A multi-faceted approach to atrial fibrillation: from lifestyle factors to invasive therapies

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Abstract

Atrial fibrillation (AF) is a leading epidemic of cardiovascular disease in developed countries, owing to an ageing population and the Western lifestyle. In addition to effects on quality of life and economic burden on the health system, AF is associated with heart failure, stroke and a higher risk of mortality. The focus of AF management over the last decade has shifted from anticoagulation and rate control to a more a more holistic and multi-faceted approach. This encompasses attention to potentially modifiable lifestyle factors and adoption of novel invasive strategies such as catheter ablation to maintain rhythm control.

The aim of this thesis is to explore these emerging strategies in AF management, with a focus on rhythm control. Initially, we assess the impact of lifestyle related factors on AF and cardiovascular disease. The emphasis initially is on the effects of habitual alcohol consumption on the atria and ventricles and the impact of abstinence in the AF population. We explore novel strategies for cardioversion of persistent AF, focussing on improving success rates in obese patients. Finally, we explore the evolution of catheter ablation as an increasingly utilized rhythm control strategy.

Chapter 1 details our evolving understanding of AF pathogenesis, and the impact of common lifestyle factors on arrhythmogenesis, with a focus on alcohol, caffeine, diet and obesity. We then explore the evidence base for rhythm control strategies, including role of anti-arrhythmics, cardioversion and catheter ablation.

Chapter 2 and 3 explore the impact of regular alcohol consumption on the atrium to determine whether there is an association with electrical and structural remodelling. Chapter 2 is a prospective observational study of 75 patients undergoing novel high-density electroanatomical mapping of their left atria at the time of AF ablation. We compare non-drinkers, mild drinkers and moderate drinkers to determine whether there are differences in voltage and conduction properties between the three groups. Chapter 3 is a prospective observational study of 160 AF patients comparing atrial size, mechanical and reservoir function based on degree of alcohol intake utilizing high-definition cardiac magnetic resonance imaging (CMR). We conclude that moderate-to-heavy levels of consumption are associated with

adverse atrial remodelling, characterised by reduction in voltage, slowing of atrial conduction, atrial dilatation and impaired mechanical function suggestive of progressive fibrosis.

Chapter 4 is a randomized controlled trial of 140 moderate habitual drinkers with a history of AF. We examine the impact of 6 months of abstinence on risk of AF recurrence, AF burden, symptom scores, blood pressure, weight and atrial structure / function. Key findings include reduction in AF recurrence rates, with small but significant reductions in systolic blood pressure and weight. This is the first randomized trial to demonstrate the benefits of abstinence from alcohol in the AF population.

Chapter 5 examines the paradox between adverse effects of moderate alcohol consumption on the atrium and AF with widely reported benefits of light-to-moderate habitual alcohol consumption with respect to cardiovascular disease, heart failure and mortality. We undertook a cross-sectional study of 165 stable outpatients comprising of lifelong non-drinkers and regular drinkers. Participants underwent cardiac MRI T1 mapping, a novel imaging sequence that examines markers of ventricular fibrosis. Interestingly, light-to-moderate drinkers displayed lower markers of fibrosis. The clinical implications of this finding require further investigation.

Chapter 6 focusses on novel and improved treatment strategies for persistent AF in obese patients. We undertook a randomized controlled trial of 125 obese patients undergoing cardioversion for AF (as well as an observational sub-study of morbidly obese patients). Key findings included higher success rates with the use of hand-held paddles, manual pressure augmentation and higher energies (up to 360 Joules biphasic). Chapter 7 also focuses on improving outcomes for cardioversion in persistent AF, looking at the strategy of early presentation for cardioversion in the emergency department. We report a retrospective cohort study of 150 patients and conclude that compared to (delayed) elective cardioversion, earlier restoration of sinus rhythm prevented adverse atrial remodelling, delaying onset of next AF recurrence and improving quality of life.

Chapter 8 examines our evolving understanding of ablation strategies for persistent AF. Recent studies highlight that adjunctive substrate modification beyond pulmonary vein isolation (PVI) may not offer additional benefit and may in fact be pro-arrhythmic. We perform a meta-analysis of 14 studies reporting outcomes from PVI alone in this patient population. We conclude that

with current technology, acceptable arrhythmia-free survival can be achieved without additional substrate modification.

Chapters 9 and 10 report observational data from our institution with the aim of critically assessing key performance measures for catheter ablation of AF over time. Chapter 9 demonstrates a significant reduction in radiation exposure over time for both operator and patient, and examines the factors responsible. Chapter 10 focuses on procedural safety over time through the prism of increasing patient complexity, greater operator experience and technological advances over time. We conclude that at a high-volume centre, catheter ablation is an acceptable strategy that can be performed safely in a large majority of patients.

Declaration

This thesis is the sole work of the author and the material contained herein has not been previously published or written by another person except where due reference has been made in the text. The work was performed by the candidate in Melbourne at the Cardiology Departments of the Royal Melbourne Hospital, the Baker Heart and Diabetes Institute, and the Alfred Hospital's Heart Centre for the express purpose of this thesis and no part thereof has previously been presented for the award of a degree at this or any other university.

I certify that the writing of this thesis, the results, interpretations, opinions and suggestions are entirely my own work. This thesis does not exceed the length of 100,000 words exclusive of table, figures, appendices and bibliography.

Aleksandr Voskoboinik

Preface

This work was performed in collaboration with a number of institutions including:

1. The Royal Melbourne Hospital (Department of Cardiology)
2. The Alfred Hospital (Department of Cardiology)
3. Baker Heart and Diabetes Institute (Clinical Electrophysiology Research)
4. Monash Medical Centre (Department of Cardiology)
5. Cabrini Health (Department of Cardiology)
6. Western Health (Department of Cardiology)
7. The University of Melbourne (Department of Medicine)

All manuscripts and publications emanating from this thesis were undertaken with the candidate as the principal author. Responsibilities included: protocol design, ethics and governance application, participant recruitment and follow-up, data collection, statistical analysis, and manuscript preparation. PhD supervisors performed limited revision and editing of submitted manuscripts only. Additional co-authors listed in publications assisted in one or more of the above aspects, in addition to critical revision of manuscripts, consistent with co-authorship requirements for the respective journals. Chapter 2 required critical input from the second listed co-author predominantly for patient recruitment and data collection, who was afforded co-principal status in the accepted manuscript, although my contribution was >50%. However no co-authors had any role in drafting the manuscripts and chapters contained herein (excluding critical revision) and those works do not form components of any other submitted body of work.

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A full list of publications and published abstracts emanating from this body of work is provided in the section entitled ‘Peer reviewed publications arising from this thesis’.

Peer-reviewed publications arising from this thesis

Chapter 1

Published manuscripts

- Voskoboinik A, et al. **Alcohol and Atrial Fibrillation.** J Am Coll Cardiol. 2016.68(23): 2567-2576

- Voskoboinik A, et al. **Caffeine and Arrhythmias: Time to Grind the Data.** JACC: Clinical Electrophysiology 2018;4(4):425-432.

- Voskoboinik A, et al. **Effect of Dietary Factors on Cardiac Rhythm.** Effect of Dietary Factors on Cardiac Rhythm. Am J Cardiol. 2018;122(7):1265-1271.

- Voskoboinik A, et al. **Cardiovascular effects of caffeinated beverages.** Trends Cardiovasc Med. 2018 Oct 4. pii: S1050-1738(18)30177-4.

Chapter 2

Published manuscript

- Voskoboinik A, et al. **Moderate alcohol consumption is associated with atrial electrical and structural changes: insights from high density left atrial electroanatomical mapping.** Heart Rhythm. 2018 Dec 24. pii: S1547-5271(18)31131-7. doi: 10.1016/j.hrthm.2018.10.041 (accepted manuscript).

Published abstracts

- Voskoboinik A, et al. **Modest alcohol consumption is associated with significant left atrial conduction slowing**. (Cardiac Society of Australia & New Zealand 2017 Perth)

- Voskoboinik A, et al. **Moderate Alcohol Consumption Is Associated with Atrial Fibrosis and Conduction Slowing in the Atrial Fibrillation Population: Insights from High Density Left Atrial Electroanatomical Mapping** (Asia Pacific Heart Rhythm Society 2018, Taiwan)

Chapter 3

Published manuscript

- Voskoboinik A, et al. **Regular alcohol consumption is associated with impaired atrial mechanical function in the atrial fibrillation population: a cross-sectional MRI-based study**. JACC Clin Electrophysiol. 2018;4(11):1451-1459

Published abstracts

- Voskoboinik A, et al. **Regular Alcohol Consumption Is Associated with Impaired Atrial Mechanical Function and Epicardial Fat Deposition in the Atrial Fibrillation Population: A Cross-Sectional MRI-Based Study** (Asia Pacific Heart Rhythm Society 2018, Taiwan).

- Voskoboinik A, et al. **Regular Alcohol Consumption Is Associated With Impaired Atrial Mechanical Function In The Atrial Fibrillation Population: A Prospective MRI-based Study**. (Heart Rhythm Society 2018 Boston)

- Voskoboinik A, et al. **Modest alcohol consumption is associated with atrial myopathy: a prospective MRI-based study**. (Cardiac Society of Australia & New Zealand 2017 Perth)

Chapter 4

Submitted manuscript

- Voskoboinik A, et al. **Alcohol Abstinence in Moderate Drinkers with Atrial Fibrillation** (under review by New England Journal of Medicine as of January 2019)

Accepted abstract

- Voskoboinik A, et al. **Impact of Alcohol Abstinence in Moderate Drinkers with Atrial Fibrillation: Results from the Alcohol-AF Randomized Controlled Trial** (accepted at American College of Cardiology Annual Scientific Sessions 2019 as a Late-Breaking Clinical Trial).

Chapter 5

Published manuscript

- Voskoboinik A, et al. **Relation of Alcohol Consumption to Left Ventricular Fibrosis Using Cardiac Magnetic Resonance Imaging.** Am J Cardiol. 2019;123(3):460-465.

Published abstracts

- Voskoboinik A, et al. **Mild-moderate alcohol consumption is associated with a reduction in ventricular fibrosis: insights from T1 mapping on CMR.** (Asia Pacific Heart Rhythm Society 2018, Taiwan)

- Voskoboinik A, et al. **Regular Alcohol Consumption Reduces Diffuse Ventricular Fibrosis: Insights Into The Potential Cardiac Benefits Of Alcohol From CMR T1 Mapping**. (Heart Rhythm Society 2018 Boston)

Chapter 6

Published manuscript

- Voskoboinik A, et al. **Cardioversion of Atrial Fibrillation in Obese Patients: Results from the Cardioversion-BMI Randomized Controlled Trial**. J Cardiovasc Electrophysiol. 2018 Oct 29. doi: 10.1111/jce.13786 (accepted manuscript).

Published abstracts

- Voskoboinik A, et al. Hand-held Paddles More Effective than Adhesive Patches for Cardioversion of AF in Obese Patients: Results From The DCR-BMI Multicenter Randomized Controlled Trial (Asia Pacific Heart Rhythm Society 2018, Taiwan).

- Voskoboinik A, et al. **Hand-held Paddles More Effective Than Adhesive Patches For Cardioversion Of Atrial Fibrillation In Obese Patients: Results From The DCR-BMI Multicenter Randomized Controlled Trial** (Heart Rhythm Society 2018 Boston)

Chapter 7

Published manuscript

- Voskoboinik A, et al. **A comparison of early versus delayed elective electrical cardioversion for recurrent episodes of persistent atrial fibrillation: a multi-center study.** International Journal of Cardiology. 2018 (accepted manuscript)

Chapter 8

Published manuscript

- Voskoboinik A, et al. **Revisiting pulmonary vein isolation alone for persistent atrial fibrillation: A systematic review and meta-analysis.** Heart Rhythm. 2017;14(5):661-667.

Published abstracts

- Voskoboinik A, et al. **Good outcomes for pulmonary vein isolation alone in persistent atrial fibrillation: a meta-analysis** (Heart Rhythm Society 2017 Chicago)

Chapter 9

Published manuscript

- Voskoboinik A, et al. **Reduction in radiation dose for atrial fibrillation ablation over time: A 12 year single centre experience of 2,344 patients.** Heart Rhythm. 2017;14(6):810-816.

Published abstracts

- Voskoboinik A, et al. **Reduction in radiation dose for atrial fibrillation ablation over 12 years: a single centre experience of 2,344 patients** (Heart Rhythm Society 2017 Chicago)

- Voskoboinik A, et al. **Significant reduction in radiation dose for atrial fibrillation ablation over time: a 12 year single centre experience** (Asia Pacific Heart Rhythm Society Seoul 2016)

Chapter 10

Published manuscript

- Voskoboinik A, et al. **Low rates of major complications for radiofrequency ablation of atrial fibrillation maintained over 14 years: a single centre experience of 2,750 consecutive cases.** Heart Lung Circ. 2018;27(8):976-983.

