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 [150] 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 cardiologist. 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 [108].

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. Few centers have the required expertise for this novel approach at the moment, and thus, there is a paucity of clinical data available to assess its relative benefits and risks. A randomized controlled trial comparing hybrid AF ablation to other ablation methods is warranted to clarify the role of hybrid procedures in AF ablation.

Integrated heart-team approach for patient care

It is important for treating clinicians to remember that the above techniques are only components of an integrated healthcare strategy for patients with AF. According to the recent 2016 ESC guidelines[155], integrated care of patients with newly diagnosed AF should address the following five domains: (1) acute hemodynamic stabilization in hemodynamically unstable patients, (2) detection and treatment of concomitant cardiovascular conditions, (3) stroke assessment and management, (4) rate control therapy options, and (5) rhythm control therapy options (Figure 8). Patients should receive treatment in these 5 domains, and this optimal management will require collaboration and cooperation between different specialists and professions in an AF heart team, including AF specialists, stroke physicians, AF surgeons, general cardiologists, general practitioners, other allied health staff, and patients[155]. There is some randomized evidence to support the benefits of integrated AF care, associated with increased use of evidence-based care, reduced cardiovascular hospitalization and death, as well as being more cost-effective compared to usual care[156, 157].

Figure removed due to copyright restrictions

Figure 8. Acute and chronic management of atrial fibrillation patients, desired cardiovascular outcomes, and patient benefits. All patients with AF should receive care directed at the five domains outlined in the figure. LV, left ventricular. Figure adapted from Kirchhof et al[155].

Objectives of thesis

The focus of the present series of publications was to examine the clinical outcomes of surgical ablation for AF, based on different approaches, energy sources, and lesion sets. The first section of the thesis explores the current reported clinical outcomes for surgical and catheter ablation for AF. Cumulative meta-analysis was used to investigate the safety and effectiveness of concomitant surgical ablation and cardiac surgery at restoring sinus rhythm (Chapter 2). Thoracoscopic epicardial surgical approaches were compared with catheter endocardial techniques based in terms of follow-up freedom from AF and complication rates based on the current existing literature (Chapter 3).

The second part of the thesis compared the outcomes of variations in ablation approaches used. There remains controversy regarding the optimal energy source used for Cox-Maze IV surgical ablation as well as for percutaneous catheter ablation for AF. A Bayesian rank probability analysis was performed to compare the outcomes of the original cut-and-sew approach with microwave, radiofrequency and cryoablation for surgical ablation (Chapter 4). The clinical outcomes and complications of biatrial versus left atrial only lesions sets were also assessed in patients with AF undergoing cardiac surgery (Chapter 5).

Given the increasing importance of obesity as a risk factor for AF, the third part of this thesis explores the relationship between obesity and atrial fibrillation. Specifically, this thesis sought to examine the relationship between obesity and postoperative AF following cardiac surgery, and whether long-term complications and survival differed according to postoperative rhythm status (Chapter 6). Finally, the recently developed hybrid ablation procedure for AF has few reported long-term outcomes published in the available literature. We conducted a retrospective database analysis to assess the long-term efficacy and morbdity of this recently introduced procedure, and whether obesity influences the 3-year success and complication rates (Chapter 7).

In summary, this body of work includes a systematic evidence synthesis on the surgical management strategies for AF in the existing medical literature as well as early preliminary results on a hybrid endocardial and epicardial approach for AF treatment. Consolidating the available evidence will serve as a platform for future research ablation treatment techniques for AF.

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Chapter 6

Obesity and postoperative atrial fibrillation in patients undergoing cardiac surgery: systematic review and meta-analysis

Abstract

Introduction: Post-operative atrial fibrillation (POAF) is one of the most common complications following cardiac surgery. However, it is unclear whether there is a relationship between obesity and POAF. We thus assessed all available evidence investigating the association between obesity and POAF, also considering any link between POAF and other post-operative conditions such as mortality, stroke, myocardial infarctions and respiratory complications.

Methods: Five electronic databases were searched and relevant studies were identified. Data was extracted and meta-analyzed from the identified studies.

Results: We found that obese patients had significantly higher odds of POAF when compared with non-obese patients (P=0.006). There was also significant heterogeneity amongst the identified studies. POAF when compared with no-POAF was associated with an increased risk of stroke (P<0.0001), 30-day mortality (P=0.005) and respiratory complications (P<0.00001). However, we found no significant link between POAF and myocardial infarctions (P=0.79)

Conclusions: Our findings suggest that obesity is associated with a moderately higher risk of POAF. While POAF is also associated with an increased incidence of stroke, 30-day mortality and respiratory complications,

further studies must be conducted before conclusions can be made about the long-term outcomes.

6.1. Introduction

There has been recent and increasing emphasis on the role of obesity as a risk factor and possible target for the integrated management and treatment of atrial fibrillation (AF) (Chapter 1). There has also been the suggestion that underlying obesity is a contributing factor to the developing of AF after cardiac surgery. Post-operative atrial fibrillation (POAF) is one of the most common complications arising from cardiac surgery, affecting between 20% and 50% of patients[1, 2]. POAF is not a benign complication and has been previously associated with risk of mortality and morbidity, as well as increased costs of additional treatment and post-operative care[3]. Although the precise pathophysiology remains to be elucidated, several risk factors have been linked to POAF including older age, male gender, obesity, pre-existing congestive heart failure, chronic renal failure and chronic lung disease[1, 4, 5]. Obesity, defined as having a body mass index (BMI) above 30 kg/m^2, is one of the more commonly studied risk factors for POAF. Obesity is associated with diastolic ventricular dysfunction and atrial enlargement, both of which in turn are risk factors for atrial fibrillation[6, 7]. This mechanism has become better understood: atrial electrophysiological and structural remodelling[8] along with diastolic ventricular dysfunction have been observed in obese patients independent of other risk factors[9]. The direct relationship between obesity and atrial fibrillation has also been observed in large, population- and community-based studies, such as the Framingham study and the Danish Diet, Cancer and Health study[10, 11]. Among cardiac surgery patients, however, this connection is not well established. A large meta-analysis included 44 647 cardiac surgery patients and 78 602 patients from population-based cohort studies[7]. Among the cohort studies, there was a graded relationship between higher BMI and risk of developing AF, with obese people 49% more likely to develop AF. However, no relationship between BMI and POAF was found in the cardiac surgery patients. However, this study included patients with pre-operative AF, a group that has between a two- and four-fold greater risk of developing POAF, potentially confounding results[12]. Another pooled analysis of 18 observational studies, which excluded studies that did not explicitly give data for the subgroup without pre-operative AF, found a small effect of obesity on POAF[13]. Small, observational studies have suggested age and gender as pre-operative predictors of POAF, however these are yet to be validated sufficiently in a meta-analysis[14]. Similarly, chronic conditions, such as diabetes and hypertension, and respiratory factors, such as chronic lung disease and smoking, have all been suggested to be risk factors for POAF[6].

The primary aim of the present study was a systematic review and meta-analysis of the current evidence investigating the association between obesity and POAF. Other risk factors, such as age, gender, hypertension, previous myocardial infarction, chronic lung disease and smoking status were also investigated. The other aim of this study was to determine the association between POAF and post-operative conditions such as mortality, stroke, MI and respiratory complications.

6.2. Methods

Literature search strategy

The present review was conducted according to recommended PRISMA guidelines[15, 16]. Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to July 2015. To achieve maximum sensitivity of the search strategy and identify all studies, we combined the terms: “obesity”, “atrial fibrillation”, “AF”, and “cardiac surgery” as either keywords or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. All identified articles were systematically assessed using the inclusion and exclusion criteria (Figure 1).

Selection criteria

Eligible cohort studies for the present systematic review and meta-analysis included those in which patients aged over 18 years underwent cardiac surgery, with information about POAF among patients regardless of whether BMI was reported categorically or as a continuous distribution in patients with and without POAF, and published in any language. Only studies that excluded the presence of preoperative AF and that showed data for the subgroup without preoperative AF were eligible. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects and in the English language. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted because of potential publication bias and duplication of results.

Data extraction

All data was extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article (K.P. and J.N.K.). Discrepancies between the two reviewers were resolved by discussion and consensus with a third reviewer (A.K.). Assessment of risk of bias for each selected study was performed according based on the key points of study quality proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Collaboration[17]. These points include: (1) clear identification of study population, (2) clear definition of outcome and outcome assessment, (3) independent assessment of outcome parameters, (4) selective loss during follow-up, and (5) important confounders or prognostic factors or both identified. Discrepancies between the two reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigator (T.D.Y.).

Statistical analysis

The odds ratio (OR) was used as a summary statistic. To be able to use the information from the subset of studies with continuous BMI information, we used the methodology reported by Chinn[18] to transform standardized mean differences to the equivalent OR per study. This method works regardless of BMI values, and the OR is assumed to be the same regardless of the chosen cut-off of BMI that is used to define obesity within a reasonable range. We then calculated the natural logarithm of the OR (logOR) and its standard error (SE[logOR]) per study for all studies in both sets. These were meta-analyzed using the inverse variance method incorporating also the between-study variance estimator along with the within-study variance in the calculations. We also evaluated, when possible, the association between obesity and secondary outcomes (stroke, respiratory failure, and operative death) and the association between the presence of POAF and secondary outcomes.

In the present study, both fixed- and random-effect models were tested. In the fixed-effects model, it was assumed that treatment effect in each study was the same, whereas in a random-effects model, it was assumed that there were variations between studies. χ^2 tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity. I^2 can be calculated as: $I^2 = 100\% \times (Q - df)/Q$, with Q defined as Cochrane's heterogeneity statistics and df defined as degree of freedom. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. In the present meta-analysis, the results using the random-effects model were presented to take into account the possible clinical diversity and methodological variation between studies. Specific analyses considering confounding factors were not possible because raw data were not available. All P values were 2-sided. All statistical analysis was conducted with Review Manager Version 5.3.2 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

6.3. Results

Search strategy

A total of 1584 references were identified through six electronic database searches. After duplicate references were removed, 1565 potentially relevant articles were retrieved. After detailed evaluation of these articles via title and abstract screen, 81 studies remained for assessment. After applying the selection criteria, 29 studies[19-47] were selected for analysis. The study characteristics of these trials are summarized in Table 1. These studies included 14 072 patients with POAF and 60 118 patients with non-POAF. Mean patient age ranged from 45 to 78.5 years. The proportion of males ranged from 34% to 96%. The mean BMI ranged from 22 to 30 kg/m^2. Most patients underwent CABG only, with patients in 4 of those studies[36, 37, 41, 43] also receiving concomitant valve operations. Six studies[35-37, 41, 43, 45] reported valve surgery alone. The most commonly reported postoperative outcomes were strokes, 30-day mortality, myocardial infarctions, and respiratory complications.

Quality of studies

Fifteen studies were prospective cohort studies[19, 21, 23, 25, 30, 31, 33-35, 37, 38, 40-42, 46]. All studies clearly identified the study population and defined the outcome (Table 2). According to the study reports, none of the studies lost patients during follow-up. All studies identified some important confounders or prognostic factors of the association between obesity/BMI and POAF. However, these were not consistently the same or defined in the same way across studies. Adjusted estimates of the association between obesity and POAF were not well reported, and therefore, no comparison with the unadjusted association was possible.

Association between obesity and outcomes

Obese patients had a higher odds of POAF compared to non-obese patients (OR 1.21; 95% CI 1.06-1.38; I^2=89%; P=0.006)(Figure 2). Significant heterogeneity was detected amongst the studies. In secondary analyses, we found that POAF compared to no-POAF was associated with a higher risk of strokes (OR 2.38; 95% CI 1.55-3.64; I^2=65%; P<0.0001)(Figure 3) and 30-day mortality (OR 2.30; 95% CI 1.28-4.14; I^2=74%; P=0.005)(Figure 4). However, no association was found between POAF with myocardial infarctions (OR 1.05; 95% CI 0.72-1.53; I^2=0%; P=0.79)(Figure 5). A significant association was also found between POAF and respiratory complications (OR 3.06; 95% CI 2.37-3.94; I^2=24%; P<0.00001)(Figure 6).

Association between baseline variables and POAF

Baseline and demographic variables and their association with POAF versus no-POAF were also tested. The proportion of males was similar between POAF and no-POAF patients (OR 1.00; 95% CI 0.90-1.11; I^2=66%; P=0.94). Being older was significantly associated with POAF (OR 4.68; 95% CI 3.97-5.39; I^2=89%; P<0.00001). Baseline chronic lung disease (OR 1.31; 95% CI 1.23-1.41; I^2=5%; P<0.00001) and hypertension (OR 1.46; 95% CI 1.38-1.53; I^2=83%; P<0.00001) were significantly associated with POAF. There was no significant association between prior myocardial infarctions (OR 1.05; 95% CI 0.98-1.12; I^2=33%; P=0.18), diabetes status (OR 1.05; 95% CI 0.88-1.24;

I^2=90%; P=0.61), or smoking (OR 0.94; 95% CI 0.69-1.26; I^2=96%; P=0.67) with POAF.

6.4. Discussion

AF is the most common cardiac arrhythmia, with hospitalizations due to AF increasing exponentially over the past decade. Population studies have demonstrated BMI, a measure of overall adiposity, to be a strong predictor of AF[10, 48]. However, this association is not as well established for POAF. In the present study, we found that obesity was associated with a moderately higher, statistically significant, risk of POAF. The magnitude of this effect was almost double what Hernandez and colleagues[13] found and was equal to their upper 95% CI. This difference is likely because of the increase in studies used in the meta-analysis: while four studies had a combined weight of over half of Hernandez and colleagues' meta-analysis, in the present meta-analysis, no study had more than a 4.8% weighting. The exclusion from this meta-analysis of patients who had pre-operative AF, a sub-group with a two- to four-fold risk of POAF, could account for the divergence between the present result and the lack of an association shown in Wanahita and colleagues' meta-analysis[7].

A causal explanation for the observed association between obesity and POAF cannot be concluded. However, the other potential risk factors included in the meta-analysis can be examined to see if their correlation with obesity could account for the causal pathway to POAF. Hypertension had a slightly higher association with POAF than obesity. Hypertension is more common in obese cardiac surgery patients; Stamou and colleagues' retrospective study[49] of 2465 cardiac surgery patients found 86.9% of obese patients had pre-operative hypertension compared to 75.2% of non-obese patients. Thus hypertension could explain some of the association between obesity and POAF. Chronic lung disease, however, had a moderate association with POAF, yet the same retrospective study mentioned above found that 15.4% of obese cardiac surgery patients had chronic lung disease compared to 14.5% of non-obese patients, a non-significant difference. Other risk factors that occur more frequently in obese patients, such as smoking, prior myocardial infarction and diabetes, were not associated with POAF. Age was strongly associated with POAF, but because this meta-analysis did not have access to individual patient data, the interaction between age and obesity is unclear. While smaller studies have found a stronger association between obesity and POAF after age is controlled, this remains to be validated.

The positive correlation between POAF and obesity can possibly be explained by the increased prevalence of obstructive sleep apnoea (OSA) in obese patients [50, 51]. OSA has been shown to increase the incidence of cardiovascular diseases, in particular AF [52, 53]. Various studies have found that OSA is independently associated with an increased risk of AF following coronary artery bypass surgery [54-56]. This association has been postulated to be a result of a variety of processes including autonomic instability, incomplete postoperative tissue vascularization and use of inotropic drugs [57]. While there are still limited studies examining the direct link between

OSA and increased POAF, studies to date have indicated that OSA may be a contributing factor to the association between obesity and POAF.

There remains the possibility that a further factor still, such as metabolic syndrome, could explain the obesity-POAF relationship, which is what Echihadi and colleagues found in patients younger than 50 years old. Also, left atrium size when introduced into the model of Wang and colleagues, completely reduced the effect of BMI on POAF[10]. Other studies have suggested elevated plasma volume[58], diastolic dysfunction[59] and inflammation[60] as mediators of the obesity-POAF relationship.

Of the other potential risk factors investigated, gender, prior myocardial infarction, diabetes and smoking were not associated with higher POAF. However hypertension and chronic lung disease were associated with a moderately higher risk of POAF, and there was a strong association between age and POAF. This result is in accordance with large studies such as the EuroSCORE multinational database of 19 030 cardiac surgery patients, which concluded that diabetes and smoking were not associated with mortality, while chronic pulmonary disease and hypertension were[61]. The mechanism of how POAF affects these outcomes is poorly understood: stroke and cardioembolic events are thought to be induced by circulatory stasis in the left atrium, while poor ventricular filling could explain respiratory failure[34, 62]. The effect of POAF on secondary outcomes was marked. POAF was strongly associated with 30-day mortality, stroke and respiratory complications, while there was no effect on myocardial infarction. These findings were similar to those found in Hernandez and colleagues' meta-analysis: the magnitude of the effects of POAF on stroke and respiratory failure were slightly larger. The magnitude of the effect of POAF on mortality was slightly smaller. This could be because a stricter definition of mortality, 30-day mortality, was used while Hernandez and colleagues included in-hospital death and long-term follow-up[13]. The long-term effect of POAF on mortality is an area for future research, particularly given findings of an 'obesity paradox', where moderately obese cardiac surgery patients had superior long-term survival in a Canadian study of 78 762 patients[63]. This direct association between obesity and mortality is the opposite of the indirect effect of obesity on POAF, which in turn adversely affects mortality. The direct association between obesity and other outcomes, like stroke, remain unclear: Habib and colleagues' propensity-matched analysis of over 1000 patients reported no statistically significant difference between very obese and normal weight patients[2].

It is important to recognise the limitations of this meta-analysis. The inability to access individual patient data forced a univariate meta-analysis to be used. A causal relationship between obesity and POAF was unable to be concluded despite testing several other risk factors. Thus other physiological factors such as metabolic syndrome or inflammation could possibly be also playing a role. Variables such as BMI and duration of postoperative stay were also unable to be analysed in association with POAF, as they were not consistently reported by the included studies. As this was a meta-analysis of observational studies, bias may be present. This is mitigated by the large selection of studies such that no study had greater than a 4.8% weighting for the primary outcome and that there was no evidence of publication bias. Another limitation was the large heterogeneity across studies selected, which is potentially due to differences in various conditions such as operative time, operative technique and also the innate heterogeneity in the population. Some risk factors and outcomes also had significantly different definitions, which resulted in greater heterogeneity in outcomes. Respiratory complications were defined alternately as prolonged intubation exceeding 24 hours only[64], prolonged intubation exceeding 24 hours, reintubation[20], and prolonged intubation exceeding 48 hours[27]. Similarly chronic lung disease was restricted to only chronic obstructive pulmonary disease in some studies, but not in others[27, 39, 49]. For a few of the less well-studied outcomes, such as respiratory failure, a lack of studies resulted in just three studies being weighted at over two-thirds of the meta-analyses. This still represents an improvement over a prior analysis where three studies were weighted at over 90%[13]. Thus the large magnitude of the observed effect of POAF on respiratory failure needs to further investigated as more studies that explicitly include this outcome are published.

In conclusion, there is strong evidence that obesity is associated with a moderately higher risk of POAF. Other pre-operative factors, such as age, chronic lung disease and hypertension are also associated with higher risk of POAF. Further research is needed to examine the interrelation of these factors, and to determine which of these relationships are causal. Finally, POAF is associated with adverse outcomes, including 30-day mortality, stroke and respiratory complications. Further studies are required to determine the effect of weight reduction on POAF.

6.5. Tables and Figures

Table 1: Characteristics of Studies Evaluating the Association of Postoperative Atrial Fibrillation and Continuous Body Mass Index. This table summarises the data for the main baseline characteristics, operation type and post-operative complications for all the included studies.

First Author	Study Design	POAF Groups	No.	Age Mean (SD) y	Male No. (%)	BMI Mean (SD) kg/m^2	Type of Operation			Postoperative Complications		
							CABG No. (%)	Valve No. (%)	CABG + Valve No. (%)	Stroke No. (%)	RF No. (%)	Operative Death No. (%)
Ducceschi 1999	RC	POAF	24	65.4 (6.3)	23 (96.0)	27.4 (2.5)	24 (100)	–	–	–	2 (8.0)	–
		No POAF	126	58.4 (8.8)	103 (82.0)	26.1 (2.7)	126 (100)	–	–	–	8 (6.0)	–
Jideus 2000	PC	POAF	29	65.7 (7.4)	23 (79.0)	25.6 (3.4)	29 (100)	–	–	–	–	0 (0)
		No POAF	51	65.8 (7.8)	44 (86.0)	27.6 (3.8)	51 (100)	–	–	–	–	0 (0)
Hakala 2002	PC	POAF	30	66.0 (9.0)	22 (73.3)	28.5 (3.7)	30 (100)	–	–	1 (1.1)	–	0 (0)
		No POAF	62	59.7 (9.7)	48 (77.4)	27.0 (3.1)	62 (100)	–	–	–	–	0 (0)
Auer 2005	PC	POAF	99	67.5 (9.1)	55 (55.5)	27.7 (3.4)	62 (62.6)	–	–	2 (2.0)	–	2 (2.0)
		No POAF	154	63.7 (11.4)	97 (63.0)	27.7 (3.3)	112 (72.7)	–	–	0 (0)	–	0 (0)
Kokkonen 2005	PC	POAF	19	72.8 (9.6)	14 (74.0)	28.8 (4.1)	–	–	–	6 (31.6)	–	3 (15.8)
		No POAF	25	69.5 (7.4)	15 (60.0)	27.3 (3.5)	–	–	–	1 (4.0)	–	0 (0)
Zacharias 2005	RC	POAF	1810	68 (10.0)	1199 (66.2)	29.6 (5.8)	1634 (90.3)	–	–	–	–	–
		No	6241	63 (11.0)	4173	29.3	5677	–	–	–	–	–

		POAF			(66.9)	(5.5)	(91.0)					
Banach (Aortic Stenosis) 2007	RC	POAF	62	65.3 (9.7)	43 (69)	26.9 (6.5)	−	−	−	5 (8.1)	4 (6.5)	5 (8.1)
		No POAF	88	58.6 (8.4)	34 (39)	26.3 (3.8)	−	−	−	4 (4.5)	4 (4.5)	3 (3.4)
Banach (Aortic Regurgitation) 2007	RC	POAF	69	63.1 (7.3)	36 (52)	26.5 (3.5)	−	−	−	5 (7.2)	3 (4.3)	7 (10.1)
		No POAF	81	58.4 (10.4)	34 (42)	26.1 (3.3)	−	−	−	3 (3.7)	4 (4.9)	4 (4.9)
Echahidi (≤50) 2007	RC	POAF	40	46 (4.0)	33 (83)	29.4 (5.0)	32 (80)	−	−	0 (0)	−	0 (0)
		No POAF	63	45 (4.0)	54 (86)	28.8 (5.0)	46 (73)	−	−	0 (0)	−	0 (0)
Echahidi (>50) 2007	RC	POAF	1329	69 (8.0)	1023 (77)	28.3 (5.1)	1130 (85)	−	−	40 (3.0)	−	40 (3.0)
		No POAF	3254	65 (8.0)	2440 (75)	27.7 (4.4)	2733 (84)	−	−	65 (2.0)	−	33 (1.0)
Mariscalco 2008	PC	POAF	570	68.4 (7.9)	440 (77.2)	26.8 (3.7)	570 (100)	−	−	16 (2.8)	68 (12.0)	19 (3.3)
		No POAF	1262	63.7 (9.1)	974 (77.2)	26.7 (4 .1)	1262 (100)	−	−	11 (0.9)	63 (5.0)	6 (0.5)
Mauermann 2010	RC	POAF	60	65.4 (10.1)	52 (87.0)	27.8 (4.4)	26 (43.3)	29 (48.3)	5 (8.3)	−	−	−
		No POAF	125	61.4 (11.5)	104 (83.0)	27.7 (4.3)	66 (52.8)	56 (44.8)	3 (2.4)	−	−	−
Melduni 2011	PC	POAF	135	72.5 (10.3)	87 (64.4)	29.3 (5.4)	52 (38.5)	41 (30.4)	42 (31.1)	4 (3.0)	−	4 (3.0)
		No POAF	216	63.1 (14.1)	149 (69.0)	28.5 (5.0)	108 (50.0)	74 (34.3)	34 (15.7)	4 (1.9)	−	8 (3.7)
Bramer 2010	PC	POAF	1122	68.5	884	27.4	1122	−	−	17 (1.5)	−	35 (3.1)

				(8.1)	(78.8)	(3.9)	(100)					
		No POAF	3976	64.0 (9.7)	3081 (77.5)	27.3 (3 .8)	3976 (100)	–	–	32 (0.8)	–	64 (1.6)
Shirzad 2010	RC	POAF	1129	–	763 (68)	26.86 (4.3)	835 (74)	186 (16.5)	108 (9.6)	–	–	2 (3)
		No POAF	14451	–	10672 (74)	27.10 (4.0)	13588 (94)	525 (3.6)	338 (2.3)	–	–	0 (0)
Tadic 2011	RC	POAF	72	63 (7.0)	53 (74)	28.1 (3.4)	–	–	–	–	–	2 (3)
		No POAF	250	59 (9.0)	178 (71)	25.6 (2.9)	–	–	–	–	–	0
El-Chami 2012	RC	POAF	3486	67.52 (9.5)	2546 (73)	29.1 (5.8)	1616 (46)	–	–	–	–	–
		No POAF	15031	61.33 (10.9)	10731 (71)	29.1 (5.6)	7096 (47)	–	–	–	–	–
Kinoshita 2012	RC	POAF	159	70.6 (10.2)	126 (79)	23.5 (3.7)	–	–	–	–	–	–
		No POAF	646	67.7 (9.8)	516 (80)	23.3 (3.1)	–	–	–	–	–	–
Cao 2013	RC	POAF	61	50.7 (9.1)	33 (54)	24.8 (2.8)	–	–	–	–	–	–
		No POAF	93	45.2 (10.9)	43 (68)	22.0 (2.5)	–	–	–	–	–	–
Nishi 2013	PC	POAF	134	68.4 (12.4)	95 (71)	23.1 (3.4)	–	–	–	–	25 (19)	1 (0.7)
		No POAF	284	58.2 (17.8)	189 (67)	22.4 (4.0)	–	–	–	–	19 (7)	7 (2.5)
O'Neal 2013	RC	POAF	2536	68 (9.0)	1900 (75)	29 (5.5)	–	–	–	–	–	–
		No POAF	10258	62 (10)	7160 (70)	29 (5.5)	–	–	–	–	–	–
Dandale 2014	RC	POAF	316	72.3 (8.6)	169 (54)	27 (4.7)	106 (33)	–	–	47 (2)	6 (2)	–
		No	514	68.8	315	26.3	149 (29)	–	–	103 (1)	51 (1)	–