Published abstracts

- Voskoboinik A, et al. **Low rates of major complications for atrial fibrillation ablation over time using radiofrequency energy: a 13-year single center experience of 2,600 cases**. (Heart Rhythm Society 2017 Chicago).

- Voskoboinik A, et al. **Low rates of major complications for atrial fibrillation ablation over time using radiofrequency energy: a 13-year single centre experience of 2,600 cases** (Cardiac Society of Australia & New Zealand 2017 Perth).

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For Lironne, Ari, Benji and Ellie

Abbreviations

AA	Anteroapical
AAD	Anti Arrhythmic Drug
ACT	Activated Clotting Time
AERP	Atrial Effective Refractory Period
AF	Atrial Fibrillation
AP	Anteroposterior
BMI	Body Mass Index
CA	Catheter ablation
CB	Cryoballoon
CCF	Congestive Cardiac Failure
CI	Confidence interval
CMR	Cardiac Magnetic Resonance
CFAE	Complex Fractionated Atrial Electrogram
CS	Coronary Sinus
CV	Cardioversion
ECV	Electrical Cardioversion
ED	Emergency Department
EDs	Energy Drinks
ED-CV	Emergency Cardioversion
EL-CV	Elective Cardioversion
GFR	Glomerular Filtration Rate
HHS	Holiday Heart Syndrome
HR	Hazard Ratio
HRV	Heart Rate Variability

HT	Hypertension
ICE	Intracardiac Echocardiogram
IHD	Ischaemic Heart Disease
LA	Left Atrium
LAEF	Left atrial emptying fraction
LAVI	Left atrial volume index
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
OR	Odds ratio
OSA	Obstructive Sleep Apnoea
PAF	Paroxysmal Atrial Fibrillation
PeAF	Persistent Atrial Fibrillation
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
RF	Radiofrequency energy
RCT	Randomized Controlled Trial
RR	Relative Risk
SCD	Sudden Cardiac Death
SD	Standard Drink
SDB	Sleep Disordered Breathing
TIA	Transient Ischaemic Attack
TOE	Transoesophageal Echocardiogram
TTI	Transthoracic Impedance
VA	Ventricular Arrhythmia
VPB	Ventricular Premature Beat

Table of Contents

Chapter 1: Literature Review

Epidemiology of Atrial Fibrillation

An ageing population and a Western lifestyle with rising prevalence of cardiometabolic risk factors have led to the emergence of atrial fibrillation (AF) as an epidemic of cardiovascular disease. Worldwide prevalence was estimated at 33.5 million in 2010, with 5 million new cases diagnosed each year, associated with a doubling in AF-related mortality[1] primarily due to heart failure and stroke. Over the same period, there has been a 23% rise in AF-related hospitalizations[2]. Annual costs associated with AF management in the United States have been estimated at $6 – 26 billion, and are primarily related to inpatient care[3]. There is also considerable morbidity associated with AF symptoms, with a high prevalence of psychological distress, depression and anxiety, with rhythm control an increasingly effective strategy for these patients[4-6].

A large section of this PhD is devoted to novel, multi-faceted strategies for reducing the morbidity associated with AF throughout effective rhythm control. These include lifestyle management (with a focus on the impact of alcohol and potential benefits of abstinence), improved cardioversion in obese patients, improving access to cardioversion and optimisation of ablation outcomes.

Pathogenesis of atrial fibrillation

Atrial fibrillation is characterised by two predominant phenotypes: ‘paroxysmal’ (PAF) whereby episodes spontaneously terminate within 7 days and ‘persistent’ (PeAF) whereby episodes last > 7 days and frequently require cardioversion (CV) to restore sinus rhythm (SR). The term ‘trigger’ is used to refer to factors that initiate

AF, while 'substrate' refers to factors within the atrium that sustain and perpetuate AF, namely electrical and structural remodelling. In his landmark study using multi-electrode mapping of 45 patients with PAF, Haissaguerre et al identified that 94% of these rapidly-firing focal triggers originated 2 – 4cm inside the pulmonary veins (PVs)[7] and could be eliminated with radiofrequency ablation targeting these triggers[8] Other putative trigger sites identified have included the Ligament of Marshall, coronary sinus, superior vena cava, crista terminalis and posterior wall[9].

A higher resting membrane potential, shorter action potential duration and lower upstroke velocity within pulmonary vein (PV) myocytes (due to ionic current differences with more abundant ERG and KvLQT1 and lower Kir2.3) have been identified as putative mechanisms resulting in more frequent early and later after-depolarisations and favourable conditions for micro re-entry within the PV myocardial sleeves[10,11]. In animal models, PVs have also been shown to display enhanced automaticity in response to increased catecholaminergic activity[12] and triggered activity due to enhanced calcium transients[13]. Higher densities of parasympathetic nerves in PV's with focal discharges and increase in triggered activity in response to acetylcholine[14] underscore the role of the autonomic nervous system in AF pathogenesis. Re-entry within the PVs is also favoured by the complex arrangements of myocardial fibres resulting in non-uniform anisotropy[13,15] conduction slowing with regions of unidirectional block[16,17] and complex fractionation[18]. The junction of the pulmonary vein and left atrium (LA) also contains properties favouring re-entry. A study of high density epicardial mapping of 18 patients demonstrated significant functional conduction delay and circuitous propagation patterns in this region[19]. Endocardial mapping of the PV-LA junction in

48 patients also found marked heterogeneity and anisotropic conduction in this region[15].

Electrical and structural atrial remodelling remain the hallmarks by which AF is sustained and further perpetuated, characterised by the common adage 'AF begets AF'. These changes in atrial substrate explain why many patients with AF are unable to be cured with pulmonary vein isolation alone and underscores the importance of upstream therapy, including risk factor management. In a study of AF induction in 12 goats, electrical changes were observed even after 24 hours of AF, including marked shortening of atrial effective refractory period (AERP) with AF more readily inducibile[20]. In a study of 20 patients without structural heart disease, even 8 minutes of induced AF was sufficient to shorten AERP demonstrating a mechanism by which AF may be self-perpetuating[21]. Intercellular atrial conduction relies on gap junctions located in the intercalated discs and changes in distribution of these proteins has been observed in animal studies. Chronic AF has been shown to increase the expression and distribution of connexin 43[22] with more heterogenous distribution patterns of connexin 40 also observed[23]. The disruption of normal myofilament architecture by these changes may result in conduction slowing, promoting re-entry.

Ionic remodelling has also been observed in AF – this 'adaptive' mechanism to enable maintenance of rapid atrial rates at low metabolic cost also sustains AF. In animal models, the outward transient potassium current I_{to} is downregulated in response to rapid rates within 24 hours, increasing over 6 weeks which reduce atrial repolarisation rate response[24,25]. Increased activity in AF has been observed in inward-rectifier potassium channel I_{K1} and the acetylcholine-dependent I_{KACh} current which both demonstrate increased activity at hyperpolarizing potentials in AF[26]. Tachycardia also

induces changes in L-type calcium current with increased atrial cardiomyocyte calcium loading (increased released from intracellular sarcoplasmic reticulum stores) and adaptive reductions in I_{CaL} (up to a 70% reduction in current density)[24,27,28]. Calcium leak from the sarcoplasmic reticulum is also modulated by hyperphosphorylation of the cardiac ryanodine receptors (RyR2), with these changes shortening action potential duration (APD) and decreasing APD rate adaptation. Abnormal intracellular calcium handling also impairs atrial contractile function, with changes observed even within minutes of AF onset[29].

The autonomic nervous system has also been implicated in the initiation and maintenance of AF. AF is a complex condition and may be sympathetically driven, exemplified by the observation that isoprenaline (a sympathetic agonist) increases the activity of focal AF triggers or by the entity of 'exercise-induced AF'[30]. Activation of beta-adrenergic signalling increases calcium transient and promotes calcium release from the sarcoplasmic reticulum leading to early and delayed afterdepolarizations thereby increased ectopic activity[31]. Some patients have parasympathetic triggers, as is observed with 'vagally-mediated AF' seen during rest / sleep or post-prandially[32]. In animal studies, vagal stimulation promotes re-entry by heterogeneously shortening AERP and action potential duration due to acceleration of atrial repolarisation by acetylcholine activated potassium channels (I_{KACh})[33]. Moreover, the PVs and posterior left atrium are richly innervated with sympathetic and parasympathetic fibres, and some studies have demonstrated that ablation of ganglionated plexi improves ablation success[34]. In a study of 77 patients with PAF undergoing Holter monitoring, the interplay between the sympathetic and parasympathetic nervous systems was found to initiate AF, with a primary increase in sympathetic tone, then an abrupt shift to vagal predominance immediately prior to arrhythmia onset[35].

In addition to electrical remodelling, structural changes form an important basis for maintenance of AF with multiple simultaneous re-entrant wavefronts with heterogenous AERP shortening and altered conduction velocities within the atrial 'substrate' continually re-exciting the atria in a chaotic fibrillatory fashion. In this 'multiple wavelet hypothesis', these wavefronts collide, fuse and form new wavefronts with AF is maintained as long as the number of wavefronts do not drop below a critical level[36,37]. Complimenting this is the 'leading circle' model which describes a leading circuit which has the smallest size and therefore rotates with the highest frequency which may 'overdrive' and 'suppress' all larger circuits while maintaining a refractory central core with a lower membrane potential[38]. More recently, special types of functional re-entry referred to as 'rotors' have been proposed as being important to AF maintenance. These spiral wavefronts identified using endocardial mapping are characterised by functional re-entry where the wavefront and wavetail meet at a focal point of phase singularity with wavefronts adjacent to this point having the slowest conduction velocity[39]. As rotors spread away from the phase singularity and core, they may fragment and degenerate after interacting with inhomogeneities in myocardium or may anchor and form stable rotors as is observed around the pulmonary veins[40]. However, despite novel technologies designed to identify and target these rotors during AF ablation[41], they have only been infrequently observed by other researchers utilizing epicardial mapping and non-invasive electrocardiographic imaging. In these studies, multiple wavelets and disorganised activity were more commonly observed and rotors rarely seen[42,43].

In all electrophysiological models of AF, atrial structural remodelling remains important to AF maintenance and disease progression. The remodelling process may

begin within the first few days of arrhythmia onset and is often a response to external stressors including inflammation, atrial stretch, ischaemia and oxidative stress[44] with microscopic changes including myolysis, apoptosis, hypertrophy and disruption of the sarcoplasmic reticulum and mitochondria[45-47]. Structural remodelling may develop as a cause or effect of AF and culminates in atrial dilatation and fibrosis, particularly involving the left atrium and its posterior wall.

The renin-angiotensin-aldosterone system (RAAS), activated in heart failure, hypertension and atherosclerosis has been implicated in AF pathogenesis, and angiotensin-II receptors are upregulated in the left atrium in patients with AF[48]. In murine models, angiotensin II receptor activation causes release of mitogen-activated protein kinases (MAPK) which alter gap junction proteins and upregulates matrix metalloproteinase 9 which promotes atrial collagen deposition[49]. Angiotensin II also activates myocardial NADPH oxidase which results in generation of reactive oxygen species[50] and upregulates inflammatory genes resulting in release of numerous pro-inflammatory cytokines (including interleukin-6, gamma interferon, oxidative stress, chemoattractant protein MCP-1, intracellular adhesion molecule-1 and P-selectin)[51]. In a meta-analysis of 26 randomised controlled trials, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers were protective against AF (OR 0.65, 95% CI 0.55-0.76) in both the primary and secondary prevention setting[52]. Similarly, in murine models exposure to aldosterone resulted in an increase in atrial fibroblasts, myocyte hypertrophy, interstitial collagen deposition with prolongation in atrial conduction times and more readily inducible AF[53].

Fibroblasts are abundant in atrial tissue[54] and several important pro-fibrotic cytokines are also involved in the formation and turnover of atrial interstitial collagen.

Transforming growth factor-β1 (TGF-β1) is a key cytokine that initiates and promotes the synthesis and metabolism of atrial interstitial collagen. In a meta-analysis of 13 studies and 3,354 patients, plasma levels of TGF-β1 were associated with increased risk of AF (SMD 0.67; 95%CI 0.29-1.05)[55]. TGF-β1 expression in surgical specimens progressively increased from sinus rhythm to paroxysmal AF and then persistent AF with a significant positive correlation observed between TGF-β1 and degree of atrial fibrosis[56]. In 242 patients undergoing electroanatomical mapping at time of ablation, higher TGF-β concentrations were associated with lower LA voltage (P=0.014) and LA dilatation (P=0.022)[57]. Platelet-derived growth factor (PDGF) which promotes atrial fibroblast type I collagen deposition is also associated with AF, with greater PDGF expression observed with longer AF duration in a canine model[58]. In a sheep model, atrial structural and electrical changes were reversible with PDGF recombinant antibody[59].