		POAF		(12.1)	(62)	(4.7)						
Drossos 2014	PC	POAF	28	66 (8.0)	22 (79)	29 (4.6)	–	–	–	–	–	–
		No POAF	55	64 (9.0)	44 (80)	30 (4.5)	–	–	–	–	–	–
Erdil 2014	RC	POAF	129	64.1 (9.4)	95 (74)	25.6 (3.9)	–	–	–	–	–	2 (2)
		No POAF	811	59.6 (9.7)	693 (79)	26.2 (3.7)	–	–	–	–	–	13 (2)
Parsaee 2014	PC	POAF	19	67.11 (9.0)	14 (74)	27.6 (4.0)	–	–	–	–	–	–
		No POAF	131	59.19 (8.6)	99 (76)	26.66 (4.8)	–	–	–	–	–	–
Pillarisetti 2014	PC	POAF	133	68 (10)	102 (77)	28 (5)	93 (70)	14 (19)	16 (21)	8 (10)	–	–
		No POAF	386	62 (13)	279 (72)	29 (6)	295 (76)	14 (56)	9 (35)	6 (24)	–	–
Sahin 2014	PC	POAF	96	63.5 (8.5)	64 (67)	28.3 (4.7)	–	–	–	–	–	–
		No POAF	501	59.7 (9.9)	387 (77)	28.5 (14)	–	–	–	–	–	–
Takahashi 2014	RC	POAF	41	78.5 (6.1)	14 (34)	22.7 (3.6)	–	41 (100)	–	–	–	1 (2.4)
		No POAF	22	71.6 (10.3)	9 (41)	22.4 (2.4)	–	22 (100)	–	–	–	0 (0)
Weidinger 2014	PC	POAF	59	63	47 (80)	29	–	–	–	3 (5.1)	–	1 (1.7)
		No POAF	325	60	235 (72)	27	–	–	–	4 (1.2)	–	2 (0.6)
Chua 2015	PC	POAF	103	66.5 (8.8)	77 (75)	26.1 (3.9)	–	–	–	3 (3)	–	3 (3)
		No POAF	247	60.4 (9.6)	191 (77)	25.9 (3.7)	–	–	–	5 (2)	–	7 (3)
Masson 2015	PC	POAF	173	60.8	128	29.3	–	113	–	–	–	–

				(12.9)	(74)	(5.3)		(65.3)				
		No POAF	389	66.5 (11.3)	276 (71)	28.8 (6.2)	−	187 (51.2)	−	−	−	−

RC, retrospective cohort; PC, prospective cohort; POAF, postoperative atrial fibrillation; SD, standard deviation; CABG, coronary artery bypass grafting; RF

Table 2. Quality of included studies

First Author	Study Design	Study Population Clearly Identified?	Clear Definition of Outcome and Outcome Assessment?	Selective Loss of Patients During Follow-up?	Important Confounders and/or Prognostic Factors Identified?
Ducceschi 1999	RC	Yes	Yes	No	Age, BMI, pre-op paroxysmal AF, 3-vessel CAD, and left atrial enlargement
Jideus 2000	PC	Yes	Yes	No	BMI, total amount of cardioplegia, and SPB/min
Hakala 2002	PC	Yes	Yes	No	Age, BMI, diabetes, hemoglobin, and heart rate variability measurements
Auer 2005	PC	Yes	Yes	No	Age, type of operation, and pre-op b-blockers usage
Kokkonen 2005	PC	Yes	Yes	No	Age and number of grafts
Zacharias 2005	RC	Yes	Yes	No	Age, race, BMI, BSA, smoking status, hypertension, COPD, PVD, cerebrovascular disease, CHF, stable angina, triple- vessel disease, left main disease, LVEF, mean EF, digitalis, steroids, diuretics, type of operation, off-pump, perfusion time, cross-clamp time, and IABP
Banach 2007	RC	Yes	Yes	No	Age, BMI, pre-op and post-op LVEF, mitral regurgitation
Echahidi 2007	RC	Yes	Yes	No	Age, sex, hypertension, DM, COPD, previous stroke, previous MI, 3-vessel CAD, metabolic syndrome, b-blocker use, HDL cholesterol, triglycerides, BMI, and CPBT

Mariscalco 2008	RC	Yes	Yes	No	Age, left atrial area, IABP, PUFA, reoperation, pericardial effusion, operation type, valve replacement, combined surgery, and preop ACE inhibitors
Mauermann 2010	RC	Yes	Yes	No	Age, sex, smoking status, type of procedure, COPD, methylprednisone, hemofiltration, BMI, duration of anesthesia, aortic cross-clamp, CPB, intubation and surgery, CPB fluids, red cell transfusions and fluid balance
Melduni 2011	PC	Yes	Yes	No	Age, BMI, hypertension, mitral regurgitation, diastolic function, type of operation, and perfusion time
Bramer 2010	PC	Yes	Yes	No	Age, BMI, BSA, COPD, PVD, prior stroke, prior MI, LVEF, creatinine, type of procedure, ECC duration, transfusion of RBCs, FFP and platelets, and reoperation for bleeding
Shirzad 2010	RC	Yes	Yes	No	Age, BMI, gender, dyslipidemia, number of diseased vessels, preoperative renal failure, diabetes, hypertension, CVA, PVD, CHF, smoking, family history, MI, operation status, and IABP insertion.
Tadic 2011	RC	Yes	Yes	No	Age, number of grafts, hypertension,diabetes mellitus,hypercholesterolemia, left ventricular segmental kinetic disturbances and WBC count
El-Chami 2012	RC	Yes	Yes	No	Age, race, gender, height, weight, BMI, body surface area, last creatinine level, angina, left main coronary artery disease, immunosuppressive therapy, preoperative insertion of an intra-aortic balloon pump, number of diseased vessels and preexisting medical conditions.

Kinoshita 2012	RC	Yes	Yes	No	Age, sex, BMI, chronic kidney disease, chronic pulmonary disease, hypertension, triple vessel disease, preoperative beta blockers, pre- operative statins, inotropic support of >24 hrs.
Cao 2013	RC	Yes	Yes	No	Age, BMI, C-reactive protein, ejection fraction, preoperative use of calcium-channel blocker, beta-blocker and angiotensin-converting enzyme inhibitor, duration of ventilation, serum sRANKL and osteoprotegerin levels and sRANKL/osteoprotegerin ratio.
Nishi 2013	PC	Yes	Yes	No	Age, hypertension, perioperative transfusion, use of cardiopulmonary bypass and thoracic aortic surgery
O'Neal 2013	RC	Yes	Yes	No	Age, sex, race, hypertension, CAD severity, heart failure, and prior stroke
Dandale 2014	RC	Yes	Yes	No	Age, sex, hypertension, BMI, rheumatic heart disease, degenerative aortic valve disease
Drossos 2014	PC	Yes	Yes	No	Age, sex, BMI, preoperative beta-blockers, cross-clamp duration, use of retrograde cardioplegia and number of bypass grafts,
Erdil 2014	RC	Yes	Yes	No	Age, additive EuroSCORE score, and prolonged ventilation
Parsaee 2014	PC	Yes	Yes	No	Gender and coronary risk factors (DM, HTN and cigarette smoking)
Pillarisetti 2014	PC	Yes	Yes	No	Aspirin, history of stroke, congestive heart failure, ejection fraction
Sahin 2014	PC	Yes	Yes	No	Age, sex, presence of hypertension and low haematocrit level
Takahashi 2014	PC	Yes	Yes	No	Type of prosthesis, operation time, cardiopulmonary by-pass time, aortic cross-clamp time and blood loss

Weidinger 2014	PC	Yes	Yes	No	Age, weight, BMI, arterial hypertension, prolonged operation time
Chua 2015	PC	Yes	Yes	No	Age, hypertension, previous stroke or TIA, renal dysfunction, and vascular disease.
Masson 2015	PC	Yes	Yes	No	Age, renal or cardiac dysfunction and EuroSCORE

RC, retrospective cohort; PC, prospective cohort; BMI, body mass index; AF, atrial fibrillation; CAD, coronary artery disease; BSA, body surface area; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; EF, ejection fraction; DM, diabetes mellitus; CPBT, cardiopulmonary bypass time; HDL, high density lipoprotein; MI, myocardial infarction; IABP, intraaortic balloon pump; PUFA, polyunsaturated fatty acids

Figure 1. PRISMA flowchart of the present systematic review and meta-analysis

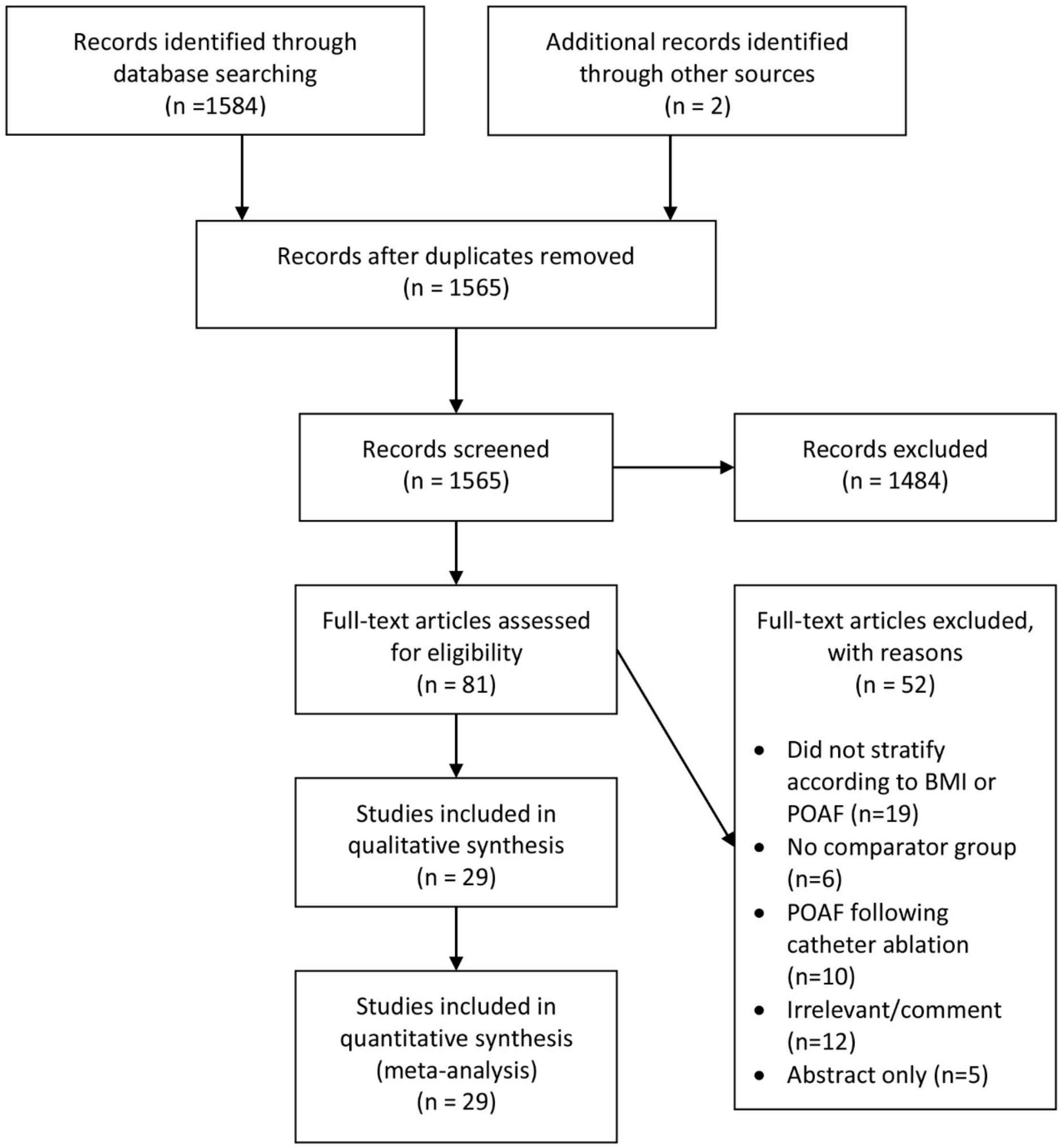


Figure 2. Forest plot of association between obesity and POAF

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Auer 2005	0	0.230867	3.1%	1.00 [0.64, 1.57]
Banach (AR) 2007	0.2133581	0.29677517	2.5%	1.24 [0.69, 2.21]
Banach (AS) 2007	0.2133837	0.30036458	2.5%	1.24 [0.69, 2.23]
Bramer 2013	0.0905	0.10829544	4.4%	1.09 [0.89, 1.35]
Cao 2013	1.93248954	0.31770638	2.4%	6.91 [3.71, 12.87]
Chua 2015	0.09628369	0.21232884	3.3%	1.10 [0.73, 1.67]
Dandale 2014	0.26957447	0.1295563	4.2%	1.31 [1.02, 1.69]
Drossos 2014	-0.3992431	0.42132085	1.7%	0.67 [0.29, 1.53]
Ducceschi 1999	-0.9292616	0.40663567	1.8%	0.39 [0.18, 0.88]
Echahidi_a 2007	0.2172	0.36623717	2.0%	1.24 [0.61, 2.55]
Echahidi_b 2007	0.23537729	0.05897389	4.7%	1.27 [1.13, 1.42]
El-Chami 2012	0	0.03402564	4.8%	1.00 [0.94, 1.07]
Erdil 2014	-0.2913149	0.17169962	3.7%	0.75 [0.53, 1.05]
Hakala 2002	0.82142088	0.4070008	1.8%	2.27 [1.02, 5.05]
Jideus 2000	-0.9886816	0.42801664	1.7%	0.37 [0.16, 0.86]
Kinoshita 2012	0.11218248	0.16026093	3.9%	1.12 [0.82, 1.53]
Kokkonen 2005	0.72037749	0.5560189	1.2%	2.06 [0.69, 6.11]
Mariscalco 2008	0.0454781	0.09134586	4.5%	1.05 [0.87, 1.25]
Masson 2015	0.15240557	0.16546736	3.8%	1.16 [0.84, 1.61]
Mauermann 2010	0.04177734	0.28428005	2.6%	1.04 [0.60, 1.82]
Melduni 2011	0.28076968	0.19886244	3.5%	1.32 [0.90, 1.96]
Nishi 2013	0.33181093	0.19004019	3.5%	1.39 [0.96, 2.02]
O'Neal (black race) 2013	0.62620059	0.04033024	4.8%	1.87 [1.73, 2.02]
O'Neal (white race) 2013	0	0.3501632	2.1%	1.00 [0.50, 1.99]
Parsaee 2014	0.37401915	0.44485506	1.6%	1.45 [0.61, 3.48]
Pillarisetti 2014	-0.3141704	0.18224829	3.6%	0.73 [0.51, 1.04]
Sahin 2014	-0.0279096	0.20165766	3.4%	0.97 [0.65, 1.44]
Shirzad 2010	-0.1079932	0.05593612	4.7%	0.90 [0.80, 1.00]
Tadic 2011	1.49928939	0.24915622	3.0%	4.48 [2.75, 7.30]
Takahashi 2014	0.16772277	0.47857727	1.4%	1.18 [0.46, 3.02]
Weidinger 2014	0.73467456	0.25750187	2.9%	2.08 [1.26, 3.45]
Zacharias 2005	0.09750697	0.04832724	4.8%	1.10 [1.00, 1.21]
Total (95% CI)			**100.0%**	**1.21 [1.06, 1.38]**