Inflammation also plays a role in AF pathogenesis, particularly following cardiac surgery. Calcium overload of atrial myocytes from AF may lead to cell death and an inflammatory response[47]. In 12 patients with paroxysmal AF undergoing atrial biopsy, 66% demonstrated inflammatory infiltrates consistent with myocarditis, which was 'active' in 25%[60]. Levels of high-sensitivity C-reactive protein (CRP) are higher in AF than in control patients, with persistent AF patients having higher levels than paroxysmal AF[61], and this may confer a higher thromboembolic risk[62]. Following cardiac surgery, patients developing AF are more likely to have elevated levels of interleukin-6 (IL-6) and CRP[63]. Several studies of AF patients undergoing cardioversion have found that lower levels of IL-6[64] and CRP[65] were associated with maintenance of sinus rhythm. Elevated levels of IL-6 and CRP were also independent predictors of AF recurrence in a study of 46 patients undergoing catheter ablation[66].

Neutrophil myeloperoxidase (MPO) may also play a role in atrial inflammation, with elevated plasma concentrations and a larger MPO burden observed in right atrial tissue in humans with AF. MPO-deficient mice appear to be protected from AF with AF more difficult to induce and markedly less atrial fibrosis observed[67].

Remodelling caused by acute and chronic atrial stretch is also associated with AF, particularly in the context of atrial pressure or volume overload as may be seen in heart failure, hypertension, mitral valve disease or obstructive sleep apnoea. In a study of 15 patients undergoing atrial epicardial mapping during cardiac surgery, atrial stretch induced by rapid volume expansion resulted in significant reductions in atrial conduction velocities and an increase in fractionated electrograms[68]. In a sheep model, artificial LA volume overload for a 3 month period resulted in LA dilatation, myolysis, lower I_{Ca} current densities, and numerous myocytes were not excitable[69]. In a study whereby left atrial stretch was induced by partial mitral valve avulsion in 19 dogs, chronic inflammation, interstitial fibrosis and increased AF inducibility were observed compared to controls at 1 month[70]. In a porcine model, acute left ventricular unloading 2 weeks following myocardial infarction resulted in alleviation of LA stretch with reduced LA passive stiffness, lower histological markers of inflammation and shortened time to spontaneous AF termination significantly[71]. Reversal of stretch-related abnormalities have also been observed in 21 patients undergoing mitral commissurotomy for mitral stenosis. Reductions in left atrial volumes and P-wave duration and increases in conduction velocity and left atrial voltage were observed immediately post-procedure, suggesting a degree of reversibility to stretch-related adverse atrial remodelling[72].

Lifestyle factors and arrhythmogenesis

Alcohol

Introduction

There is a somewhat arbitrary distinction exists between the quantity of alcohol that is cardioprotective and that which is contributory to heart disease. Atrial fibrillation and/or flutter (AF) are the most common symptomatic arrhythmias worldwide, and the combination of an aging population and lifestyle factors has propelled AF to an "emerging epidemic" of cardiovascular disease. Increasingly, attention has shifted towards modifiable risk factors to prevent AF onset and progression.

The association between excessive drinking and various forms of cardiovascular disease is well established. In particular, significant alcohol consumption is associated with a higher risk of AF, hypertension, left ventricular hypertrophy (LVH), obstructive sleep apnoea (OSA), and cardiomyopathy. However, smaller amounts of alcohol may reduce the incidence of coronary disease. Counterbalanced is an acceptance that even moderate levels of habitual consumption are associated with AF.

Epidemiology

Alcohol is ubiquitous in Western countries, with 53% of Americans regularly consuming alcohol and 61 million (44% of drinkers) consuming ≥5 standard drinks on a single occasion (binge drinking) in the last month[73]. "Holiday heart syndrome" (HHS) remains a common emergency department presentation, with AF precipitated by alcohol in 35% to 62% of cases[74,75]. Three large meta-analyses have demonstrated that moderate habitual consumption, even after correcting for binge drinking, increases the incidence of AF in a dose-dependent manner[76-78], with men and women equally

affected. Alcohol consumption has been defined as: light <7 standard drinks/week; moderate 7 to 21 standard drinks/week; and heavy >21 standard drinks/week, where 1 standard drink is approximately 12 g of alcohol.

Alcohol may act as a trigger for AF (Figure 1) and facilitate progressive atrial remodelling with regular long-term consumption (Figure 2).

Electrophysiological effects of alcohol

Sustained short-term alcohol consumption may induce electrical atrial remodeling, producing an arrhythmogenic substrate. In rabbits, a 5-day alcohol infusion significantly reduced L-type calcium ($I_{Ca,L}$) and sodium (I_{Na}) current density[79]. An up-regulation in protein expression of the acetylcholine-sensitive potassium channel Kir3.1 (I_{KACh}) was seen in rat atria exposed to ethanol and its metabolite acetaldehyde. Increased I_{KACh} activity shortens the action potential by promoting repolarization[80]. Similarly, alcohol administration shortened pulmonary vein action potential duration by increasing I to outward potassium current activity in rabbit pulmonary vein cardiomyocytes, although it did not alter automaticity or triggered activity[81]. In a closed-chest porcine model, Anadon et al. demonstrated that acute intoxication increased AF susceptibility following burst atrial pacing[82]. The direct effect of alcohol shortening the atrial action potential and, as such, atrial wavelength provides the electrophysiological milieu for re-entry and AF.

The acute cardiac effects of alcohol in humans were first described in 14 patients who underwent electrophysiological studies before and after ~5 standard drinks of whiskey. As in animal models, alcohol shortened the effective refractory period, and also slowed

intra-atrial conduction[83]. In a study of habitual moderate-heavy drinkers, ingestion of ~6 standard drinks of whiskey prolonged the HV interval and shortened sinus node recovery time, with an atrial or ventricular tachyarrhythmia inducible in 71%[84]. Interatrial conduction, as determined by signal-averaged sinus P-wave duration, is significantly longer in patients with a history of AF following a binge compared with age-matched controls. However, following 1.5g/kg ethanol, P-wave duration was prolonged in the control group with no history of AF[85], suggesting that alcohol directly slows interatrial conduction in all. Interatrial electromechanical delay has also been demonstrated acutely on tissue Doppler echocardiography[86].

In 48 patients with AF, atrial effective refractory periods were significantly shorter in drinkers compared with nondrinkers[87]. Conduction slowing, in combination with shortening of atrial refractoriness, shorten wavelength and facilitate re-entry. To date, electrophysiological changes during the washout or hangover period have not been well characterized. Hypokalemia is also common in chronic heavy drinkers, and is primarily mediated by inappropriate kaliuresis from the coexistent hypomagnesemia present in 30% of heavy drinkers[88]. Potassium loss may be exacerbated by vomiting during a binge, and predisposes to AF by increasing excitability, as cellular hyperpolarization lowers the resting membrane potential, which may increase sodium channel recruitment, leading to a faster upstroke.

Autonomic effects of alcohol

Alcohol has effects on autonomic modulation, which may contribute to AF. Maki et al. demonstrated a sympathetic response to 1.25 g/kg alcohol with a 29% increase in blood lymphocyte β-receptor density in patients with previous alcohol-induced AF[89].

However, even lower alcohol doses stimulate the sympathetic nervous system, promoting adrenaline secretion from the adrenal medulla. Perman found significant increases in urinary adrenaline excretion in 43 patients consuming 0.27 to 0.54 g/kg wine or whiskey, with differences seen even at alcohol concentrations <0.04%[90].

In patients without prior AF, there is a significant reduction in short-term heart rate variability (HRV) following acute alcohol ingestion[91]. Süfke et al. demonstrated a sustained increase in the ratio between low- and high-frequency components of HRV[92]. This "hyperadrenergic state" persists at least 24 h after intoxication, and may explain why some patients present with AF the day after a binge.

Alcohol may affect the parasympathetic system. Quintana et al. reported significantly more "high frequency HRV" in habitual light-moderate drinkers, consistent with parasympathetic modulation of autonomic tone[93]. Moreover, vagal triggers, such as rest, sleep and eating, are common provocateurs in alcohol-mediated paroxysmal AF[94]. Vagal activation shortens atrial refractoriness and may give rise to single or multiple dominant rotors, resulting in waves of excitation and fibrillatory conduction, whereas sympathetic activation increases intracellular calcium and spontaneous release from the sarcoplasmic reticulum[95]. Moreover, AF itself may be triggered by simultaneous discharge of both sympathetic and parasympathetic limbs[96]. Patterson *et al.* demonstrated that concurrent infusion of noradrenaline and acetylcholine caused early afterdepolarization and triggered activity, promoting arrhythmogenesis[97].

Atrial structural effects of alcohol

Alcohol has direct effects on atrial excitation-contraction coupling and may cause tissue fibrosis. Rats consuming alcohol for 2 months had a reduction in myofilament calcium sensitivity and an attenuated response to inotropes[98]. Ultrastructural changes in "alcoholic animals" drinking for >1 year included localized dilation and cystic changes in intercalated discs critical to cell-cell impulse propagation[99]. In patients with paroxysmal AF undergoing pulmonary vein isolation (PVI), daily drinking was an independent multivariate predictor of discrete atrial fibrosis, the hallmark of structural remodeling in AF. The probability of regional low voltage increased by 10% for every standard drink consumed[100].

Although consumption of ≤14 standard drinks/week did not alter the prognosis in 6,797 patients with severe systolic dysfunction[101], heavier drinking may cause cardiomyopathy. Alcohol and its metabolite, acetaldehyde, have direct cardiotoxic effects. Alcohol may impair excitation-contraction coupling, inhibit calcium release from the sarcoplasmic reticulum, and cause oxidative stress, protein damage, and lipid peroxidation[102]. Myocarditis with a lymphocytic infiltrate and focal necrosis is present in 30% of patients with alcoholic cardiomyopathy[103]. In otherwise healthy binge drinkers, cardiac magnetic resonance imaging demonstrates transient increases in ventricular T2-signal intensity representative of myocardial edema, and global relative enhancement consistent with hyperemeia, with associated troponin elevations suggestive of acute inflammation[104]. Whether similar changes occur in the atria following binge drinking is yet to be determined.

Alcohol and Binge Drinking: "Holiday Heart Syndrome"

Ettinger et al. first coined the term "holiday heart syndrome" (HHS)[105] in 24 patients hospitalized with AF following a weekend binge. Although many of these were regular drinkers, subsequent studies showed that HHS also occurred in infrequent and nondrinkers after a binge[106]. Interestingly, although many patients develop AF at the time of intoxication, others may present 12 to 36 h later[107]. In fact, a "hangover" may be merely a manifestation of mild alcohol withdrawal, characterized by sympathetic hyperactivity, with a 17% heart rate increase observed in healthy nonalcoholics 12 h post-binge[108]. Alcohol also has a diuretic effect, elevating antidiuretic hormone and aldosterone, potentially causing electrolyte disturbances that further contribute to a proarrhythmic state. Acetaldehyde, a potent cardiac toxin and alcohol metabolite, also has effects that may persist into the hangover period[109].

Although AF usually terminates within 24 h in HHS, 26% of patients have recurrences at 1 year with subsequent binges[110]. Liang et al. found that binge drinking (>5 standard drinks) in addition to habitual moderate consumption of ≤21 standard drinks/week was associated with a similar risk of AF as habitual heavy drinking[111]. Although HHS is often considered benign, heavy binge drinking has been linked with sudden cardiac death, particularly in patients with pre-existing structural heart disease. In 309 sudden cardiac death patients with 2.8 risk factors for coronary disease, the relative risk of dying within 2 h of drinking was 3.00 (95% CI: 1.61 to 5.68)[112]. In this vulnerable group, alcohol may precipitate ventricular tachycardia by QTc prolongation. Rossinen et al. demonstrated QTc prolongation (13 to 25 ms; $p < 0.05$) following 0.72 g/kg alcohol in patients with stable coronary disease, with similar findings unrelated to autonomic changes in healthy controls[113].

A meta-analysis of 29,457 participants in 23 studies demonstrated the complex physiological interplay of alcohol at different time points after consumption. Moderate consumption was associated with an immediately higher cardiovascular risk that was attenuated after 24 h, and became protective against ischemic stroke within 1 week. The investigators speculate that an increase in plasminogen activator inhibitor activity is responsible for events in the first 1 to 3 h, with improvements in endothelial function, flow-mediated vasodilation, and fibrinolytic factors seen by 12 to 24 h[114].