Heterogeneity: Tau² = 0.10; Chi² = 285.82, df = 31 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.77 (P = 0.006)

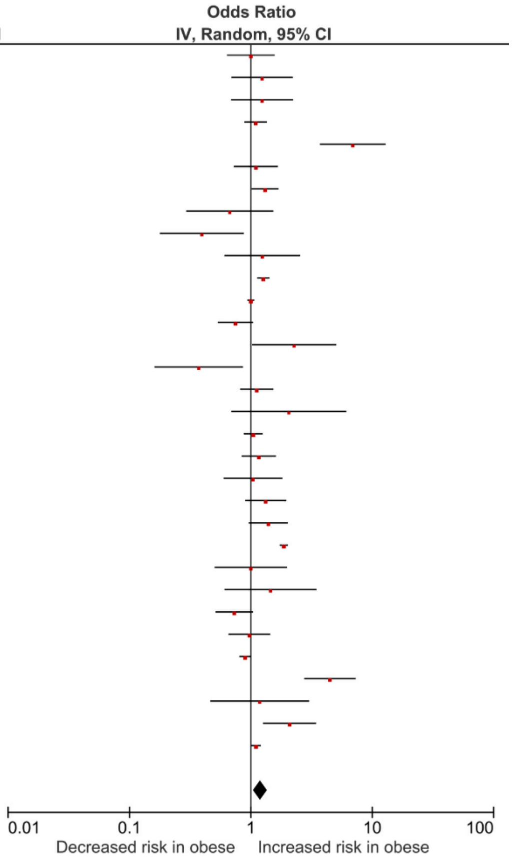


Figure 3. Forest plot of strokes in POAF versus non-POAF patients

Study or Subgroup	POAF Events	POAF Total	no-POAF Events	no-POAF Total	Weight	Odds Ratio M-H, Random, 95% CI
Auer 2005	2	9	0	154	1.7%	103.00 [4.53, 2340.87]
Banach (AR) 2007	5	69	3	81	5.7%	2.03 [0.47, 8.83]
Banach (AS) 2007	5	62	4	88	6.4%	1.84 [0.47, 7.16]
Bramer 2013	17	1122	32	3976	13.4%	1.90 [1.05, 3.43]
Chua 2015	3	103	5	247	5.8%	1.45 [0.34, 6.19]
Echahidi_b 2007	40	1329	65	3254	15.6%	1.52 [1.02, 2.27]
Kinoshita 2012	1	19	0	25	1.6%	4.14 [0.16, 107.30]
Kokkonen 2005	1	19	0	25	1.6%	4.14 [0.16, 107.30]
Mariscalco 2008	16	570	11	1262	11.3%	3.28 [1.51, 7.12]
Melduni 2011	3	135	6	216	6.1%	0.80 [0.20, 3.24]
O'Neal (black race) 2013	21	370	103	10528	14.7%	6.09 [3.76, 9.85]
O'Neal (white race) 2013	47	2537	103	10528	16.1%	1.91 [1.35, 2.71]
Total (95% CI)		**6344**		**30384**	**100.0%**	**2.38 [1.55, 3.64]**
Total events	161		332			

Heterogeneity: Tau² = 0.26; Chi² = 31.38, df = 11 (P = 0.0010); I² = 65%
Test for overall effect: Z = 3.98 (P < 0.0001)

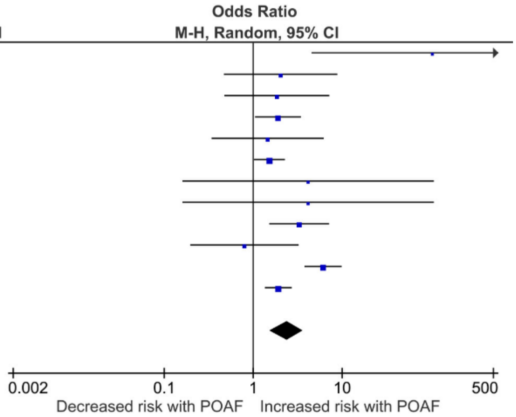


Figure 4. Forest plot of 30-day mortality in POAF versus non-POAF patients

Study or Subgroup	POAF Events	POAF Total	no-POAF Events	no-POAF Total	Weight	Odds Ratio M-H, Random, 95% CI
Erdil 2014	1	129	4	911	3.0%	1.77 [0.20, 15.97]
Mariscalco 2008	20	570	50	1252	51.2%	0.87 [0.52, 1.48]
Nishi 2013	1	314	1	284	1.9%	0.90 [0.06, 14.52]
O'Neal (black race) 2013	2	370	43	10528	7.1%	1.33 [0.32, 5.49]
O'Neal (white race) 2013	13	2537	43	10528	36.9%	1.26 [0.67, 2.34]
Total (95% CI)		**3920**		**23503**	**100.0%**	**1.05 [0.72, 1.53]**
Total events	37		141			

Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)

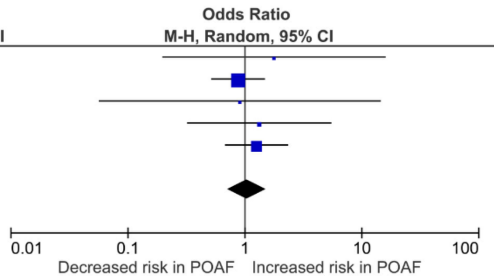


Figure 5. Forest plot of myocardial infarctions in POAF versus non-POAF patients

Study or Subgroup	POAF Events	POAF Total	no-POAF Events	no-POAF Total	Weight	Odds Ratio M-H, Random, 95% CI
Erdil 2014	1	129	4	911	3.0%	1.77 [0.20, 15.97]
Mariscalco 2008	20	570	50	1252	51.2%	0.87 [0.52, 1.48]
Nishi 2013	1	314	1	284	1.9%	0.90 [0.06, 14.52]
O'Neal (black race) 2013	2	370	43	10528	7.1%	1.33 [0.32, 5.49]
O'Neal (white race) 2013	13	2537	43	10528	36.9%	1.26 [0.67, 2.34]
Total (95% CI)		**3920**		**23503**	**100.0%**	**1.05 [0.72, 1.53]**
Total events	37		141			

Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)

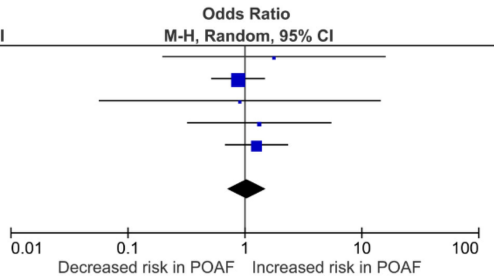
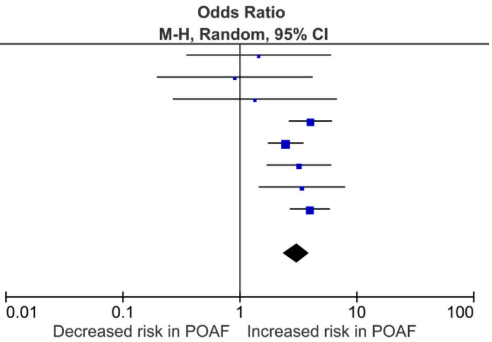


Figure 6. Forest plot of respiratory complications in POAF versus non-POAF patients

	POAF		No-POAF			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Banach (AR) 2007	4	62	4	88	3.0%	1.45 [0.35, 6.03]
Banach (AS) 2007	3	67	4	81	2.6%	0.90 [0.19, 4.18]
Ducceschi 1999	2	24	8	126	2.4%	1.34 [0.27, 6.74]
Echahidi_b 2007	53	1369	37	3717	21.7%	4.01 [2.62, 6.12]
Mariscalco 2008	69	570	67	1262	26.8%	2.46 [1.73, 3.49]
Nishi 2013	25	134	19	284	12.3%	3.20 [1.69, 6.05]
O'Neal (black race) 2013	6	370	51	10528	7.6%	3.39 [1.44, 7.94]
O'Neal (white race) 2013	48	2537	51	10528	23.5%	3.96 [2.66, 5.89]
Total (95% CI)		**5133**		**26614**	**100.0%**	**3.06 [2.37, 3.94]**
Total events	210		241			

Heterogeneity: Tau² = 0.03; Chi² = 9.25, df = 7 (P = 0.24); I² = 24%
Test for overall effect: Z = 8.64 (P < 0.00001)



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Chapter 7

Effectiveness and safety of simultaneous hybrid thoracoscopic endocardial catheter ablation of atrial fibrillation in obese and non-obese patients

Abstract

Background: We evaluated the safety and effectiveness of the hybrid thoracoscopic endocardial epicardial ablation technique for the treatment of atrial fibrillation in obese versus non-obese patients.

Methods: Between January 2010 and January 2015, a cohort of 61 patients were retrospectively identified to undergo ablation of atrial fibrillation as a stand-alone procedure using a thoracoscopic, hybrid epicardial-endocardial technique. 40% of the obese cohort had persistent or long-standing AF, compared to 54.9% of the non-obese cohort. Follow-up for all patients included 7-day Holter monitoring at 3-year follow-up.

Results: There were no deaths or conversion to cardiopulmonary bypass required. At 3-year follow-up, 60% of the obese group were in sinus rhythm with no episode of atrial fibrillation, atrial flutter or atrial tachycardia lasting 30 seconds off anti-arrhythmic drugs. This was compared to 72% in the non-obese group, with no significant difference between the groups (P=0.468). The succes rate for the overall group was 68.9% at 3-year follow-up. For success rates on anti-arrhythmic drugs, this was 80% in the obese group compared to 86% in the non-obese group at 3-year follow-up (P=0.637), and 83.6% success rate for the overall group. No patient died and no

thromboembolic/bleeding events or procedure-related complications occurred during the follow-up.

Conclusions: In a retrospective cohort with approximately half with persistent or long-standing AF, thoracoscopic hybrid epicardial endocardial ablation proved to be equally effective and safe in obese versus non-obese patients. This represents a new suitable alternative option to treat stand-alone atrial fibrillation. Current preliminary findings require further validation in future multi-institutional prospective studies.

7.1. Introduction

The prevalence of atrial fibrillation (AF) is increasing, with projected prevalence rates of 12 to 15 million individuals in the United States [1, 2]. When coupled with the obesity epidemic [1], the two diseases often occur together. The body mass index (BMI) is a commonly used parameter used to define obesity (BMI≥30), with increasing evidence demonstrating significant associations between obesity and AF [3, 4]. One systematic review suggested that obesity increased risk of AF by 49% over the general population[5], whilst another meta-analysis estimates 3.5%-5.3% excess risk of AF for every unit of BMI increase[6]. Given the proliferative rise in AF incidence in the setting of an obesity epidemic, there is a strong need to understand their associations and complex interplay of risk factors from a clinical perspective and particularly when considering medical, interventional and surgical therapies for AF.

Catheter ablation, primarily by pulmonary vein isolation (PVI), is an effective treatment for atrial fibrillation. PVI can be achieved in more than 95% of patients by the conclusion of the procedure. The advantages offered by the percutaneous catheter approach include the use of multipolar catheters and three-dimensional mapping technologies, which allows identification of the nature of the atrial substrate and allows for customizable lesion sets for ablations. Approximately three quarters of all patients achieve freedom from atrial fibrillation when treated with ablation [7-9]. Although promising, these results are suboptimal, particularly in patients with persistent and long-standing persistent AF [10, 11], which is partly due to the lack of transmurality of in some lesions as well as gaps in ablation. In some cases of persistent or long-standing AF or AF refractory to medical and catheter ablation, surgical ablation offers an alternative option. In the FAST randomized controlled study[12] as well as the meta-analysis in Chapter 3, it was demonstrated that the video-assisted surgical approach may achieve superior success rates to catheter ablation in the short term, although the patient is at risk of higher procedural complications including pneumothorax, major bleeding and pacemaker requirements.

The development of new technologies and advanced techniques has seen an increase in a multidisciplinary approach in the treatment of AF involving both cardiac surgeons and electrophysiologists [13]. In Chapter 1, the hybrid ablation approach was introduced as one example of such new approach and concept in the real of AF treatment. The hybrid approach has been introduced in an attempt to improve results in catheter ablation and surgical ablation alone. This approaches combines the advantages of both catheter and surgical ablation approaches, with a procedure that produces superior transmural lesions epicardially, whilst allowing endocardial identification of ablation targets to customize lesion sets and endocardial touch-ups to close conduction gaps. The procedure combines both thoracoscopic epicardial ablation with a percutaneous trans-septal procedure [14, 15]. The efficacy and benefits of the hybrid procedure appear promising, with reported freedom from AF rates of 78% to 100% at 6 months[16]. However, the long-term outcomes of the hybrid ablation procedure beyond 24-months has been rarely reported in the available literature.

There have been previous reports that obesity is an independent predictor of procedural failure after catheter ablation[17]. On the other hand, some studies have reported no differences in efficacy of catheter ablation in obese and non-obese patients [18, 19]. Metabolic syndrome has also been associated with higher recurrence rates after catheter ablation[20]. Given that the hybrid ablation procedure has only been recently introduced, there are currently there are no studies examining the differences in efficacy of hybrid thoracoscopic epicardial ablation and catheter ablation in patients with and without obesity.

Therefore, the objectives of this chapter are: (1) to report the long-term efficacy and complication rates of the new hybrid ablation procedure at 3-years follow-up and beyond, and (2) to determine if there are any differences in freedom from AF success rates in obese versus non-obese patients in patients undergoing the hybrid ablation procedure.