Habitual Alcohol Consumption as a Risk Factor for AF

Although heavy habitual alcohol consumption and binge drinking are closely associated with AF, the relationship between light-moderate habitual consumption and dose-dependent risk of AF has emerged in 3 large meta-analyses.Larsson et al[76] reported a 12-year follow-up of 859,420 patients together with a meta-analysis of 7 prospective studies, including 12,554 AF cases. After excluding binge drinkers and adjusting for other AF risk factors, all 7 studies reported a positive association between alcohol and AF. For each extra alcoholic drink per day, AF incidence increased 8%. The relative risks (RR) were: 1.08 for 7 standard drinks/week (95% CI: 1.06 to 1.10); 1.17 for 14 standard drinks/week; 1.26 for 21 standard drinks/week; 1.36 for 28 standard drinks/week; and 1.47 for 35 standard drinks/week. Of those consuming >14 standard drinks/week, only wine (RR: 1.35; 95% CI: 1.08 to 1.68) and liquor (RR: 1.46; 95% CI: 1.18 to 1.81) were associated with AF, but not beer (RR: 1.03). This may be related to the higher alcohol concentration of wine and liquor, and differences in consumption behaviour between drinkers of different beverages.

Kodama et al reported similar findings in an earlier meta-analysis of 14 retrospective and prospective studies, encompassing both case controls and cohort studies. The pooled estimate of RR for the highest category of alcohol consumption compared with the lowest category was 1.51 (95% CI: 1.31 to 1.74), with an 8% increase in AF risk for each 6 standard drinks/week consumed[77]. Samokhvalov et al. found a slightly higher threshold for AF risk, but also demonstrated a dose-response curve. The risk of AF was increased by 17% in women consuming >14 standard drinks/week and by 25% in men consuming >21 standard drinks/week[78].

Many of the individual studies were underpowered to demonstrate a relationship between alcohol and AF, particularly in the primary prevention population, where the incidence of AF was relatively low. Therefore, the conclusions regarding the relationship between low-moderate levels of alcohol intake and AF are largely drawn from the meta-analyses. There are important limitations when interpreting large population-based observational studies. Firstly, all studies (Table 1) determine the quantity of alcohol by self-reporting, rather than by objective blood or urine samples. This may have underestimated the AF risk due to under-reporting of alcohol consumption. Secondly, AF episodes may be asymptomatic, with the majority of studies largely relying on symptomatic episodes and presentation for electrocardiograms (ECGs), rather than dedicated monitoring. For instance, the Framingham[115] and Copenhagen City Heart[116] studies only performed routine ECGs every 2 to 4 and 5 to 10 years, respectively, with AF largely determined from hospital admissions, rather than routine monitoring or primary practice. Thirdly, “AF events” often excluded atrial flutter. In studies[100,117,118] (Table 1) investigating patients with prior AF, the follow-up was generally shorter and the risk of AF recurrence consistently higher with light-moderate habitual consumption.

Heavy habitual consumption is a well-established risk factor for AF, and may be a more important risk factor than hypertension or obesity. In a cohort of 8,602 subjects, the HR of developing AF was 2.68 for heavy drinkers (≥40 standard drinks/week), compared with 1.72 for obesity and 1.02 for hypertension[119]. In a longitudinal study of 26,163 earthquake survivors, drinking >25 standard drinks/week was the strongest predictor of AF, with a HR of 3.8, compared with HRs of 1.9 for obesity and 1.08 for hypertension[120].

Alcohol and Other AF Risk Factors: An Intermediary or a Confounding Variable?

Although there is little doubt that alcohol is independently associated with AF, its interaction with other AF risk factors, particularly in habitual drinkers, may be understated. In particular, hypertension, obesity, OSA, and cardiomyopathy may be caused or exacerbated by alcohol. Alcohol may be responsible for 16% of hypertensive disease[121], with the incidence of hypertension increased by 40% if consuming >14 standard drinks/week. In a meta-analysis of 15 randomized trials, alcohol reduction significantly lowered systolic and diastolic blood pressures in a dose-dependent fashion[122]. Hypertension may be present in up to two-thirds of AF patients[123], and AF is often preceded by LVH and atrial hypertrophy[124]. In those with LVH, AF incidence is reduced by 40% if a systolic blood pressure <130 mm Hg is achieved[125].

Obesity is a powerful determinant of left atrial (LA) size and a well-recognized modifiable AF risk factor[126]. Despite alcohol's relatively high energy content, it has not been consistently shown to cause weight gain or metabolic syndrome in light-moderate drinkers[127]. Moderate consumption (7 to 21 standard drinks/week) may even reduce new-onset diabetes by 30%[128]. However several observational studies indicate that

drinking >21 standard drinks/week and binge drinking can increase body mass index, waist circumference, and waist-to-hip ratio[129]. Recently published studies have focused on the benefits of structured weight reduction and exercise in reducing AF symptoms, beneficial cardiac remodelling, and sinus rhythm maintenance following PVI[126]. The impact of the recommended intake of <3 standard drinks/week was not specifically addressed.

Sleep-disordered breathing (SDB), encompassing OSA, is an established AF risk factor linked with alcohol. An Apnoea Hypopnea Index (AHI) >5 increases the risk of incident AF by 55% over 12 years[130]. SDB predisposes to AF in multiple ways, including hypercapnoeic hypoxia, increased oxidative stress, and inflammation causing LA remodelling. AF episodes may be triggered by sympathetic hyperactivity and acute hypertension during apnoeic episodes, and large negative intrathoracic pressure swings causing LA stretch[131]. Scanlan et al. showed that even modest alcohol consumption (0.5g/kg) before sleep increased the AHI[132]. Mechanisms include oropharyngeal muscle hypotonia, depressed arousal mechanisms, sleep fragmentation, and reduced hemoglobin affinity for oxygen[133]. Epidemiological studies have confirmed the association between alcohol and SDB in a dose-dependent manner. Peppard et al. reported a 25% increased risk of SDB for each standard drink/day increment[134]. Tanigawa et al. demonstrated that moderate-heavy consumption (0.5 to 1 g/kg/day) is associated with SDB, with the mean oxygen desaturation index correlating with alcohol intake[135].

Although lighter alcohol intake may reduce the risk of heart failure, habitual heavy drinkers may suffer the deleterious cardiotoxic effects of alcohol and develop an alcoholic cardiomyopathy. This may progress from unexplained LVH[136] to overt

systolic heart failure, particularly if consuming >7 standard drinks/day for 5 years[137]. Even if systolic function is normal, one-third of heavy drinkers have echocardiographic evidence of diastolic dysfunction, with deterioration of diastolic parameters correlating with degree of alcohol consumption[138]. Elevated LA pressures associated with left ventricular diastolic and/or systolic dysfunction may predispose to AF by stretch-mediated mechanisms.

Alcohol and AF: Prognostic Implications

Those who continue to consume alcohol have higher rates of progression from paroxysmal to persistent AF, more AF recurrences following PVI, and potentially higher rates of adverse outcomes, such as thromboembolism. In a cohort of paroxysmal AF patients, 70 of 418 (17%) progressed to persistent AF over 2.7 years. Moderate-heavy alcohol consumption (>14 standard drinks/week) was the strongest risk factor for progression (OR: 3.0, 95% CI: 1.1 to 8.0) [117]. Alcohol was also one of the strongest predictors of recurrent AF (RR: 2.3; 95% CI: 1.2 to 4.4) in patients with a first episode of "idiopathic" AF[118]. In 122 consecutive patients undergoing PVI, 1-year arrhythmia-free survival was 81% in abstainers, 69% in light-moderate drinkers (1 to 14 standard drinks/week in men, 1 to 7 standard drinks/week in women), and 35% in "heavy" drinkers[100].

A longitudinal cohort study of 3,107 AF patients reported a significantly higher risk of thromboembolism or death (HR: 1.33; 95% CI: 1.08 to 1.63) in male heavy drinkers (>27 standard drinks/week). Thromboembolism was significantly higher in women consuming >20 standard drinks/week (HR: 2.78; 95% CI: 1.02 to 7.60), even after adjusting for anticoagulation and CHA_2DS_2-VASc score[139]. These findings contradict

a previous observational study of 2,012 patients with AF, whereby moderate consumption (≥14 standard drinks/week) reduced stroke risk (RR: 0.4; p = 0.04)[140]. The relationship between alcohol and thrombogenesis in the AF population remains poorly understood.

Nevertheless, the long-term cardiovascular benefits of light-moderate alcohol consumption are represented by a U-shaped curve derived from a meta-analysis (Figure 3)[141]. More than 100 nonrandomized studies have demonstrated that light-moderate intake (especially 7 standard drinks/week for women and 14 standard drinks/week for men) may decrease the risk of new-onset coronary artery disease, angina, myocardial infarction, and cardiovascular mortality[142] in nearly one-third of drinkers. The pooled RR for long-term cardiovascular mortality in drinkers was 0.75 (95% CI: 0.68 to 0.81) compared with nondrinkers. Proposed mechanisms include improved lipid profile (increased high-density lipoprotein, apolipoprotein A-I), and reduced platelet aggregation and inflammation (decreased interleukin-5, fibrinogen)[143]. However, these studies predominantly included healthy adults, and should not be extended to those with a history of AF or structural heart disease.

Caffeinated beverages

There is considerable public interest in the impact of coffee, tea, and energy drinks in arrhythmogenesis. The latest AHA/ACC/HRS guidelines for management of patients with atrial fibrillation[144] and ventricular arrhythmias[145] address the role of alcohol as a potential trigger for arrhythmias, however do not mention caffeinated beverages which are equally ubiquitous in Western culture. Coffee is a stimulant and is the most common form of cognitive enhancement[146]. It has been assumed that because of the effects of

caffeine on enhancing the mind and heart rate that it may contribute to arrhythmias. This public perception is often based on anecdotal experience however extends to the medical community with over 80% of U.S physicians recommending abstinence or reduction in caffeine intake for patients with palpitations or documented arrhythmias[147]. Extensive research over the past decade suggests that many widely held beliefs regarding caffeine may not be evidence based.

Caffeine pharmacology

Caffeine is the primary constituent in coffee (1 cup of coffee ~ 95 mg caffeine) and is also found in tea, soft drinks and energy drinks (Table 2). It acts as a methylxanthine alkaloid and central nervous system stimulant. Caffeine's half-life is 5.7 hours, with near 100% bioavailability and maximum concentrations reached within 1 hour of consumption[148]. Caffeine has a range of effects on sympathetic activation, intracellular calcium trafficking, adenosine receptors and is an antioxidant. Caffeine increases the sinus rate via sympathomimetic effects mediated by phosphodiesterase inhibition and rises in cytosolic calcium concentration by blocking calcium reuptake into the sarcoplasmic reticulum[149] (Figure 4). An increase in intracellular calcium has the potential to induce atrial arrhythmias by enhancing automaticity of atrial pacemaker cells and afterdepolarization-induced triggered activity[150]. A dose of 250mg of caffeine (3 cups of coffee) acutely increases norepinephrine and epinephrine by 75% and 207% respectively[151]. At very high doses caffeine may be proarrhythmic. In a murine study, the administration of 15 mg/kg/min of caffeine resulted in sympathetic over-activation with sinus tachycardia and ventricular ectopy culminating in ventricular fibrillation in all. Effects were partially reversed by administration of beta blockers[152].

Proposed antiarrhythmic properties of caffeine may in part be mediated by non-selective inhibition of adenosine A_1 and A_{2A} receptors[153]. Adenosine shortens atrial refractoriness and may trigger atrial fibrillation during acute administration[154]. In addition caffeine, as well as polyphenols found in coffee have antioxidant properties which may bind reactive oxidant species responsible for adverse atrial remodelling and atrial fibrillation[155]. In fact, coffee has a higher antioxidant activity (292-948 min) than black tea (67-277 min) or herbal tea (6-78 min) on a cup-serving basis[156]. As such there are putative mechanisms by which caffeine may enhance or reduce arrhythmogenesis.

Coffee

Experimental and population based studies have sought to determine the impact of caffeine on heart rhythm disorders. In a canine model, an intravenous injection of 1-5 mg/kg of caffeine unexpectedly reduced AF inducibility[157]. In a human study Lemery et al administered 5 mg/kg caffeine 57±13 minutes prior to electrophysiology study in patients with supraventricular tachycardia (SVT), and was unable to demonstrate an effect on atrial or ventricular refractory periods or the inducibility of SVT[158]. Dobmeyer et al also failed to show acute effects on interatrial and intra-atrial conduction in humans[159]. In a community-based cohort of 1,388 participants undergoing 24-hour Holter monitoring, Dixit et al[160] failed to demonstrate any association between higher caffeine intake and atrial or ventricular premature beats (VPBs). Single high-dose caffeine (400mg) did not affect electrocardiographic P-wave duration or P-wave dispersion in healthy volunteers[161]. To date clinical studies have failed to show deleterious effects of caffeine on atrial and ventricular electrophysiologic properties.

Population based studies have consistently demonstrated a reduction in atrial fibrillation with increasing levels of caffeine ingestion. Incident AF events in 57,053 participants followed for 13.5 years were lower in regular coffee drinkers at all levels of consumption (hazard ratio 0.79 for 6 – 7 cups per day[162]. A meta-analysis of six prospective cohort studies with 228,465 participants similarly demonstrated an inverse relationship, with AF incidence decreasing by 6% for every 300 mg/d increment in regular caffeine intake[163]. In a further meta-analysis of 115,993 patients, pooled results demonstrated a significant 13% reduction in incident AF risk[164]. In a population based study of 130,054 people, 3,137(2.4%) were hospitalized for arrhythmias over 17.6 years follow up. Caffeine intake was again inversely related to arrhythmia risk (HR highest quartile vs lowest = 0.6; p = 0.03)[165]. Table 3 summarizes 11 major human studies (360,980 patients, 15,198 AF cases) examining the relationship between caffeinated beverages and atrial arrhythmias. One small case control study with no adjustments for other confounders[166] reported coffee as detrimental, while 3 studies consistently demonstrated a benefit and the remainder no significant interaction.

Nevertheless, one must exercise caution when extrapolating data from healthy volunteers and registries to individual patients. In all long-term observational studies, investigators followed regular long-term coffee drinkers, and caffeine tolerance may explain the lack of association with arrhythmias. Moreover, there may be individual differences in susceptibility to the effects of caffeine on electrophysiological and autonomic factors which trigger arrhythmias in some. Twenty-five percent of patients report coffee as an AF trigger[74], and those with a clear temporal association between coffee intake and documented AF episodes should accordingly be counselled to abstain.

Caffeine does not appear to increase the likelihood of ventricular arrhythmias (VAs). A study of 22 patients with a history of ventricular arrhythmias who underwent electrophysiology study before and 1 hour post coffee (275mg caffeine) ingestion demonstrated no significant difference in inducibility of VAs[167]. In five placebo-controlled trials, caffeine in doses up to 500 mg daily (~6 cups of coffee) did not increase the severity or frequency of VAs[168]. In 50 consecutive patients with a history of malignant ventricular arrhythmias receiving either coffee (containing 200mg of caffeine) or a decaffeinated drink, there was no significant difference observed in ventricular ectopy or tachycardia, despite increases in serum catecholamine levels in the caffeinated group[169]. A meta-analysis of seven human studies found that caffeine consumption had no impact on incidence of ventricular ectopy[170].

Numerous randomized studies have explored the impact of caffeine intake and restriction on ventricular arrhythmias. In a randomized study of 103 post myocardial infarction patients, regular caffeine (average 353 mg/day) resulted in improved heart rate variability, increased parasympathetic activity and no significant arrhythmias compared to controls[171]. More recently, Zuchinali et al performed a double-blinded crossover trial of 51 patients with moderate-to-severe LV dysfunction at high risk of VAs consuming either 500 mg of caffeine or placebo. No significant differences were observed in supraventricular or ventricular ectopy, nor non-sustained ventricular tachycardia during continuous monitoring at rest and with exercise[172]. In a randomized double-blind trial of caffeine restriction utilizing decaffeinated coffee in patients with symptomatic VPBs, no significant changes were seen in palpitations scores or ectopic burden[173]. Moreover, large epidemiological studies suggest that regular caffeine drinkers have lower cardiovascular[174] and all-cause mortality[175], with a potentially attenuated risk of coronary heart disease, heart failure and stroke.

A summary of major human studies examining coffee and ventricular arrhythmias is presented in Table 4. Of 8 studies involving 232,717 patients, 6 demonstrated no association, including 3 well-designed prospective trials[169,170,176]. Only two older studies (a case control and cross-sectional survey) demonstrated an association between coffee and ventricular arrhythmias at very high levels of coffee intake only (>10 cups per day[177] and >9 cups per day[178] respectively).

Tea

There is limited observational data that tea (particularly green tea) may be beneficial. Tea contains less caffeine than coffee and is rich in epigallocatechin gallate (EGCG), a catechin with anti-oxidant and anti-inflammatory properties. In a rabbit model, supplementation with EGCG was associated with prolongation of atrial effective refractory period (AERP) together with a reduction in AF inducibility and atrial fibrosis[179,180]. In a case control of 801 subjects, green tea intake led to a significant reduction in paroxysmal and persistent AF (OR 0.35, 95% CI: 0.25-0.48)[180].

Benefits of tea may also extend to ventricular arrhythmias. In a rat model, pre-treatment with 4 weeks of black tea raised the threshold dose of aconitine for inducing VT ($p<0.001$) and significantly reduced VT and VF duration compared with controls[181]. In humans, moderate tea consumption (up to 14 cups/week) was associated with a significant reduction in ventricular arrhythmias (OR 0.7; 95% CI 0.6-0.9) in 3,882 patients following myocardial infarction (MI)[182]. In a meta-analysis, consumption of 3 cups of tea per day significantly reduced the risk of cardiac death (RR 0.74; 95 % CI: 0.63–0.86)[183].

Energy drinks

Energy drinks (EDs) often contain caffeine at significantly higher concentrations than coffee & tea, which has inhibitory effects on phosphodiesterases, promoting calcium release from intracellular stores and increasing myofilament sensitivity to calcium, mimicking the effects of adrenaline[184]. Pro-arrhythmic effects may be augmented by other energy-boosting substances, such as guarana, sugar, ginseng, yohimbine, and ephedra[185], as well as concurrent intake of alcohol and illicit drugs. Guarana, in particular, has a higher caffeine concentration than coffee and contains theophylline which also has stimulant properties[186].

There have been increasing numbers of case reports relating to the temporal association between EDs and arrhythmias, including young patients without structural heart disease presenting with AF, SVT, ventricular tachycardia, and ventricular fibrillation (VF) shortly after consuming these beverages[187]. Three quarters of patients consuming 2 or more EDs/day reported palpitations within 24 hours, compared to only 12% of occasional consumers ($p<0.001$)[188].

In observational studies, energy drinks have been shown to lower heart rate variability[189] and prolong QTc interval[190]. In patients with congenital long QT syndrome, dangerous QTc prolongation of ≥50ms following ED consumption has been reported[191]. There are isolated case reports of EDs unmasking long QT and Brugada syndromes[192]. ED ingredients other than caffeine are responsible for the prolongation of QTc interval. In a randomized, double-blind crossover study of 18 healthy individuals consuming either ED or caffeinated controls (each containing 320mg

caffeine), significant QTc prolongation (0.44±18.4 ms vs −10.4±14.8 ms; *P*=0.02) was demonstrated in the ED group[193].

Energy drinks may be responsible for a pro-thrombotic state particularly relevant in patients with pre-existing structural heart disease or atrial fibrillation. Studies in healthy volunteers undergoing platelet function testing before and 60 minutes after ED consumption demonstrated a significant increase in platelet aggregation via arachidonic acid-induced activation[194] and endothelial dysfunction[195].

The concerns regarding the potential deleterious effects of energy drinks have been expressed in public policy. The U.S Food and Drug Administration has forced companies to include conventional Nutritional Facts panels with exact caffeine concentrations following the reclassification of EDs as 'beverages' rather than 'dietary supplements' in an attempt to improve consumer safety. The International Society of Sports Nutrition recommend that patients with pre-existing cardiovascular conditions who are taking medications that may be affected by caffeine and other stimulants refrain from use of EDs and warn that more than one ED/day even in healthy individuals may be harmful[196].

Many clinicians continue to counsel patients with atrial or ventricular arrhythmias to avoid all caffeinated beverages, particularly coffee despite an absence of evidence to support this approach. In individual cases where a clear temporal association between arrhythmia episodes and caffeine intake is apparent then avoidance is sensible. Large scale population based studies and randomized controlled trials suggest coffee and tea are safe and may even reduce the incidence of arrhythmias. While there is no clearly

defined caffeine threshold for harm, a regular intake of up to 300 mg/day appears to be safe and may even be protective against heart rhythm disorders.

Dietary factors

Mediterranean Diet

The Mediterranean diet consists predominantly of plant-based foods, rich in extravirgin olive oil with moderate fish intake and low in saturated fat, processed dairy and meat. It is not only beneficial for cardiovascular disease but may positively influence heart rhythm disorders. In the landmark PREDIMED RCT of 6,705 patients, the Mediterranean diet with extravirgin olive oil significantly reduced the risk of incident AF (HR 0.62; 95%CI 0.45-0.85). This diet reduces thromboxane and Nox2 levels, markers of platelet activation and oxidative stress[197], which may also reduce stroke risk in AF patients. In a case control study of 800 patients, the highest quartile of adherence to the Mediterranean diet was associated with the highest rate of spontaneous conversion of AF to sinus rhythm (OR 1.9; 95%CI 1.58-2.81)[198].

In a prospective cohort of 93,122 postmenopausal women followed for 10.5 years, a higher Mediterranean diet score was associated with a significantly lower adjusted risk of SCD (HR 0.67; 95%CI 0.46-0.99)[199]. In a RCT of 605 MI survivors followed for 27 months a Mediterranean diet supplemented by α-linoleic acid (a plant-derived essential omega-3 fatty acid) from canola-based margarine was associated with a significant reduction in mortality (RR 0.30; 95% CI 0.11-0.82)[200].

In the prospective Nurses' Health study of 81,722 women, there was a significant reduction in mortality in those whose diet most closely resembled the Mediterranean

diet especially rich in fruit, vegetables, whole grains, nuts, legumes, fish with low saturated fat and processed / red meat (RR 0.60; 95%CI 0.43-0.84, $p < 0.001$[201]). These benefits may relate to improved autonomic function, with higher vegetable intake potentially an important factor. In a cross-sectional study of twins, Dai et al found that the closer one's diet was to the Mediterranean diet, the greater the heart rate variability[202]. In a study comparing 35 vegetarians with 35 well-matched omnivores, the vegetarian group had significantly higher heart rate variability and improved baroreflex sensitivity[203]. Park et al also demonstrated that a higher intake of green leafy vegetables was associated with favourable changes in heart rate variability with enhanced parasympathetic and reduced sympathetic tone[204].

Nuts

Nuts contain several potentially antiarrhythmic constituents, including α-linolenic acid, magnesium, potassium and antioxidant vitamins. In a cohort of 61,364 Swedish adults followed prospectively for 17 years Larsson et al demonstrated an inverse relationship between nut consumption and risk of incident AF. Those consuming nuts at least 3 times per week had an 18% lower risk of AF (HR 0.82; 95% CI 0.68-0.99)[205]. However other observational studies have not found similar benefits. In a different prospective study of 21,454 participants over 17 years, those consuming nuts ≥ 2 times/week had a 47% lower risk of SCD (multivariate-adjusted RR 0.51; 95% CI 0.28-0.94). The relationship between nut consumption and SCD appeared linear[206]. Walnuts, flaxseed and canola oil contain the highest concentrations of α-linolenic acid. Several studies have examined anti-arrhythmic effects of α-linolenic acid, including direct antiarrhythmic effects on cardiac potassium channels (esp. I_{to}, I_K, I_{ATP}) with subsequent QTc interval shortening, improved autonomic function & heart rate variability and anti-

inflammatory/anti-oxidant effects[207]. Nuts may also be protective against SCD secondary to beneficial effects on cardiovascular disease, owing to abundance of phytochemicals with anti-oxidant, anti-coagulant, anti-inflammatory and lipid-lowering properties[208].

Chocolate

There is some evidence that moderate chocolate intake may reduce the likelihood of developing AF. Cocoa and chocolate are rich in magnesium and flavanols (esp. dark chocolate) which possess anti-inflammatory and anti-oxidant properties that may prevent atrial fibrosis. In a cohort study of 55,502 people with 3,346 incident AF cases, individuals consuming >1 serving per month of any chocolate had a lower incidence of AF, with the greatest benefit derived from 2–6 servings per week (HR 0.80; 95% CI 0.71-0.91)[209]. In a double-blind RCT, flavanol-rich chocolate (FRC) significantly improved endothelial function and reduced platelet adhesion[210], which may have added anticoagulant effects in AF patients. However in the smaller Physicians' Health Study of 18,819 people there was no association between chocolate and incident AF or atrial and ventricular ectopy[211].

Omega-3 poly-unsaturated fatty acids

The potential antiarrhythmic benefits of omega-3 poly-unsaturated fatty acids (PUFAs), abundant in cold water oily fish and fish oil, have been studied extensively. Earlier animal models postulated a beneficial role in stabilization of the myocyte cell membrane with inhibition of fast, voltage-dependent sodium channels and L-type calcium currents. Other proposed mechanisms included inhibition of pro-inflammatory cytokines and indirect anti-oxidant effects[212].

In the primary prevention observational study of 57,053 participants with 3,345 incident cases of AF observed over 14 years, a U-shaped relationship between omega-3 PUFA and incident AF was demonstrated, with the lowest AF risk at 0.63 g/day[213]. Cohort studies relying on dietary questionnaires to determine PUFA consumption have yielded conflicting results. Two large prospective cohort studies that measured circulating levels of PUFA demonstrated a reduction in AF with higher PUFA levels. There was a 35% reduction in AF among the highest vs lowest quartile of PUFA levels[214], with a 9% AF risk reduction for every 1% increase in n-3 PUFA (RR 0.91; 95% CI, 0.85–0.97)[215].