7.2. Methods

Study Population

This is a retrospective cohort study using a database for which, according to the Dutch Law WMO (Wet maatschappelijke ondersteuning), no approval of the institutional board or informed consent is needed. Documentation (in Dutch) which specifically outlines this regulation can be found here: http://www.ccmo.nl/en/non-wmo-research and http://www.ccmo.nl/attachments/files/wgbo-pdf.pdf. For our retrospective analysis, all consecutive patients from January 2010 to January 2015 undergoing PVI and posterior left atrial wall isolation with linear lesions by hybrid thoracoscopic ablation for symptomatic persistent, long-standing persistent and paroxysmal AF in the University Hospital, Maastricht, were identified and included. The population comprised 10 obese patients (BMI≥30) and 51 non-obese (BMI<30) patients.

In our centre, the indications to hybrid thoracoscopic ablation are given to patients with persistent, long-standing persistent or paroxysmal AF and severe atrial dilation. Definitions of persistent, long-standing persistent and paroxysmal AF, success and failure, and complications were based on the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF [21]. Exclusion criteria included presence of intracavitary thrombus, uncontrolled heart failure, presence of severe coronary artery disease, and moderate or severe valvular disease.

Pre-procedural management

The left ventricular ejection fraction, intracavitary dimensions, and presence of structural and valvular disease were assessed by transthoracic echocardiography (TTE) no more than 1 week prior to the procedure. Transoesophageal echocardiography (TOE) was performed on the day of the procedure to exclude the presence of thrombi. Pulmonary vein anatomy was evaluated the day before ablation by cardiac computed tomography (CT). Oral anti-coagulation therapy (OAC) was interrupted 2 days prior and replaced by low-molecular-weight heparin (LMWH) therapy. For patients taking novel anticoagulant agents, medication was stopped as follows: (i) the last dose of rivaroxaban was given in the morning 1 day prior to ablation and (ii) the last dose of dabigatran or apixaban was given in the evening 1 day prior to ablation. All patients provided written informed consent for the ablation procedures. The study was approved by the local ethics committee of our institution.

Hybrid procedure: Thoracoscopic epicardial ablation

The procedure was performed in the cardiac electrophysiology laboratory as previously described[22]. All procedures were performed by the same cardiac surgeon (Mark La Meir, University Hospital, Maastricht, The Netherlands). Briefly, general anaesthesia was used with a double-lumen endobroncheal tube placement for selective lung ventilation. In all patients, bilateral thoracoscopic access with 5 mm ports was used. Antral isolation of both pairs of pulmonary veins was performed with 4-6 applications using a bipolar RF clamp (AtriCure, Inc., West Chester, OH, USA). Then, a roof line (connecting both superior pulmonary veins) and an inferior line (connecting both inferior pulmonary veins) were performed epicardially using a bipolar RF pen or a linear pen device (Isolator Pen and Coolrail, AtriCure, Inc.) achieving the ‘box’ lesion for the posterior wall isolation. Furthermore, if the right atrium was dilated, two additional ablation lines were created: one encircling the superior vena cava (SVC) using the clamp and the other connecting both caval veins using the pen (bicaval line). Left atrial appendage (LAA) clipping was performed in 21 patients (33.9%; AtriClip, Atricure, Inc.).

Hybrid procedure: Percutaneous electrophysiological examination and ablation

Via the femoral approach, a decapolar coronary sinus catheter (Biosense Webster, Inc., Diamond Bar, CA, USA) was placed under fluoroscopy, and a doube transeptal puncture was performed using a long 8-Fr sheath (SL0, St Jude Medical) under both the TOE and fluoroscopy guidance. Directly after the first transseptal puncture, patients underwent heparinization (1000 U heparin per 10 kg body weight with subsequent additional applications) with targeted activated clotting time >300 s. A detailed electroanatomic map of the left atrium (LA) was created with a non-fluoroscopic navigation system (CARTO system; Biosense Webster, Inc.) using the circular mapping catheter (Lasso, Biosense Webster, Inc.) and the open-irrigated 3.5-mm tip RF ablation catheter (NaviStar ThermoCool; Biosense Webster, Inc.). Initially, pulmonary vein entry and exit block were confirmed along with the verification of posterior wall isolation. The entry block of the pulmonary veins and the posterior box was defined as the absence of atrial bipolar signals and was evaluated with a circular mapping catheter. Exit block was defined as local capture in the pulmonary vein or posterior wall during pacing (output 10 mA and pulse width 2 ms) without conduction to the LA. If the block was not present, additional endocardial RF ablation was performed to close the conduction gaps. A power-controlled mode with a power limit of 35 W and a maximum temperature of 48 °C was used until the block was not achieved. If the patient was known to have typical flutter or if this arrhythmia occurred during the procedure, the cavotricuspid isthmus (CTI) was ablated endocardially, and a mitral line was achieved if the patient developed mitral isthmus-dependent flutter during the procedure. Furthermore, if AF persisted, left and right continuous fractionated atrial electrogram (CFAE) mapping ablation was performed. The target sites were defined as the fastest local repetitive electrical activity, multiple component fragmented signal, or activation delay between the distal and proximal bipolar electrodes covering the majority of the cycle length. The endpoint for ablation was regularization or disappearance of the local signal, conversion to sinus rhythm (SR) or to stable atrial flutter. In patients who did not convert to SR during the ablation, electrical cardioversion was performed. All ablation lines were revisited in SR to confirm bidirectional conduction block using the standard criteria.

Post-procedural management

After the procedure, patients underwent continuous telemetric monitoring until discharge from the hospital. Before discharge, TTE was performed in all patients in order to exclude post-procedural pericardial effusion. LMWH was started the same evening following the ablation, and on the third postoperative day OAC was reinitiated. Patients restarted their preoperative antiarrhythmic drug (AAD) regimes as soon as possible. Oral anticoagulation and AADs were continued for at least 3 months.

Follow-up

Clinical follow-up consisted of physical examinations, electrocardiogram and 24-h Holter recording performed every 6 months. Any symptoms following ablation were deemed as deserving Holter monitoring. A blanking period of 3 months was considered for the study. All documented episodes of atrial tachycardia lasting ≥30 s were considered as a recurrence.

Statistical Analysis

Normal values were expressed as mean ±1 standard deviation (SD), non-normal values as median and IQR, and categorical variables as percentages. The Mantel-Haenszel Chi Square was employed to establish differences among groupings. Univariate analyses of relevant risk factors for success rates on AAD or off AAD were conducted by Chi-square or Fisher's exact tests of categorical data and Student's t tests of continuous data to compare the differences between patients with freedom from AF on AAD or off AAD. Statistical analysis was performed using SPSS release 12.0 (SPSS, Chicago, IL, USA). P values less than 0.05 were considered significant.

7.3. Results

Study population

Sixty-two patients (45 males, 60±9 years) were considered for the present retrospective analysis. Ten patients were obese (BMI≥30) and fifty-one were not obese (Table 1). The indication for the hybrid procedure was persistent AF in 25 non-obese patients and 4 obese patients (47%), long-standing persistent AF in 3 non-obese patients and no obese patients (5%) and paroxysmal AF in 24 non-obese patients and 6 obese patients (48%). There was no difference between obese versus non-obese cohorts in terms of the proportion of paroxysmal AF (60% vs 45.1%, P=0.496), persistent AF (40% vs

49%, P=0.735) or permanent AF (0% vs 5.9%, P=1.00). All patients had failed ≥1 Class I or III AADs.

The average age of the obese and non-obese groups (58.2 vs 59.7 years, P=0.672) were found to be similar. In terms of baseline medical comorbidities, no significant differences between the obese versus non-obese groups was found in terms of hypertension, peripheral vascular disease, carotid artery disease, coronary artery disease, renal disease, lung disease, bleeding, prior TIA or strokes, or cardiac failure. The obese group had a significantly higher proportion of patients with diabetes compared to the non-obese group (20% vs 0%, P=0.025). With regards to the use of anti-arrhythmic medications and other medications, there was no significant difference found between the obese versus non-obese cohorts (Table 2).

In terms of baseline ECG and echocardiographic parameters (Table 3), the mean left atrial diameter was 45±4 mm in obese patients versus 44±5 mm in non-obese patients (P=0.497). The mean left atrial volume was 91±18 cm^3 in obese patients versus 93±25 cm^3 in non-obese patients (P=0.812). The mean left ventricular ejection fraction was 58+8% in obese patients versus 59±7% in non-obese patients (P=0.768). The mean EHRA score of AF-related symptoms was 2.1±0.9 in obese patients versus 2.3±0.7 in non-obese patients (P=0.522). Overall, the mean duration of having AF was 5.2±4.6 years for the population studied. 21 (33.9%) patients had a prior ablation procedure for AF prior to the present hybrid ablation.

Hybrid procedure

Operative details are outlined in Table 4. There was no significant differences between the groups in terms of the ablation devices used (CryoCath catheter, AtriCure bipolar clamp, AtriCure cool rail, and AtriCure isolator pen). In terms of the ablation lines used, there was also no significant differences between the obese versus non-obese cohorts including roof lines, inferior lines, left isthmus, intercaval line, IVC, SVC, and right isthmus lines. Endocardial touch-up following the primary hybrid procedure was required in 70% of the obese group and 49% of the non-obese group, but this difference was not found to be significantly different (P=0.307).

Outcomes

At 3-year follow-up, there was no significant difference found between success on AAD between the obese versus non-obese groups (80% vs 86%, P=0.637)(Table 5). Furthermore, success off AAD were also found to be comparable between obese versus non-obese patients (60% vs 72%, P=0.468). There were no major adverse complications in either cohort of patients. With regards to the use of AAD at 3-year follow-up, the obese group had 2 patients on flecainide and 2 patients on sotolol. The non-obese group had 2 patients on amiodarone, 6 patients on flecanide and 2 patients on sotalol. With regards to cardiovascular medications at 3-year follow-up, the only significant difference found was for diuretics, which was significantly higher in the obese group versus non-obese group (30% vs 3.9%, P=0.029). Univariate analysis demonstrated that none of age, BMI, MAP, atrial flutter nor

AF type were significantly associated with success rates on AAD (Table 6) or off AAD (Table 7).

7.4. Discussion

Our results suggest that hybrid thoracoscopic epicardial and catheter-based endocardial ablation is equally efficacious in patients with and without obesity. Although the sample size was small, we found freedom from recurrence of AF at X months of 60% in obese and 72% in non-obese patients. Given the mixed reports on the benefits of ablation in obese patients [17-19], our results suggest that the hybrid procedure may be a viable option in obese and non-obese patients.

Obesity has been associated with known risk factors for atrial fibrillation, including inflammation, autonomic dysfunction, atrial enlargements and diastolic dysfunction [23]. Obesity and AF have been increasing in epidemic proportions in the US, with over 10 million patients in the US affected by AF by 2050, of which 60% will be due to obesity[2]. This highlights the importance of understanding how obesity can impact the outcomes of the interventional and surgical treatments for AF patients, particularly in the context of rapidly evolving techniques such as hybrid epicardial and catheter ablation.

There are numerous proposed mechanisms by which obesity is associated with AF. Obesity is known to cause structural and electrical atrial remodelling, and is associated with increasing atrial volume, fibrosis and lipidosis[24]. Weight gain can also induce structural and histological changes in cardiomyocytes, which may predispose patients to chaotic rhythms such as AF[24, 25]. Furthermore, obesity may also be associated with pericardial fat, causing increased inflammation and local atrial infiltration, leading to increased risk of AF[23]. Obesity has been found to induce impaired diastolic function, leading to atrial stretch, which can lead to greater signal complexity at the pulmonary vein-atrial junction[26]. Additionally, obesity leads to increased risk of hypertension, structural heart disease, diabetes mellitus and obstructive sleep apnoea that in turn beget atrial fibrillation[18]. Furthermore, weight fluctuations has been shown to be associated with AF recurrence [27], whilst weight increases has been associated with AF progression [28]. The converse has also been shown in landmark studies demonstrating that weight loss is associated with lower recurrence of AF and increased AF-free survival following ablation[27, 29]. It is not unreasonable to expect similar outcomes for patients undergoing thoracoscopic surgical ablation and hybrid ablation for AF, however, there is limited evidence available for these procedures to address these specific questions.

Thoracoscopic surgical ablation is an effective method of ablation which incorporates many of the lesions in the Cox IV maze surgical procedure. There have been reports of 70% to 87% success rates in patients with paroxysmal AF[30-32] and a lower rate of 39% to 62% for persistent AF at 6 months[30]. The primary rationale behind the hybrid procedure incorporating catheter ablation is the ability to identify gaps and offer additional ablation of these gaps, which can be achieved via the endocardial approach with multipolar catheters and three-dimensional mapping technologies. In this way, the surgeon uses a video-assisted thoracoscopic approach to isolate the pulmonary veins and the posterior wall of the left atrium epicardially whereas the electrophysiologist can evaluate the endpoints of the ablation and offer additional endocardial ablation as needed. Furthermore there may be some lesions that are difficult to access from an epicardial surface. Finally, combining an endocardial with an epicardial approach can help ensure transmurality of lesions, particularly in areas of scarred or thick heart tissue. Ablation in patients who have persistent or long-standing persistent AF is less effective and has poorer outcomes[33]. Outcomes for catheter ablation for persistent and especially long standing persistent AF have been poor, as PVI alone has had success rates as low as 21%[10, 11]. The outcomes of the hybrid procedure in a study of only patients with long standing persistent AF, showed that 84% of patients were free of AF at 1-year whilst off anti-arrhythmic drugs[34]. Our obese population did not have a significantly different proportion of patients with persistent AF compared to the non-obese patients (40% and 49%). Obese patients face greater risks of complications from ablation procedures due to their comorbidities. During catheter ablation, hemodynamic intolerance to general anaesthesia, increased risk of stroke and difficulty with endotracheal intubation are all concerns. Additionally, procedure times are usually longer and radiation exposure greater in obese patients[18]. Endocardial ablation is more likely to fail in patients with structural heart disease, a group significantly more likely to be obese[35]. A previous study has suggested that a hybrid ablation procedure may be superior to repeat endocardial ablation[15].

A large prospective study comparing 485 patients with metabolic syndrome and 1,011 control patients undergoing catheter ablation showed that metabolic syndrome patients had higher rates of arrhythmia recurrence in the non-paroxysmal subgroup. However the metabolic syndrome patients had improved physical quality of life, which was not seen in the non-metabolic syndrome group[36]. Reports from the AFFIRM trial on 2492 patients, identified better outcomes, including 3-year mortality rates in obese patients compared to non-obese patients after ablation. This offers an encouraging prospect for obese patients with AF as our data suggests they may be possible candidates for the newer hybrid procedure. As such, the present study demonstrates that obese patients should not be discouraged from undergoing the hybrid endocardial and epicardial ablation for AF if this procedure is indicated.

Limitations

The present study was constrained by several limitations. Firstly, there was a small sample size of 61 patients which may have underpowered the study. Despite this, the present study is significant because very few centers worldwide have the capabilities and facilities at the moment to perform this newly introduced hybrid ablation procedure. As such, the present study represents the early evidence available specifically for this technique. Future studies should compare larger multi-institutional cohorts of obese and non-obese patients using the hybrid procedure. Secondly, the present study only focused on patients undergoing hybrid ablation procedure with a retrospective study design, which may be susceptible to selection bias. Currently, a randomized controlled trial is underway to compare outcomes of hybrid versus catheter ablation for persistent AF (HARTCAP-AF). This may provide higher quality evidence to address the role of hybrid ablation in treatment of AF in obese and non-obese patients. A strength of the current study is the moderate and consistent follow-up results for the 61 patients at 3-years, demonstrating favourable success rates compared to published outcomes in the literature. The longer term outcomes of hybrid ablative procedures are yet to be evaluated.

Conclusions

Our study offers the first insight into the longer-term efficacy of the hybrid thoracoscopic epicardial and catheter based endocardial ablation for AF. The initial outcomes suggest that this novel technique may be efficacious in obese patients, however, the present results require validation with further studies of larger sample sizes with longer follow-up.

7.5. Tables

Table 1. Baseline characteristics (n=61)

Baseline Characteristic	Mean (SD) or N (%)			
	Total	Obese (BMI≥30) n=10	Not obese (BMI<30) n=51	P-value
Age, yr	59.6 (9.18)	58.2 (10.2)	59.7 (9.1)	0.672
Gender (male/female)	45/17 (72.6/27.4)	9/1 (90/10)	36/15 (71/29)	0.267
BMI	26.9 (3.23)	31.6 (1.53)	26.0 (2.62)	-
Hypertension	26 (41.94)	6 (60.0)	19 (37.3)	0.292
Diabetes	2 (3.23)	2 (20.0)	0 (0.0)	0.025
Peripheral vascular disease	1 (1.61)	0 (0.0)	1 (2.0)	1.000
Carotid disease	0 (0)	0 (0.0)	0 (0.0)	-
Myocardial infarction	2 (3.23)	0 (0.0)	2 (3.9)	1.000
Coronary disease	9 (14.52)	2 (20.0)	7 (13.7)	0.633
Renal disease	0 (0)	0 (0.0)	0 (0.0)	-
Chronic lung disease	6 (9.68)	1 (10.0)	5 (9.8)	1.000
Minor bleeding	1 (1.61)	1 (10.0)	0 (0.0)	0.164
Major bleeding	0 (0)	0 (0.0)	0 (0.0)	-
Cancer	7 (11.29)	1 (10.0)	6 (11.8)	1.000
Prior TIA	2 (3.23)	0 (0.0)	2 (3.9)	1.000
Prior Stroke	2 (3.23)	0 (0.0)	2 (3.9)	1.000
Congestive cardiac failure	3 (4.84)	1 (10.0)	2 (3.9)	0.421
Atrial flutter	23 (37.1)	5 (50.0)	18 (35.3)	0.481
Paroxysmal AF	30 (48.39)	6 (60.0)	23 (45.1)	0.496
Persistent AF	29 (46.77)	4 (40.0)	25 (49.0)	0.735
Permanent AF	3 (4.84)	0 (0.0)	3 (5.9)	1.000
EHRA score	2.23 (0.78)	2.10 (0.88)	2.29 (0.70)	0.522

N, number of patients; BMI, body mass index; TIA, transient ischemic stroke; AF, atrial fibrillation; SD, standard deviation

Table 2. Baseline antiarrhythmic medications and other cardiovascular medications

Baseline Characteristic	Mean (SD) or N (%)			
	Total	Obese (BMI≥30) n=10	Not obese (BMI<30) n=51	P-value
Antiarrythmic medications:				
None	10 (16.13)	1 (10.0)	9 (17.6)	1.000
Amiodarone	11 (17.74)	0 (0.0)	11 (21.6)	0.184
Disopyramide	4 (6.45)	0 (0.0)	3 (5.9)	1.000
Flecainide	21 (33.87)	6 (60.0)	15 (29.4)	0.079
Dronedarone	0 (0)	0 (0.0)	0 (0.0)	-
Procainamide	0 (0)	0 (0.0)	0 (0.0)	-
Propafenone	1 (1.61)	0 (0.0)	1 (2.0)	1.000
Quinidine	2 (3.23)	1 (10.0)	1 (2.0)	0.303
Sotalol	15 (24.19)	2 (20.0)	13 (25.5)	1.000
Other cardiovascular medications:				
None	2 (3.23)	0 (0.0)	1 (2.0)	1.000
Beta blocker	24 (38.71)	4 (40.0)	20 (39.2)	1.000
ACE inhibitor	14 (22.58)	2 (20.0)	11 (21.6)	1.000
ARB	18 (29.03)	4 (40.0)	14 (27.5)	0.663
Digoxin	10 (16.13)	2 (20.0)	8 (15.7)	1.000
Diltiazem/Verapamil	12 (19.35)	2 (20.0)	10 (19.6)	0.081
Other CCB	5 (8.06)	1 (10.0)	4 (7.8)	1.000
Nitroglycerin	0 (0)	0 (0.0)	0 (0.0)	-
Insulin	0 (0)	0 (0.0)	0 (0.0)	-
Aldosteron Receptor Blocker	0 (0)	0 (0.0)	0 (0.0)	-
Diuretics	11 (17.74)	3 (30.0)	8 (15.7)	0.367
Nitrates	0 (0)	0 (0.0)	0 (0.0)	-
Hydralazine	1 (1.61)	1 (10.0)	0 (0.0)	0.164
Statins	15 (24.19)	3 (30.0)	12 (23.5)	0.696
ASA	4 (6.45)	1 (10.0)	3 (5.9)	0.521
Plavix/Plasugrel	4 (6.45)	0 (0.0)	3 (5.9)	1.000
VKA	52 (86.67)	9 (90.0)	43 (84.3)	1.000
Other	1 (1.61)	0 (0.0)	1 (2.0)	1.000

ACE, angiotensin converting enzyme; ARB, aldosterone receptor blocker; CCB, calcium channel blocker; VKA, vitamin K antagonist; SD, standard deviation; BMI, body mass index

Table 3. Baseline electrocardiographic (ECG) and echocardiographic parameters

Baseline ECG and Echo parameters	Mean (SD) or N (%)			
	Total	**Obese (BMI≥30)**	**Not obese (BMI<30)**	**P value**
BPM	68.05 (17.59)	69.78 (18.96)	67.72 (17.51)	0.769
Aorta Diameter (mm)	34.96 (3.91)	37.00 (4.36)	34.53 (3.72)	0.144
LA size (mm)	44.04 (5.12)	45.00 (4.36)	43.85 (5.27)	0.497
LA volume (cc)	92.03 (24.49)	91.22 (18.42)	92.92 (25.35)	0.812
RA volume (cc)	67.94 (22.76)	69.11 (15.62)	67.70 (24.10)	0.827
LV EDD (mm)	49.68 (4.61)	52.00 (3.00)	49.23 (4.76)	0.036
LV ESD (mm)	33.77 (3.92)	36.00 (4.18)	33.34 (3.77)	0.105
IVSEDWD (mm)	9.07 (1.67)	9.33 (0.87)	9.02 (1.79)	0.430
PWEDWD (mm)	8.75 (1.16)	8.89 (0.78)	8.72 (1.22)	0.596
LV EF	58.53 (7.77)	57.78 (8.24)	58.67 (7.77)	0.768
LV Mass (g)	173.15 (39.16)	193.22 (29.97)	168.51 (39.88)	0.054
LV Mass Index (g/m2)	85.81 (16.32)	89.67 (15.91)	84.89 (16.49)	0.437
Tricuspid flow (m/sec)	2.27 (0.56)	2.00 (1.13)	2.31 (0.45)	0.577
Vena cava diameter (mm)	18.38 (4.43)	16.44 (3.97)	18.79 (4.46)	0.138
Vena cava collapse index	73.06 (11.31)	78.50 (5.55)	72.02 (11.87)	0.025
E/A ratio	1.41 (0.56)	1.27 (0.34)	1.45 (0.60)	0.313
Normal sinus rhythm	39 (62.9)	8 (80.0)	31 (63.3)	0.469
Atrial fibrillation	16 (25.8)	2 (20.0)	14 (28.6)	0.713
Atrial flutter	3 (4.8)	0 (0.0)	3 (6.1)	1.000
Paced	1 (1.6)	0 (0.0)	1 (2.0)	1.000
Left ventricular hypertrophy	21 (33.9)	5 (50.0)	16 (32.7)	0.306
Mitral regurgitation	24 (38.7)	3 (30.0)	21 (41.2)	0.726
Mitral stenosis	0 (0.0)	0 (0.0)	0 (0.0)	-
Aortic regurgitation	4 (6.5)	1 (10.0)	3 (5.9)	0.521
Aortic stenosis	1.0 (1.6)	1 (10.0)	0 (0.0)	0.164
PR interval (msec)	179.66 (32.4)	169.20 (35.57)	181.16 (32.70)	0.511
QRS duration (msec)	96.89 (15.41)	94.40 (13.88)	97.12 (15.82)	0.589
QT interval (msec)	429.58 (39.89)	418.50 (46.81)	430.98 (38.59)	0.444
P axis degrees	52.19 (23.76)	39.00 (21.31)	55.55 (22.97)	0.166
R axis degrees	35.9 (23.97)	37.70 (28.66)	35.73 (23.47)	0.841
T axis degrees	34 (35.61)	40.50 (75.69)	33.14 (21.94)	0.767

ECG, electrocardiogram; BPM, beats per minute; LA, left atrial; RA, right atrial; EDD, echo end-diastolic diameter; ESD, echo end-systolic diameter; IVSEDWD, interventricular end diastolic width; PWEDWD, posterior wall end diastolic width; LV, left ventricular; EF, ejection fraction; SD, standard deviation; BMI, body mass index

Table 4. Ablation devices and ablation lines used for hybrid ablation of obese and non-obese patients

Operative details	N (%)			
	Total	**Obese (BMI≥30)**	**Not obese (BMI<30)**	**P value**
Ablation devices:				
CryoCath catheter	8 (12.9)	1 (10.0)	7 (13.7)	1.000
AtriCure bipolar clamp	60 (96.77)	10 (100.0)	50 (98.0)	1.000
AtriCure cool rail	52 (83.87)	7 (70.0)	44 (86.3)	0.345
AtriCure isolater pen	33 (53.23)	4 (40.0)	29 (56.9)	0.490
Ablation lines:				
RSPV	60 (96.77)	10 (100.0)	50 (98.0)	1.000
RIPV	58 (93.55)	10 (100.0)	48 (94.1)	1.000
LSPV	56 (90.32)	10 (100.0)	46 (90.2)	0.580
LIPV	56 (90.32)	10 (100.0)	46 (90.2)	0.580
Roof line	53 (85.48)	7 (70.0)	45 (88.2)	0.157
Inferior line	49 (79.03)	7 (70.0)	41 (80.4)	0.432
Left Isthmus	6 (9.68)	2 (20.0)	4 (7.8)	0.253
Intercaval line	20 (32.26)	2 (20.0)	18 (35.3)	0.474
IVC	4 (6.45)	0 (0.0)	4 (7.8)	1.000
SVC	21 (33.87)	3 (30.0)	18 (35.3)	1.000
Right Isthmus	12 (19.35)	4 (40.0)	8 (15.7)	0.096
Right superior GP	10 (16.13)	1 (10.0)	9 (17.6)	1.000
Right inferior GP	11 (17.74)	1 (10.0)	10 (19.6)	0.673
Left GP	8 (12.9)	1 (10.0)	7 (13.7)	1.000
Endocardial touch up	33 (53.23)	7 (70.0)	25 (49.0)	0.307

N, number of patients; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; IVC, inferior vena cava; SVC, superior vena cava; GP, ganglionated plexus; BMI, body mass index