However, when PUFA supplementation was subjected to prospective randomized trials no reduction in AF was observed. The three largest double-blind randomized controlled trials (RCTs) in the secondary prevention cohort, failed to demonstrate a reduction in AF recurrence[216]. Meta-analyses of 8 RCTs in secondary prevention[217] and 6 placebo-controlled RCTs in post-cardiac surgery[218] failed to demonstrate a reduction in AF with PUFA supplementation.

A reduction in sudden death following MI in those receiving chronic PUFA supplementation was demonstrated in the GISSI-Prevenzione trial[219] however subsequent studies failed to support these initial results. A 2012 meta-analysis of 20 RCTs of 68,680 patients failed to demonstrate a lower risk of SCD (RR 0.87; 95% CI 0.75–1.01)[220] with PUFA supplementation. An RCT of fish oil vs placebo in patients with patients with ischemic cardiomyopathy implanted with ICDs demonstrated a trend towards lower rates of VT terminated with anti-tachycardia pacing in the fish oil group (2.8 ± 13.7 vs. 0.5 ± 2.1, respectively; p = 0.077)[221]. Sala-Vila et al also demonstrated

a borderline significant 52% reduction in SCD (*P*=0.069) with a high fish consumption of at least 500 mg/day of PUFA in those at high cardiovascular risk without established coronary disease[222].

Saturated and trans fat

Excessive consumption of fat, in particular saturated and trans fat found in pastries, biscuits, meat (especially deep-fried), cheese and butter has been linked with atrial and ventricular pro-arrhythmia in numerous animal studies. After a 2 month fat-rich diet in mice, there were significant increases in P wave duration, AF inducibility, conduction slowing and inflammatory cytokine expression[223]. In addition there was shortening of atrial ERP and an increase in Kv1.5 and Kv4.2/3 potassium channels[224].

A high-fat diet has similar pro-arrhythmic effects in the ventricle. An 8 week high fat diet in rats was associated with an increase in inducible VAs in the absence of a significant weight gain related to sympathetic hyperinnervation and abnormal gap junction expression[225]. McCully et al also demonstrated sympathetic hyperinnervation and high sympathetic outgrowth in 'obesity-resistant' rats fed a high-fat diet compared with controls[226]. Ashrafi et al demonstrated a significant upregulation of ion channel mRNA, with increased expression of $Ca_V1.2$, HCN4, $K_{ir}2.1$, RYR2, NCX1, SERCA2a, and RYR2 predisposing to VAs by prolonging ventricular action potential duration and increasing intracellular Ca^{2+} transient[227]. Observational studies have also reported a link between obesity and ventricular arrhythmias as well as SCD in young patients[228]. A detailed summary outlining the relationship between obesity and atrial fibrillation in the next section.

Minerals

Magnesium has several important electrophysiological properties including maintenance of cellular membrane sodium gradient by a magnesium-dependent Na^+-K^+-ADPase, intracellular magnesium regulation of voltage-gated calcium current, regulation of rapid inward component of the delayed rectifier potassium channel (I_{Kr}), AV-nodal slowing and suppression of early afterdepolarizations[229]. Magnesium-rich foods include grains, nuts, dark chocolate, green vegetables (esp. spinach) & avocadoes. The Framingham Heart Study (n=3530) demonstrated an association between low serum magnesium and a 50% higher risk of incident AF[230]. This was supported by the ARIC study (n=14,290) with similar associations between serum magnesium and AF. However no association was demonstrated between dietary magnesium and AF risk[231].

Randomized trials of magnesium supplementation in different AF populations have not demonstrated a reduction in AF occurrence. In a double-blind placebo-controlled RCT of 261 patients undergoing electrical cardioversion there was no benefit with adjunctive intravenous magnesium for conversion of AF to sinus rhythm (86.4% vs 86.0%; P=0.94)[232]. Similarly in a RCT of 170 patients treated with long-term oral magnesium vs placebo, there was no significant difference in the maintenance of sinus rhythm. In the post-cardiac surgery setting, results are conflicting. A meta-analysis of five well-designed double-blind RCTs (minimal heterogeneity; I^2=40%; p=0.15) showed that prophylactic magnesium did not prevent AF after cardiac surgery (OR 0.94; p=0.77)[233]. However, when all 35 studies are included, parenteral magnesium appeared to play a role in preventing AF following cardiac surgery (RR 0.69, 95% CI 0.56-0.86, p=0.002)[234]. Nevertheless, in patients with a history of AF, no randomized studies have demonstrated a benefit of dietary magnesium supplementation. In patients at risk of

ventricular arrhythmias, the antiarrhythmic & membrane-stabilizing effects of potassium & magnesium supplementation were confirmed in a randomized double-blind trial of 232 patients with frequent ventricular ectopics. The group receiving oral magnesium & potassium supplementation demonstrated a 17.4% reduction in ventricular ectopy (p=0.001)[235].

Hypertension is an established risk factor for AF, and thus a diet low in sodium (<2.4 g/day), present in many processed and frozen foods may lower blood pressure and, as a result, AF. Hypokalemia, is a recognized precipitant of AF with bananas, artichokes, lentils, avocadoes and spinach high in potassium. An observational study of 255 hypertensive patients, demonstrated an association between sodium and potassium intake determined by urinary sodium and potassium concentrations and ventricular arrhythmias. Those consuming more sodium (r = 0.2; P = 0.001) and less potassium (r = −0.396; P < 0.001) had a significantly higher burden of ventricular ectopy[236]. In a study of 64 normotensive individuals, a week-long high sodium diet resulted in significant QTc interval prolongation (60.3 ± 19.4 vs. 55.6 ± 19.4, p<0.05), which was then reversed by potassium supplementation (42.6 ± 15.1 vs. 47.4 ± 19.0, p<0.05)[183]. Foods high in sodium include smoked, cured, salted and canned meat, fish or poultry, and table salt.

Antioxidant vitamins

Excessive reactive oxygen species (free radicals) may have a role in AF pathogenesis, which may be opposed by antioxidants such as Vitamins C, D and E. While animal studies suggest possible antiarrhythmic properties, high-quality randomized data outside the post-operative setting are lacking. Vitamin C is abundant in citrus fruits, red

pepper, and kale. Following cardiac surgery, where inflammation is predominantly responsible for AF, Vitamin C was associated with a significant reduction in post-operative AF (OR, 0.47; 95% CI, 0.36-0.62)[237] in a meta-analysis of 8 RCTs. The largest RCT in the post cardiac surgery setting of 203 patients comparing 'antioxidant reinforcement' with n-3 polyunsaturated fatty acids (2 g/day) combined with Vitamin C (1 g/d) and Vitamin E (400 IU/d) vs placebo, showed that 'antioxidant reinforcement' dramatically reduced post-operative AF (9.7% vs 32%; $p<0.001$)[238]. In this study, NADPH oxidase p47-phox subunit protein and mRNA expression was significantly higher in patients who developed AF, suggesting oxidative stress plays an important role in pathogenesis of post-operative AF.

However these findings cannot be extrapolated to beyond the perioperative setting where AF mechanisms are different. Unfortunately the data outside the surgical setting is predominantly based on animal & observational studies. In 144 patients undergoing cardioversion, low serum Vitamin E (present in almonds and sunflower seeds) was a multivariate predictor of AF recurrence (HR 0.73; 95% CI, 0.61–0.89)[239]. One observational study, the EPIC-Norfolk study in 10,350 women reported a 13% relative reduction in incident AF for each 20 μmol/l increase in plasma vitamin C[240]. However, like many population-based studies, the investigators did not pre-specify a hypothesis, looked at numerous factors and the possibility of a chance finding and publication bias must be considered.

Vitamin D, present in cooked salmon, canned tuna & cod liver oil has a role in myocardial calcium homeostasis, in addition to anti-oxidant properties and inhibitory effects on the renin-angiotensin-aldosterone system. In isolated rabbit atria, Vitamin D treatment demonstrated fewer & shorter AF episodes and reduced AF inducibility[241]. A

meta-analysis of 8 observational studies including 27,307 patients demonstrated a modest association between Vitamin D deficiency and new AF (OR 1.31, 95%CI 1.06-1.62)[242]. In paroxysmal AF patents undergoing catheter ablation, serum Vitamin D levels were significantly lower than controls, and lower levels were associated with more extensive left atrial fibrosis (OR: 0.72, 95% CI: 0.54-0.97)[243]. In an observational study of 84 patients, Vitamin D deficient patients had significantly more inter-atrial electromechanical delay, which improved with replacement[244].

In summary, while the Mediterranean diet has the strongest evidence for benefit with respect to atrial and ventricular arrhythmias, there are emerging data that regular intake of nuts, coffee, tea, antioxidant vitamins and even chocolate may have some antiarrhythmic effects. Numerous studies have failed to demonstrate consistent anti-arrhythmic benefits with respect to omega-3 PUFA and magnesium supplementation. Saturated fat, added salt and excessive alcohol and energy drink consumption are likely to be harmful in those with rhythm disorders. A Food Pyramid (Figure 5) for patients with rhythm disorders has been used to summarise these findings, with a caveat that the Level of evidence for these recommendations is low-to-moderate, based primarily on non-randomized data. Moreover, any dietary effects on the rhythm must be counterbalanced by the potential effects on cardiovascular disease. Table 5 summarizes the evidence base for dietary effects on atrial and ventricular arrhythmias as well as sudden cardiac death (SCD) using the GRADE approach[245] to assess the evidence quality. Findings in Table 5 are juxtaposed with the latest major society-recommendations[246,247] with respect to cardiovascular disease. Potential mechanisms for antiarrhythmic benefits of different food groups in the AF population are further summarized in Figure 6.

Obesity

The combination of a Western diet and an increasingly sedentary lifestyle has led to an obesity epidemic. Obesity is one of the leading population-attributable risk factors for AF, thought to be responsible for 1 in 5 new AF cases in population-based studies[248]. In a meta-analysis of 16 cohort studies and 587,372, AF developed in 6.3% of obese patients (BMI > 30 kg/m^2) as opposed to 3.1% of non-obese patients (RR 1.51; 95% CI 1.35-1.68, p<0.001)[249]. In a separate meta-analysis of 51 studies encompassing incident, post-operative and post-ablation AF, Wong et al found incrementally higher AF risk for each 5 unit increase in BMI[250].

The pathogenic mechanisms by which obesity causes AF are multi-factorial. In addition to elevated atrial pressures from increased left ventricular hypertrophy, systemic and pulmonary hypertension, obesity-related adverse left atrial remodelling due to direct atrial toxicity has been widely described[251], culminating in LA dilatation and fibrosis. In a study of 30 obese sheep, Abed et al reported elevated serum levels of adipocytokines and pro-inflammatory cytokines (transforming growth factor ß and platelet derived growth factor) in combination with LA dilatation, fibrosis and inflammatory infiltration[252]. Induction of obesity over a 36 week period in sheep was associated with marked atrial remodelling, with LA dilatation, higher LA pressures, increased voltage and conduction heterogeneity and lower voltages in the posterior LA wall coupled with higher AF susceptibility[253]. In a study of 63 consecutive AF patients, those with a body mass index (BMI) > 30 kg/m^2 had impaired echocardiographic LA strain, larger LA volumes and higher pressures with shorter effective refractory periods increasing susceptibility to AF compared to those with normal BMI (≤25 kg/m^2)[254]. Higher volumes of biologically-active epicardial and pericardial adipose tissue in obese

patients, are thought to be an important putative mechanism. These fat deposits secrete growth / remodelling factors and inflammatory cytokines which have local effects on surrounding LA tissue. In a recent human study of 26 patients undergoing detailed invasive electroanatomical mapping together with cardiac MRI, electrical changes in substrate observed in obese patients (low voltage zones, conduction slowing, greater complex fractionation) were more commonly seen adjacent to epicardial fat deposits, further highlighting the critical link between epicardial fat and atrial substrate[255].

It is not surprising that these obesity-related changes in atrial substrate have considerable implications for prognosis in the AF population. In an observational study of 701 patients undergoing catheter ablation, AF recurrence rates were significantly higher in overweight and obese patients compared to controls (51% and 57% respectively vs 39.9%; p=0.007)[256]. Moreover, in those undergoing AF ablation, morbid obesity (BMI > 40) is associated with a 5% higher risk of peri-procedural complications for each 1 unit increase in BMI[257]. Pleasingly, the adverse sequelae associated with obesity in the AF population appear to be reversible with lifestyle modification. In a randomized trial of 150 patients randomized to either goal-directed weight loss or control, weight loss (14.3kg vs 3.6kg) was associated with dramatic benefits. These included reduction in AF burden and severity, left atrial size and left ventricular septal thickness[258]. Long-term maintenance of weight loss in the LEGACY study of 355 patients followed for 4 years, weight loss ≥10% was associated with a 6-fold increase in AF-free survival[259] with 88% of patients 'reversing' their AF phenotype from persistent to paroxysmal (or absence of AF)[260]. Importantly, the current paradigm for AF management now comprises four key pillars: prevention of thromboembolism, rate control, rhythm control, and most recently risk factor management.