Table 5. Outcomes of hybrid ablation in obese versus non-obese patients

Outcomes	N (%)			
	Total	Obese (BMI≥30)	Not obese (BMI<30)	P value
Success on AAD	51 (83.6)	8 (80.0)	43 (86.0)	0.637
Success off AAD	42 (68.9)	6 (60.0)	36 (72.0)	0.468
Major adverse events*	0 (0.0)	0 (0.0)	0 (0.0)	-
AAD at 3 year follow up:				
None	49 (79.0)	7 (70.0)	41 (80.4)	0.403
Amiodarone	2 (3.23)	0 (0.0)	2 (3.9)	1.000
Disopyramide	0 (0.0)	0 (0.0)	0 (0.0)	-
Flecainide	8 (12.9)	2 (20.0)	6 (11.8)	0.610
Dronedarone	0 (0.0)	0 (0.0)	0 (0.0)	-
Procainamide	0 (0.0)	0 (0.0)	0 (0.0)	-
Propafenone	0 (0.0)	0 (0.0)	0 (0.0)	-
Quinidine	0 (0.0)	0 (0.0)	0 (0.0)	-
Sotalol	4 (6.45)	2 (20.0)	2 (3.9)	0.126
Other CVS medications at 3 year follow up:				
None	10 (16.1)	4 (40.0)	6 (11.8)	0.052
Beta blocker	17 (27.4)	3 (30.0)	13 (25.5)	1.000
ACE inhibitor	19 (30.7)	3 (30.0)	15 (29.4)	1.000
ARB	11 (17.7)	3 (30.0)	8 (15.7)	0.371
Digoxin	0 (0.0)	0 (0.0)	0 (0.0)	-
Diltiazem/Verapamil	6 (9.7)	0 (0.0)	6 (11.8)	0.577
Other CCB	3 (4.8)	1 (10.0)	2 (3.9)	0.427
Nitroglycerin	0 (0.0)	0 (0.0)	0 (0.0)	-
Insulin	0 (0.0)	0 (0.0)	0 (0.0)	-
Aldosterone Receptor Blocker	0 (0.0)	0 (0.0)	0 (0.0)	-
Diuretics	5 (8.1)	3 (30.0)	2 (3.9)	0.029
Nitrates	1 (1.6)	1 (10.0)	0 (0.0)	0.167
Hydralazine	0 (0.0)	0 (0.0)	0 (0.0)	-
Statins	17 (27.4)	5 (50.0)	12 (23.5)	0.128
ASA	18 (29.0)	1 (10.0)	17 (33.3)	0.256
Plavix/Plasugrel	2 (3.2)	1 (10.0)	1 (2.0)	0.308
VKA	20 (32.3)	4 (40.0)	15 (29.4)	0.711
Other	3 (4.8)	0 (0.0)	3 (5.9)	1.000
Interventions in 3 years of follow up:				
PCI	0 (0)	0 (0.0)	0 (0.0)	-
CABG	0 (0)	0 (0.0)	0 (0.0)	-
Emergency admission	3 (4.9)	1 (10.0)	2 (3.9)	0.427
Hospital admission (overnight stay)	1 (1.6)	0 (0.0)	1 (2.0)	1.000

Mitral Valve Surgery	0 (0)	0 (0.0)	0 (0.0)	-
Aortic Valve Surgery	0 (0)	0 (0.0)	0 (0.0)	-
Pacemaker	1 (1.6)	0 (0.0)	1 (2.0)	1.000
ICD	0 (0)	0 (0.0)	0 (0.0)	-
MAZE operation	1 (1.6)	0 (0.0)	1 (2.0)	1.000
Cardiac Ablations: AF ablation	2 (3.3)	0 (0.0)	2 (3.9)	1.000
Cardiac Ablations: AFL ablation	2 (3.3)	0 (0.0)	1 (2.0)	1.000
Cardiac Ablations: Other	2 (3.3)	0 (0.0)	2 (3.9)	1.000
Cardioversions: Electrical	4 (6.6)	1 (10.0)	3 (5.9)	0.528
Cardioversions:Pharmacological	2 (3.3)	0 (0.0)	1 (2.0)	1.000

*Includes death, myocardial infarction, ischemic stroke, peripheral embolism, haemorrhagic stroke, heart failure, asystole>3seconds, unstable angina, TIA, pulmonary embolism, other major bleeding, syncope

Table 6. Univariate analysis of success rates on antiarrhythmic drugs (AAD)

Covariates for success rates on AAD	**P-value**
Logistic regression:	
Age	0.611
BMI	0.677
MAP	0.462
Atrial flutter	0.648
Paroxysmal AF	0.711

AAD, antiarrhythmic drugs; BMI, body mass index; MAP, mean arterial pressure; AF, atrial fibrillation

Table 7. Univariate analysis of success rates off antiarrhythmic drugs (AAD)

Covariates for success rates off AAD	**P-value**
Logistic regression:	
Age	0.363
BMI	0.412
MAP	0.315
Atrial flutter	0.405
Paroxysmal AF	1.000

AAD, antiarrhythmic drugs; BMI, body mass index; MAP, mean arterial pressure; AF, atrial fibrillation

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Chapter 8

Overall Discussion

The field of ablation for atrial fibrillation (AF) has expanded significantly in recent years. Prior to the 21st century, invasive treatments for AF were limited and included the left atrial isolation procedure(1), corridor procedure(2), atrial transection procedure and the Maze procedure(3, 4). In contrast to the other techniques which aimed to isolate AF, the Maze procedure aimed to ablate AF. Only the Maze procedure proved to be successful over time, and led to the first effective surgical approach for the treatment of AF (5-7).

What was the rationale and origin of the Maze approach for AF? Early studies based on animal studies, computer modelling and three-dimensional computerized mapping had demonstrated that induced AF was characterized by two or more large macro-reentrant circuits in atria (8-11). Thus, this resulted in efforts to study different lesion sets that would disrupt the chaotic macro-reentrant circuits of AF but not affect the sinus node impulses required for atria and ventricular activation. This goal, in combination with the understanding that atrial lesions when placed close enough can prevent formation of large macro-reentrant circuits(3), culminated in the Maze procedure – involving “cut-and-sew” of the cardiac tissue in a Maze pattern. This was successful in terminating the macro-reentrant circuits whilst maintain normal cardiac function. Results for the original cut-and-sew Maze procedure was positive, with claims of greater than 90% success rates at an average follow-up of 5 years(7, 12). Whilst this is a likely overestimation of success given the current guidelines and definitions for AF recurrence, the results still attest to the long-term efficacy of this procedure. Despite this, uptake of the Cox-Maze III procedure in the cardiothoracic and cardiology communities was slow and cautious, given the technique difficulty and complexity of this procedure(13). It has only been in recent years that this procedure has been simplified with a lesser lesion set in the Cox-Maze IV procedure and the use of alternative energy sources such as radiofrequency or cryoenergy to create ablation lesions, although results have not been as compelling compared to the original cut-and-sew techniques(14, 15). However, such new developments although easing the technical difficult of the procedure, brought in an array of heterogeneous techniques based on little or no experimental or clinical evidence at the time. This included left atrial lesions, right atrial lesions, pulmonary vein isolation alone, or a combination of different lesions(16, 17).

In 1988, Haissaguerre published a landmark study which demonstrated that AF can be induced by focal triggers in the atria(18). He noted that 90% of these triggers were found in and around the pulmonary vein orifices, whilst the other 10% were located elsewhere such as the right atria, crista terminalis, and left atrial appendage. This study lead to the notion of pulmonary vein isolation in an attempt to curb AF by eliminating the focal triggers in or around the pulmonary veins(19-21). This became the cornerstone of future efforts by cardiologists and cardiac surgeons for AF treatment, with a multitude of catheter-based approaches and energy sources used to target these structures specifically(22, 23). This understanding has led to effective catheter ablation treatment for paroxysmal AF in millions of patients worldwide. However, it is still controversial whether this understanding can be so readily applied to patients with persistent or long-standing AF. There are two main schools of thought where: (1) persistent or long-standing AF is attributed to well-established macro-reentrant circuits that are not driven or perpetuated by such focal triggers(24), or (2) persistent or long-standing AF is primarily driven by focal triggers that thus successful ablation of these focal sites can treat AF(19, 25-28). Certainly, the advantages of the percutaneous endocardial approach the minimally invasiveness, no cardiopulmonary bypass required, as well as the benefit of real-time visualization and mapping of ablated tissue. However, the outcomes have not been durable with a recent systematic review suggesting that long-term outcomes of catheter ablation in non-paroxysmal AF beyond 3-years is 41.8% for a single procedure, and 79.8% for multiple procedures(29).

Despite our incomplete understanding of the pathophysiology of AF, it is generally agreed that current treatment modalities achieve variable results in persistent long-standing AF and for cases refractory to medical therapy(30). This is part due to the heterogeneity of techniques used for ablation of AF. The present thesis attempts to address some of these questions in the surgical field for AF by extensive analysis of the published literature.

Concomitant AF ablation and cardiac surgery

For patients with AF undergoing cardiac surgery for some other pathology, this provides an opportunity for the surgeon to treat both conditions simultaneously. However, current data suggests that only 1 in 4 cases does the surgeon take the opportunity to treat concomitant AF(31). An independent survey conducted in 2010 to elucidate why such opportunities were ignored and suggested that in the majority of cases, surgeons were concerned regarding the added morbidity and mortality risk of an add-on pulmonary vein isolation or Maze procedure(22).

In order to directly address this question, we performed a systematic review and cumulative meta-analysis of all randomized controlled trials available where cardiac surgery was performed with and without concomitant AF ablation (Chapter 2). From sixteen randomized studies included in the analysis, we were able to show no significant differences between ablation versus no ablation groups in terms of follow-up mortality, pacemaker implantations, and neurological events. Cumulative meta-analysis demonstrated that these trends have remained stable over time and future randomized studies are unlikely to yield different results. As such, pooled Level I evidence from the literature demonstrates that added on ablation during concomitant cardiac surgery does not add additional morbidity or mortality risk, but maintaining sinus rhythm at follow-up. Our results clearly demonstrate the advantages of performing surgical ablation when such opportunity arises in patients who are otherwise undergoing a different cardiac surgical procedure.

Thoracoscopic surgical versus catheter approaches for AF

Surgical ablation performed for stand-alone AF using open median sternotomy is not commonly performed, due to the invasiveness of this procedure and associated complications. In the last decade, a less invasive video-assisted thoracoscopic procedure has been developed based on epicardial ablation on the beating heart(32-34), with the goal of reducing approach-related complications whilst maintaining the effectiveness or transmurality of lesion procedure. Currently, the minimally invasive thoracoscopic approach for AF ablation in multiple settings. A recent survey of members of the European Heart Rhythm Association demonstrate that the main indications include: failed catheter ablation (30%), longstanding persistent AF (24%), the wish to exclude the left atrial appendage (15%), patient preference (16%), and shorter waiting list (12%)(23).

In Chapter 3, we performed a systematic review and meta-analysis to compare the outcomes of minimally invasive thoracoscopic ablation versus catheter ablation, including three randomized single-center studies and five retrospective observational studies. We found that at 12-month follow-up, there was a significantly higher freedom from arrhythmias rate in the surgical ablation group compared with catheter ablation (78% vs 53%), and this different was maintained for both paroxysmal AF (82% vs 63%) and non-paroxysmal AF (74% vs 51%). We also found repeat ablations to be lower for the surgical ablation group. However, there was a higher complication rate (28% vs 8%). On closer inspection of this data, the higher complication rate was attributed to pleural effusions and pneumothorax, which may be associated with the learning curve associated with this procedure. It is acknowledged that the current data is limited by the relatively short follow-up available, as well as small patient populations, as well as the lack of quality of life data(35).

What are possible explanations for the differences in treatment outcomes? Disadvantages of the percutaneous approach include the inconsistent ability to produce long-lasting transmurality of the lesions, due to the nature of the point-by-point technique(21). This is also associated with limitations in energy delivery, even though proof of acute bidirectional electrical isolation is sought in most cases of endocardial ablation(36). Although a similar problem may be encountered with Cox-Maze IV procedures using energy sources rather than cut-and-sew techniques, it appears to have a lesser impact(36). Furthermore, endocardial ablation may be associated with risks including pulmonary vein stenosis and esophageal perforation. The advantages offered by catheter techniques is the ability to perform electro-anatomical mapping with foci and signals such as complex fractionated electrograms, thus producing a "customized" lesion set for each patient. One possible solution is to perform a hybrid procedure, where transmural epicardial lesions can be produced with percutaneous endocardial mapping and touch-up if there has any gaps in conduction connection within one procedure(37). The outcomes of the hybrid ablation approach for AF is considered in Chapter 7.

Energy sources for surgical ablation of AF

Controversy still surrounds optimal energy sources used for surgical ablation of AF. Alternative energy sources were introduced to replace the traditional cut-and-sew techniques, with the aim of producing simpler, shorter and safer lesion sets epicardially (Cox-Maze IV procedure)(12, 13). Alternative energy sources include hypothermic sources (cryoablation) and hyperthermic sources (radiofrequency, microwave, laser, ultrasound). Common challenges across all epicardial approaches include risk of atrial esophageal fistula as well as the presence of epicardial fat which could limit the effectiveness of lesions produced(38). Mitral annulus connection lesions are also difficult to produce epicardially due to the nature of the anatomy, the circumflex artery and left main coronary artery is at inherent risk of injury by ablation(39).

We performed a network meta-analysis to compare different energy sources with cut-and-sew techniques. This type of analysis allows multiple groups to be compared simultaneously, rather than the traditional pairwise meta-analysis(40). Chapter 4 results demonstrated that the cut-and-sew approach is associated with the highest rates of sinus rhythm at follow-up, although also at highest mortality risk. It remains a good reference standard against which the outcomes of new energy sources. Cryoablation based on current data was less effective than radiofrequency ablation but with both energy sources had similar complication profiles. This difference may be attributed to the "cooling sink" effect more often seen in epicardial compared to endocardial ablation(41). This is where the effectiveness of cryothermia may be mitigated by the blood supply acting as a "cooling sink", thus reducing the reliability of the transmural lesions created(41). Microwave ablation may be associated with higher risk of strokes. Although the validity of this analysis is constrained by the quality of available data, it must also be acknowledged that statistically powered, direct head-to-head comparisons between different strategies are unlikely to occur in the short term future. Bayesian network meta-analysis is another approach that may allow indirect comparative analysis to help assess the available energy sources.

Biatrial versus left atrial lesion sets

Chapter 5 addresses another dilemma in the surgical realm – whether extensive left-atrial lesions alone can produce similar effectiveness rates compared to biatrial lesion sets, the latter which follows the founding principles of the cut-and-sew Maze procedure(42). Previous studies have suggested that ablation in the right atrium may result in postoperative bradyarrhythmias due to injury to the cardiac conduction system, requiring pacemaker implantations(43), however this result has not been consistent in the reported literature. Some proponents of the left atrial lesion set suggest that it may associated with lower complication rates and shorter procedural and bypass durations(44).

Our systematic review and meta-analysis of 10 studies including 2225 patients demonstrated that sinus rhythm prevalence was higher in the biatrial cohort compared to left atrial ablation cohort at 6-12 month follow-up, but this difference attenuated at follow-up beyond one year. Permanent pacemaker requirements were found to be higher in the biatrial lesion set group, but other complications were similar between the two approaches. As such, the current data suggests that it is possible to achieve similar outcomes and sinus rhythm prevalence using only left-atrial lesion sets compared to biatrial lesion sets, and furthermore the chance of requiring a permanent pacemaker is deemed lower based on pooled literature results.

Hybrid ablation for AF in obese patients

There is increasing evidence to demonstrate a complex interplay of risk factors as well as a strong association between obesity and atrial fibrillation(45-49). There are numerous proposed mechanisms by which obesity is associated with AF. Obesity is known to cause structural and electrical atrial remodeling, which can promote the development of AF(47). Weight gain can also induce structural and histological changes in cardiomyocytes(45, 47). Additionally, obesity may also be associated with pericardial fat, causing increased inflammation and local atrial infiltration(48), leading to increased risk of AF. Furthermore, weight fluctuations has been shown to be associated with AF recurrence(46), whilst weight increases has been associated with AF progression(49).

Post-operative atrial fibrillation (POAF) is one of the most common complications arising from cardiac surgery, affecting between 20% and 50% of patients(50, 51). Whilst the pathophysiology of POAF remains to be fully elucidated, this complication has been previously associated with risk of mortality and morbidity, as well as increased costs of additional treatment and post-operative care(52). The association between obesity and POAF has not been as well explored.

In Chapter 6, we assessed all available evidence investigating the association between obesity and POAF, also considering any link between POAF and other post-operative conditions such as mortality, stroke, myocardial infarctions and respiratory complications. Based on pooled data from 29 studies and 14 072 patients, it was found that obese patients had significantly higher odds of POAF when compared with non-obese patients. POAF when compared with no-POAF was associated with an increased risk of stroke, 30-day mortality and respiratory complications. As such we concluded that there is strong evidence that obesity is associated with a moderately higher risk of POAF.

Given the strong associations between obesity and AF as well as now POAF, there is a strong impetus to consider the effects of obesity of the effectiveness of ablation for AF. In Chapter 7, a retrospective analysis was performed on 61 patients who underwent simultaneous hybrid thoracoscopic endocardial catheter ablation of atrial fibrillation. The 3-year follow-up outcomes were directly compared in obese versus non-obese patients. We found that in a retrospective cohort with approximately half with persistent or long-standing AF, thoracoscopic hybrid epicardial endocardial ablation proved to be equally effective and safe in obese versus non-obese patients. The overall prevalence of sinus rhythm at 3-year follow-up was over 80% for both groups on anti-arrhythmic drugs, which is considerably higher than literature results for first-time catheter ablation techniques at the same follow-up.

Our results are consistent with prior published studies on the hybrid approach which utilized bipolar, bilateral thoracoscopic ablation(37, 53, 54). Less impressive results have been achieved in groups which have used unipolar energy source for the surgical component of the hybrid procedure, with success ranging from 37%-89% (37, 55-58). It is important to note that hybrid ablation is not without risk of complications. Although no complications were found in our present series, prior studies have reported that the hybrid approach may put patients at risk of post-procedural pericarditis, which is readily managed with steroids and opioids(55). There is also surgical risks in terms of intra-abdominal bleeding and collateral organ injury (55). Other studies have reported conversion to sternotomy, tamponade, hemothorax, pleural bleeding, and bleeding complications(59).

Overall, these studies demonstrate the feasibility of the hybrid ablation procedure as an alternative option to treat refractory stand-alone AF. This is especially considering the cost-ineffectiveness and potential increase in complications associated with multiple repeat interventions for treatment of long-term AF. Obese patients should not be discouraged from undergoing the hybrid endocardial and epicardial ablation for AF if indicated.

Our findings in context of national guidelines

Evidence from this thesis demonstrates that surgical ablation can be performed at the same time as mitral valve and coronary artery bypass grafting cardiac procedures without additional risks and complications for the patients. These add-on procedures significantly improve freedom from AF rates at follow-up to at least 1-year. Given that surgical ablation can be applied without increase in operative risk of mortality or major morbidity, and that benefits to long-term rhythm control appear consistent, there may be a role for more frequent performance intraoperative surgical ablation, and this should be reflected in updated guidelines. This is reflected in the 2016 European Society of Cardiology (ESC) guidelines(60), which state that for AF patients undergoing open heart surgery, AF surgery is recommended to improve symptoms if the patient decision is informed by the AF heart team (Figure 1). Similar recommendations have also been made in recent consensus guidelines by the Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and European Cardiac Arrhythmia Society

(ECAS)(61), as well as in the guidelines by the Society of Thoracic Surgeons (STS)(62). Further research is required for patients with stand-alone AF that is symptomatic and refractory to other treatment options.

Figure 1. Flowchart representing the decision making process for concomitant AF surgery during cardiac surgery, according to the 2016 European Society of Cardiology (ESC) guidelines.

National Australian guidelines should also be updated to recommend thoracoscopic surgical ablation as an alternative treatment to repeat catheter ablation in patients with already multiple failed attempts at catheter ablation for symptomatic long-standing AF. Currently, the National Heart Foundation consensus statement for ablation of atrial fibrillation states “Minimally invasive surgical approaches for ablation of AF are under ongoing evaluation”(63).

Our preliminary investigations also demonstrate that outcomes of hybrid ablation represents an effective technique with reasonable outcomes up to 3-years follow-up, and the outcomes were not influenced by patient BMI. The role of hybrid ablation within the context of the AF heart team and integrated care for AF is not well elucidated in the current guidelines(60, 61), likely to due lack of current evidence. It is hoped that evidence from Chapter 7 will form the basis for the recommendation for hybrid ablation as an alternative treatment option to thoracoscopic ablation and catheter ablation at least in persistent and long-standing AF. Furthermore, it is not unreasonable to extrapolate the current results and speculate that patients undergoing catheter or surgical ablation should not be discriminated based on body mass index. However, in the context of the AF heart team and integrated AF care, all measures should be taken to optimize preoperative patient factors including application of a weight loss strategy, risk factor modification, and dietary monitoring.

Implications for the AF heart team and integrated pathways

Currently to date, the available guidelines do not address the potential role of the hybrid ablation procedure in the AF heart team or integrated pathways.

The hybrid ablation approach provides the opportunity for direct collaboration between the electrophysiologist and cardiac surgeon to effectively treat AF via transmural epicardial and endocardial lesions. The reasons for the lack of discussion of the hybrid approach include the fact that it is a relatively new procedure with a lack of long-term outcomes published, and that there are only few expertise centers worldwide which have the training, technology and appropriate staff to perform this procedure. This thesis provides non-randomized evidence of the long-term efficacy of the hybrid procedure, which is at least equivalent if not better than reported rates for catheter ablation or surgical ablation at 3-years in the available literature. As such, the hybrid ablation procedure should be included in the armamentarium of tools available for the AF heart team for treatment of patients with AF.

Implications for patient decision making

Clinician and decision making with regards to interventions for AF has always been a controversial area, given the lack of standardisation of technique in the available literature to date. The parameters in question include energy sources, lesion sets, combined veersus isolated cardiac surgeries, duration of AF, and anti-arrhythmic medications. This thesis attempted to pool the evidence where appropriate to determine overall trends with regards to some these parameters, to help the clinician and patient make better informed decisions regarding the optimal treatment strategy for AF. The data synthesised from this thesis provides support to the notion that if patients are already undergoing cardiac surgery for another reason already, further added ablation during this cardiac procedure has adds no further surgical risks, but with the additional benefit of improved freedom from AF and atrial tachycardias to at least 1-year follow-up. In terms of options available for treatment, for patients with symptomatic long-standing AF with multiple failed catheter procedures, evidence from this thesis demonstrate that thoracoscopic epicardiac surgical ablation to be a reasonable approach with superior efficacy rates at the cost of increased risk of pleural effusions and pneumothorax. For patients with a poor quality of life, this may represent a viable option compared to further catheter ablation procedures with low rates of success. Thirdly, our thesis also demosntrates that the hybrid procedure can produce promising long-term results at 3-year follow-up with a low complication rate profile. This provides an expansion of options available for patients at centers where the expertise is available for such a treatment option.

Conclusions

Based on our systematic analyses of the literature, there clearly remains significant heterogeneity between different clinicians and centers with regards to energy sources, lesion sets, and ablation techniques. This is likely secondary to the lack of high quality prospective and randomized evidence available to guide best practice, in addition to heterogeneity in the definition of “success” used in different studies as well as variability in follow-up duration. The present thesis attempts to address this via a series of systematic reviews and meta-analyses, in an attempt to improve the level of evidence in the surgical ablation literature.

Controversy still remains in the literature with regards to percutaneous catheter approaches performed by electrophysiologists in comparison to thoracoscopic surgical ablation techniques performed by surgeons. The catheter approach is limited by the lower single-procedure success rates particularly in persistent long-standing AF, and the need for multiple interventions(64). Not only is this associated with higher cumulative complication risk with each procedure(65), but the cost-ineffectiveness and financial implications means that there is a strong need for better outcomes for patients and society(64). The thoracoscopic surgical approach has demonstrated promising efficacy results in the context of higher procedural complications and invasiveness(65), but can be further improved by the additional of endocardial touch-up ablations for gaps in ablation lesions and the ability to "customize" the lesion sets based on electro-anatomical three-dimensional mapping(66, 67). The surgical approach allow for direct visualization of structures for ablation and also offers the opportunity for other procedures such as left atrial appendage excision. The future is likely guided by taking advantage of the benefits of both techniques and refined into a single hybrid procedure in the heart team setting. However, there are currently very few published studies reporting the outcomes of hybrid ablation in stand-alone AF(37, 45, 53, 68, 69). Questions surrounding the hybrid procedure that requires future investigation include: How to optimize the logistics of the hybrid electrophysiologist and surgeon team? Can the edema from epicardial lesions reduce the effectiveness of endocardial lesion? Should the procedures be performed simultaneously or be staged, and if so, should the surgical component go first or should the catheter component go first? Are the complications associated with the surgical component result in higher risk compared to the benefits of the procedure? How much does each stage of the hybrid procedure add to the overall success?

The benefits of a heart-team approach has already been demonstrated in multiple settings in cardiovascular medicine and surgery, including transcatheter aortic valve replacement, endovascular thoracic or abdominal aortic repair, as well as combined percutaneous coronary intervention with structural heart intervention. The expansion of hybrid suites optimized for both surgical operations as well as high-resolution angiographic capability will facilitate hybrid procedures such as combined endocardial and thoracoscopic epicardial ablation for AF.

Future studies should look towards large, multi-center and prospective-randomized trials to determine whether the hybrid approach may represent the most effective treatment for persistent and long-standing AF, where the success rates of catheter ablation have been disappointing. Current surgical ablation approaches have provided better outcomes in this specific population, but a significant number of failures still exist and results have been suboptimal. The hybrid approach is promising as it allows checking of the epicardial ablation lines and if necessary, making additional endocardial lines to produce the most complete lesion set.

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Appendix

Publications included in this thesis with declaration

1. Surgical ablation for treatment of atrial fibrillation in cardiac surgery: a cumulative meta-analysis of randomised controlled trials. Heart 2014 100(9):722-30.

   Kevin Phan: Study design; Data collection; Statistical analysis; Manuscript writing; Editing

   Ashleigh Xie: Data collection

   Mark La Meir: Academic supervision

   Deborah Black: Statistical support

   Tristan D Yan: Academic supervision

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   Kevin Phan

2. Thoracoscopic surgical ablation versus catheter ablation for atrial fibrillation. Eur J Cardiothorac Surg 2016 49(4):1044-51.

Kevin Phan: Study design; Data collection; Statistical analysis; Manuscript writing; Editing

Steven Phan: Editing

Aravinda Thiagalingam: Academic supervision

Caroline Medi: Academic supervision

Tristan D Yan: Academic supervision

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Kevin Phan

3. Comparing energy sources for surgical ablation of atrial fibrillation: a Bayesian network meta-analysis of randomized, controlled trials. Eur J Cardiothorac Surg 2015 48(2):201-11.

Kevin Phan: Study design; Data collection; Statistical analysis; Manuscript writing; Editing

Ashleigh Xie: Data collection

Narendra Kumar: Study design

Sophia Wong: Study design

Caroline Medi: Academic supervision

Mark La Meir: Academic supervision

Tristan D Yan: Academic supervision

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Kevin Phan

4. Biatrial ablation vs. left atrial concomitant surgical ablation for treatment of atrial fibrillation: a meta-analysis. Europace 17(1):38-47.

Kevin Phan: Study design; Data collection; Statistical analysis; Manuscript writing; Editing

Ashleigh Xie: Data collection, Editing

Yi-Chin Tsai: Editing

Narendra Kumar: Editing

Mark La Meir: Academic supervision

Tristan D Yan: Academic supervision

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Kevin Phan

5. Obesity and postoperative atrial fibrillation in patients undergoing cardiac surgery: Systematic review and meta-analysis. Int J Cardiol. 2016 217:49-57.

Kevin Phan: Study design; Data collection; Statistical analysis; Manuscript writing; Editing

Jacqueline N Khuong: Data collection

Joshua Xu: Editing

Aran Kanagaratnam: Editing

Tristan D Yan: Academic supervision

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6. Effectiveness and safety of simultaneous hybrid thoracoscopic endocardial catheter ablation of atrial fibrillation in obese and non-obese patients. In submission.

Kevin Phan: Study design; Data collection; Statistical analysis; Manuscript writing; Editing

Laurent Pison: Study design, Data collection, Academic supervision

Narendra Kumar: Study design, Data collection

Tristan D Yan: Academic supervision

Mark La Meir: Academic supervision

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Kevin Phan

7. Atrial fibrillation: review of current treatment strategies

Jessica Luc: Manuscript Writing

Joshua Xu: Editing

Kevin Phan: Study design; Data collection; Synthesis; Manuscript writing; Editing

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