Obstructive sleep apnoea

Linked closely with obesity and other AF risk factors is obstructive sleep apnoea (OSA) – an increasingly recognized AF risk factor. Prevalence of moderate-to-severe OSA has been estimated to be as high as 49.7% in men and 23.4% in some population-based studies[261]. In a meta-analysis of 9 studies including 19,837 patients, OSA doubled the risk of developing AF (OR 2.12; 9+5% CI 1.85 – 2.44)[262], and there was a progressive increase in AF risk as Apnoea Hypopnoea Index (AHI) increased (HR 1.31; 95% CI 1.14 - 1.50)[263]. Even an AHI > 5 (mild OSA) has been associated with a higher risk of AF in population-based cohort studies[130]. In a study of 90 patients with paroxysmal or persistent AF, 'high' frequency of AF episodes was observed in those with sleep-disordered breathing (75 vs 43%, p=0.01) and with more severe OSA (mean AHI 28±23 vs 17±15; p=0.02) [264]. In a meta-analysis of 7 observational studies encompassing 4,572 patients undergoing catheter ablation for AF, OSA was associated with a higher risk of arrhythmia recurrence (OR 1.70; 95% CI 1.40-2.06, $I^2 = 0$) [265].

There are several proposed mechanisms explaining the relationship between OSA and AF. In an analysis of 2,816 polysomnograms from the Sleep Heart Health Study, AF was much more likely to occur within 90 seconds of a respiratory disturbance (OR 17.5; 95% CI 5.3 – 58.4). These events may trigger AF by a number of mechanisms, including hypoxia, hyperpnoea, nocturnal arousal, atrial stretch, and large swings in intrathoracic pressure triggering baroreflexes[266]. In a sheep model, hypercapnoea initially prolonged AERP and increased conduction time, however AF vulnerability increased on return to eucapnoea at which point AERP had normalized but conduction time was still prolonged[267]. Left ventricular diastolic dysfunction causing elevated atrial pressure and stretch may also be a factor, and continuous positive airway pressure (CPAP) treatment for a 12-week period has been shown to improve diastolic

parameters[268]. Autonomic imbalance may also be a factor. In a canine model, simulation of OSA increased sympathetic and parasympathetic activity in the first 30 minutes of hypoxia, followed by further increases in parasympathetic activity (HF) and a drop in the ratio of low to high frequency hear rate variability indices which shortened atrial ERP and increased AF inducibility over the next 30 minutes ($p<0.05$)[269]. Other studies have demonstrated sympathetic stimulation and increased intracellular calcium loading following tracheal obstruction, thereby shortening action potential duration and increasing susceptibility to AF[270]. Hypoxaemia may trigger inflammation and elevated inflammatory markers, including CRP, IL-6 and Tumour Necrosis Factor (TNF-α) are more commonly seen in patients with OSA[271-274]. Atrial inflammation may in part explain the changes in atrial substrate observed in patients with OSA compared with controls.

In a study of 40 AF patients with OSA undergoing invasive electroanatomical mapping, OSA was significantly associated with biatrial conduction velocity slowing, lower voltage, more complex fractionation and longer corrected sinus node recovery time than non-OSA controls [275]. In a study of 86 PAF patients Anter et al reported similar abnormalities in bi-atrial electrical remodelling and also identified a higher prevalence of non-pulmonary vein triggers (41.8% vs 11.6%, $p=0.003$) in those with OSA[276]. In a murine model of OSA, Iwasaki et al demonstrated a 71% increase in histological atrial fibrosis, 58% downregulation in connexin-43 in conjunction with atrial conduction slowing and heightened AF inducibility compared to non-OSA rats[277]. Ramos et al found significant structural changes in rats with OSA, including 43% higher atrial interstitial collagen fraction as well as higher Angiotensin-I Converting Enzyme and IL-6 expression in both atria[278].

Treatment of OSA with CPAP therapy appears to improve clinical outcomes in the AF population. In a recent meta-analysis of 7 cohort studies and 3 randomized trials of 1,217 patients undergoing AF ablation, treatment with CPAP was associated with a marked reduction in AF recurrence rates (24.9% vs 42.5%; RR 0.60; 95% CI 0.51-0.70) and reduction in left atrial size (LA diameter mean difference -6.28; 95% CI -7.00 to -5.56)[279]. In AF patients managed medically without ablation, a meta-analysis of 7 cohort studies found that CPAP was associated with a significant reduction in AF recurrence (RR 0.58, 95% CI 0.36 – 0.96)[280]. In an analysis of 10,132 participants in the ORBIT-AF registry, CPAP therapy was also associated with a lower risk of AF progression to more permanent forms of AF[281].

Hypertension

Hypertension is highly prevalent in the general community, and hence is the most common co-morbidity in AF patients. In a large cohort of 34,221 community dwelling adults, both systolic and diastolic blood pressure were associated with progressively higher rates of incident AF ($p<0.01$ for trend) in multivariate analysis (HR 2.74 for systolic BP > 160 mmHg, HR 2.15 for diastolic BP > 95 mmHg)[282]. In a separate cohort study, even upper normal BP (systolic BP 128 – 138 mmHg) was associated with an increased risk of AF (HR 1.50; 95% CI 1.10 – 2.03)[283]. Nevertheless, uncontrolled hypertension appears to be an important factor in risk of AF recurrence following ablation. In a cohort study of 531 patients AF ablation followed up for 19±8 months, AF recurrence rates were significantly higher in those with poorly controlled hypertension (40.6%, $p=0.003$), with no significant difference between those with treated hypertension (28.1%) no history of hypertension (25.7%)[284].

Left ventricular hypertrophy (LVH) from long-standing hypertension leads to development of diastolic dysfunction, with elevated left atrial filling pressures and LA dilatation. In a meta-analysis of 10 studies with 27,141 patients, presence of LVH significantly increased the odds of developing an atrial / supraventricular tachyarrhythmia (OR 3.39, 95% CI 1.57 – 7.31)[285]. Moreover, a number of important systemic processes are activated in essential hypertension that are important in development of left atrial substrate and AF pathogenesis. These include the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system[286], which interact closely with each other: RAAS activation increases sympathetic flow and sympathetic activation increases juxtaglomerular cell renin synthesis. Small observational studies suggest there may be benefits of renal sympathetic denervation in those with hypertension and AF, including improved global atrial conduction velocities and reduction in fractionation[287], reduction in left atrial size and atrial ectopic burden[288], and lower AF recurrence rates when performed together with pulmonary vein isolation (41% vs 63%, p=0.01)[289]. Untreated hypertension results in atrial electrical and structural remodelling. Lau et al induced hypertension induced in 21 sheep and demonstrated progressive biatrial hypertrophy and increased atrial inflammation after 5 weeks, and conduction slowing and interstitial fibrosis after 10 weeks. In a study of 101 patients with PAF undergoing ablation, any history of hypertension was associated with increased LA wall thickness, however those with poor BP control (BP > 140/90) developed LA dilatation and had higher AF recurrence rates (HR 2.35, p = 0.033)[290].

There has been considerable interest in the role of 'upstream' anti-hypertensive therapy, particular ACE inhibitors, angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) in preventing and treating AF. In a meta-analysis of 14

randomized trials and 92,817 patients, ARBs (RR 0.78, 95% CI 0.66 – 0.92) but less so ACEIs (RR 0.79, 95% CI 0.65 – 1.00, p=0.05) reduced the risk of incident AF[291]. Animal studies of the MRA eplerenone have shown promise in preventing atrial remodelling. Atria from eplerenone treated sheep demonstrate less collagen-III expression, interstitial fibrosis and myocyte hypertrophy[292]. Eplerenone-treated mice demonstrated reduced expression of pro-fibrotic molecules induced by TGF-β1 with inhibition of atrial fibrosis[293]. In a meta-analysis of 14 prospective studies, treatment with MRAs (spironolactone or eplerenone) reduced new onset AF (OR 0.52, 95% CI 0.37-0.74) and recurrent AF (OR 0.37, 95% CI 0.24-0.57)[294]. In the secondary prevention of AF, a meta-analysis of 15 randomized trials of ACEIs / ARBs demonstrated efficacy in reducing risk of further AF episodes (OR 0.50, 95% CI 0.37 – 0.69)[295], highlighting the role of the renin-angiotensin-aldosterone system in AF pathogenesis. It is unclear whether aggressive blood pressure management improves AF outcomes beyond standard control. Parkash et al undertook a randomised trial of 184 patients undergoing catheter ablation, whereby aggressive blood pressure control (BP target <120/80) was not associated with reduced AF recurrence risk (61.4% vs 61.2%, p=0.76) compared to standard therapy (BP target <140/90)[296].

Rhythm control versus rate control in AF

While rate or rhythm control remain important aspects of AF management, a meta-analysis of eight prospective randomized controlled trials comparing the two strategies have not been able to consistently demonstrate significant differences in hard clinical outcomes such as all-cause mortality (RR: 0.95; CI: 0.86-1.05) or ischaemic stroke (RR: 0.89; CI: 0.52-1.53)[297]. However, the largest trial examining this (AFFIRM) was prior to the emergence of catheter ablation (CA) and rhythm control was maintained

using antiarrhythmic drugs (AADs) which have lower efficacy than CA and higher systemic and pro-arrhythmic toxicity. In fact, only 1% of patients in the rhythm control arm underwent invasive rhythm control therapy and 63% had tried amiodarone. While all-cause mortality was similar in both groups, the presence of sinus rhythm (SR) was associated with a 46% reduction in mortality[298]. Moreover, consistent across several randomised trials is the observation that a greater time spent in SR is associated with improved New York Heart Association (NYHA) functional class and quality of life[299].

Some argue that the results from RCTs comparing rate and rhythm control should perhaps not be interpreted as lack of benefit of SR, but rather the limitations in antiarrhythmic drug efficacy and their associated adverse effects. In pooled comparisons with placebo, the three most common AADs amiodarone (OR 0.22, 95% CI 0.16-0.29), flecainide (OR 0.31, 95% CI 0.19–0.49) and sotalol (OR 0.40, 95% CI 0.31–0.52) had superior efficacy in preventing AF recurrence. However, there was a trend towards higher mortality with sotalol (OR 3.44, 95% CI 1.02-11.59) owing largely to long-QTc related ventricular pro-arrhythmia and serious adverse events with amiodarone (OR 2.91, 95% CI 1.66-5.11) which has a range of systemic toxicities affecting the thyroid, liver and lungs[300].

Recent large-scale randomized trials comparing AADs with CA have demonstrated superior efficacy of CA at maintaining SR. In the CABANA trial of 2,204 patients randomised 1:1 to CA or pharmacology therapy and followed for 5 years, time to AF recurrence was significantly lower with CA (HR 0.53, 95% CI 0.46-0.61, $p < 0.0001$)[301]. Amiodarone was also inferior to CA at maintain SR in the AATAC multicentre RCT of 203 patients with HR (HR 2.5; 95% CI 1.5-4.3; $P<0.001$)[302]. Moreover in the sicker heart failure cohort with higher 'event rates', recent randomized

trials demonstrate survival benefits associated with CA compared to medical therapy. This was observed in both CASTLE-AF (363 patients, 37.8 months follow-up, 13.4% vs 25% all cause mortality; HR 0.53; 95% CI 0.32-0.86) and AATAC (8% vs 18%; p=0.037) studies. In a meta-analysis of 6 RCTs comparing CA with pharmacological therapy in the heart failure population (775 patients total), CA significantly improved LVEF by 5.9%, quality of life (mean difference -9.0, 95% CI -15.6 – -2.5), and functional capacity (difference 25.8; 95% CI 5.46-46.2), while lowering heart failure readmissions (OR 0.5; 95% CI 0.32-0.78) and all-cause mortality (OR 0.46; 95%CI 0.29-0.73)[303].

Current 'rhythm control' now incorporates a combination of risk factor management, antiarrhythmic medications, cardioversion and catheter ablation – tailored to the individual. The latest evidence appears to support a rhythm control strategy for improvement of quality of life in patients with AF-related symptoms and for prognostic reasons in those with concurrent heart failure. There appears to be a paucity of long-term follow-up data to guide clinicians in managing younger patients (<65 years old) who are asymptomatic, and re-assessment after a trial of rhythm control is often pursued[304].

Cardioversion

Restoration of sinus rhythm in persistent AF is most commonly achieved through external electrical (direct current) cardioversion (CV). It relies on application of energy using two electrodes which depolarize the atrial myocardium including conduction tissue involved in re-entry simultaneously, with a subsequent period of refractoriness that further interrupts re-entry and enables the sinus pacemaker to take over[305]. Success

rates in published series for AF range from 70 – 95%[306,307]. Patient factors associated with higher rates of CV failure include obesity[308], epicardial fat thickness, left atrial dilatation[309], left ventricular dysfunction[310], prolonged AF duration[311], female gender[312], diabetes and absence of beta blockade[313]. These factors likely relate to more advanced atrial substrate and higher transthoracic impedance (TTI). Transthoracic impedance, namely impedance presented by the patient during cardioversion is a critical factor influencing CV success. In an analysis of 703 patients receiving 1,055 shocks, Sadek et al demonstrated that each 10-Ω increase in TTI was associated with progressively higher first and last shock failure rates ($p<0.001$ for both)[314]. Measures that may lower TTI include appropriate electrode size (8 – 12cm diameter), salt-containing gels for coupling with skin, administering shocks at end-expiration[315], and firm paddle pressure[316,317,318].

Numerous studies have examined the most appropriate technique for successful external cardioversion in AF. Biphasic waveforms require less energy for the same efficacy[319] and are associated with greater improvements in myocardial function in studies looking at ventricular arrhythmias[319]. In a meta-analysis of 23 trials including 3,046 patients, biphasic waveforms had significantly higher 1st shock efficacy (OR 3.2; 95% CI 2.2-4.7) and subsequent shock efficacy (OR 2.4; 95% CI 1.5-3.9)[320]. Higher starting energy in AF appears to be associated with improved success without an increase in adverse events or procedure duration. In a randomized trial of 380 patients, first shock success was higher in those randomised to 200J versus 100J (71% vs 48%; $p<0.01$)[321]. Electrode type may influence shock success. In a randomised trial of 201 patients, hand-held paddles were more successful than adhesive patch electrodes for persistent AF (96% vs 88%; $p=0.04$)[322], which the

authors attribute to reduction in TTI and improved contact between electrode and skin.

Electrode position appears to be less important in determining success. In a meta-analysis of 10 trials and 1281 AF patients, an anterior-posterior (AP) electrode position had similar success rates to an anterior-apical (AA) position (RR 1.02, 95% CI 0.96-1.09), with AP position perhaps being more efficacious in the setting of left atrial dilatation (LA diameter≤45 mm) and lone AF in subgroup analysis[323]. In a study of 15 predominantly obese patients with failed external cardioversion, Mehidrad et al demonstrated that repositioning electrode pads to better encompass both atria restored SR in 8 patients, with 6 patients successfully reverting with internal cardioversion[324]. More recently, adoption of the Ottawa-AF cardioversion protocol in 500 consecutive patients, which involved a starting energy of 200J biphasic in the AP position, followed by switching patches to AA position, then addition of manual pressure to patch electrodes and finally escalation to 360J resulted in an improvement in success rates (99.2 vs 91.8%, p <0.001)[325]. In a canine study, only 4% of the transthoracic current delivered reached the heart, with 96% shunted to either the thoracic cage or lungs[326]. These studies suggest that there is scope to improve cardioversion techniques before a diagnosis of 'permanent AF' is accepted.

Pre-treatment with anti-arrhythmics has been shown to improve cardioversion efficacy. In a randomized study of 92 patients, pre-treatment with amiodarone was associated with greater shock efficacy 88% vs 65% (p<0.05). Rates of spontaneous conversion to sinus rhythm were also higher (25% vs 3%, p<0.005)[327]. In a randomized study of 100 PeAF patients, pre-treatment with Class III anti-arrhythmic ibutilide also significantly increased the likelihood of CV success (100% vs 72%;

p<0.001). Pharmacological cardioversion is significantly less effective than electrical cardioversion for persistent AF, but is often used in paroxysmal AF. In a systematic review of 403 studies, intravenous flecainide (number needed to treat NNT 1.8) was significantly more efficacious than amiodarone, ibutilide, procainamide, propafenone, and sotalol (NNT 4.3)[328]. An oral 'pill-in-the-pocket' approach using class Ic antiarrhythmics flecainide or propafenone was successful at terminating AF episodes in 139/165 (84%) PAF patients and was associated with a significant reduction in monthly hospitalisations (1.6 vs 15.0, p<0.001).

Catheter Ablation

Pulmonary vein isolation

The cornerstone of AF ablation remains pulmonary vein isolation (PVI), namely creating permanent lesions (most commonly using either radiofrequency energy or cryoballoon) around the pulmonary veins to disconnect the focal PV triggers from a 'vulnerable' atrial substrate. In the paroxysmal AF population with less extensive substrate, a recent meta-analysis of 13 studies including 1,774 patients demonstrated 'cure' rates (primarily defined as freedom from >30 seconds of AF) of 78% (95%CI 76 – 86%) at 12 months and 59% (56 – 64%) at 62 months from PVI alone (as a single procedure)[329]. Recurrences are usually attributed to PV reconnection, electrical & structural atrial remodelling and non-pulmonary vein triggers. There has been a significant evolution in both technology and understanding over the past two decades that has led to improvements in safety and efficacy. In a randomized trial of 80 PAF patients, Oral et al demonstrated that wide antral circumferential ablation was superior to segmental ostial isolation (6-month arrhythmia free survival 88% vs 67%, p=0.02). This was attributed to elimination of AF anchor points / drivers at the PV-LA antrum

and posterior wall, autonomic denervation, ablation at the arrhythmogenic vein of Marshall and reduction in LA area available for wavelet propagation[330]. This approach also minimises risk of pulmonary vein stenosis. Once PVI is achieved, current guidelines suggest confirmation of bidirectional block after a 30-minute waiting period to exclude re-connection[331]. This may occur due to non-transmural lesion formation, resolution or delayed recovery following initial injury[332]. Administration of adenosine to assess for dormant PV conduction has also been shown in a large meta-analysis of 7 studies and 3,049 patients to reduce subsequent AF recurrence rates (33% vs 37%; RR 1.11, 95% CI 1.01, 1.22)[333].

Ensuring effective transmural lesion formation has been the subject of much research. For delivery of radiofrequency energy (RF), irrigated contact force-sensing catheters (CF) are now the standard of care at many centres. In a randomised study of 300 PAF patients, those patients for whom optimal CF (>90% of ablation with >10g of force) was achieved had a lower AF recurrence rate (24.1% vs 41.9%, p=0.018)[334]. In a recent meta-analysis of 34 studies, Virk et al demonstrated a small overall improvement in freedom from AF (RR 1.10, 95% CI 1.02 – 1.18) with significant reductions in procedure duration (15 min, 95% CI 7 – 24 min) and fluoroscopy time (5.7 min, 95% CI 2.5 – 8.92 min) without any difference in complication rates[335]. The cryoballoon (CB) has gained popularity at many international centres for PVI. In a randomised trial of 762 PAF patients, there was no significant difference in AF recurrence rates (34.6% CB, 35.9% RF, HR 0.96; 95%CI 0.76 – 1.22) with no differences observed in overall complication rates (although phrenic nerve palsy was more commonly observed in the CB group – 2.7% vs 0%)[336]. A higher rate of phrenic nerve palsy using CB was the only difference observed in a meta-analysis of 8 RCTs comparing RF and CB, with no significant differences in AF-free survival, procedure duration and fluoroscopy time[337].

Given the presence of more extensive atrial remodelling in persistent AF (PeAF), earlier studies have looked at adjunctive strategies beyond PVI alone, primarily targeting atrial substrate. In a pooled meta-analysis of studies from 2008 – 2011, 12-month single-procedure success rates for AF ablation were estimated at 51.9%[338]. While an analysis of adjunctive ablation techniques is provided below, it is important to note that the largest randomized trial (STAR AF-II) of 589 patients comparing PVI alone with substrate modification found no improvement in arrhythmia-free survival with adjunctive ablation beyond PVI (59% PVI alone vs 49% PVI with complex fractionated electrogram ablation vs 46% PVI with linear ablation, p=0.15). This landmark study highlighted the potential for pro-arrhythmia with additional lesion sets, further emphasising the importance of measures that may reduce substrate beyond ablation, such as risk factor modification[339].

Substrate modification

START AF-II highlighted the potential for pro-arrhythmia with adjunctive LA ablation, despite earlier studies proposing that linear lesions (inc. LA roof line, LA floor line, mitral isthmus) could successfully modify atrial substrate in many. Importantly, in a series of 180 consecutive PeAF patients, Knecht et al reported that those undergoing linear ablation without complete block achieved had significantly higher incidences of gap-related macro-reentrant atrial tachycardias[340]. In a randomised trial of 66 patients, additional linear ablation was associated with an identical arrhythmia-free survival, however fluoroscopy time was longer (91 vs 73 min, p=0.04)[341]. Of 155 atrial tachycardias occurring after initial AF ablation, 115/120 (96%) left atrial macro-reentrant atrial tachycardias were due to gaps in previous ablation lines[342].

The findings of STAR AF -II in combination with a large meta-analysis (13 studies, 1415 patients) demonstrating no incremental benefit with complex fractionated atrial electrogram (CFAE) ablation as an adjunct to PVI (OR 0.80; 95% CI 0.46 – 1.38 for PAF, OR 1.01; 95% CI 0.63 – 1.64 for PeAF)[343] have led to a tempering in enthusiasm for this technique. In addition to consider inter-observer variability for identifying CFAEs[344], there is still ongoing debate about their underlying pathophysiology. Proposed hypotheses include multiple wavelets propagating through regions of conduction slowing[345], fractionation of mother rotors approaching regions with heterogeneity in refractoriness and conduction velocity[346] or hyperactivity of autonomic ganglia[347] . Moreover, the occasional presence of CFAEs in regions of healthy bystander tissue even in the PAF population during an AF episode and the observation that CFAE distribution throughout the left atrium is highly variable in sinus rhythm, coronary sinus pacing and AF (in the same patient) highlights the challenges faced with this approach[348].

With improved lesion delivery owing to improvements in ablation technology and greater operator experience, attention has shifted to the role of posterior wall isolation (PWI), not specifically assessed in STAR AF-II. The posterior LA wall shares a common embryological origin with the PVs[349] with clinical data suggesting a clustering of rotors and AF drivers as well as autonomic ganglionated plexi in this location[350,351]. Despite the technical requirement to achieve roof and floor line block to achieve isolation, a recent meta-analysis of 5 observational and 594 patients demonstrated lower arrhythmia recurrence rates when PWI was added to PVI (RR 0.81, 95% CI 0.68 – 0.92)

without additional complications[352]. Randomized studies are currently underway to more definitively assess the efficacy of this approach in PeAF.

Non-pulmonary vein triggers

While the role of the left atrial appendage (LAA) in thrombus formation is well-established, its role as a trigger for AF has only recently been described. In a series of 987 patients presenting for repeat AF ablation (71% PeAF), Di Biase et al reported that the LAA was responsible for 27% of arrhythmias[353]. A subsequent randomised study of 173 patients by the same group demonstrated that empiric LAA isolation in those with long-standing PeAF was associated with lower arrhythmia recurrence rates at 12 months (28% vs 56%, p=0.001)[354]. A meta-analysis of 7 studies reported lower arrhythmia recurrence rates with empiric LAA isolation (OR 0.38; 95% CI 0.16 – 0.90) without an increase in thromboembolic risk, although LAA occlusion was employed in the majority of patients[355]. A recent observational study reported a significant increase in risk of stroke or TIA associated with LAA isolation (HR 23.6, p<0.001) and in light of this concern, there remains a need for further randomised studies before this technique is universally adopted[356].

An individualised approach using standardised induction protocols (high dose isoproterenol and cardioversion of induced AF) to assess, map and ablate for non-pulmonary vein foci is used at many centres as an adjunct to PVI in both PAF and PeAF. In a randomised trial of 500 PAF patients comparing elimination of non-PV triggers with stepwise substrate modification, arrhythmia recurrences at 26 months follow-up were lower when non-PV triggers were ablated (32.2% vs 43.8%, p=0.01)[357]. Mohanty et al showed that targeting non-PV triggers was associated with lower

recurrence rates, even in PAF patients with significant LA scarring. When combined with PVI, this strategy was superior to PVI alone and PVI with scar homogenization at achieving long-term AF-free survival (85% vs 62% vs 62%, $p<0.01$) in an observational study of 177 patients[358]. In a series of 381 consecutive patients with long-standing PeAF (<2 years duration), addition of non-PV trigger ablation to PVI with posterior wall isolation resulted in lower arrhythmia recurrence rates (86.0% vs 69.2%, $p<0.001$)[358].

Ganglionated plexi (GP) containing both sympathetic and parasympathetic neurons are located on the epicardial surface of the heart, closely associated with the PVs and adjacent atrial myocardium[359]. Given the role of the autonomic nervous system in AF pathogenesis, some postulate that ablation of these GP is important in achieving freedom from AF (particularly 'vagal AF'). In a canine model, Lemola et al demonstrated that ablation of autonomic ganglia overlying the PV ostia, rather than electrical isolation of all 4 PVs suppressed the shortening in ERP associated with cervical vagal stimulation[360]. Lemery et al found that these regions can be identified at the time of ablation using high frequency stimulation, with sites frequently located along the PVI ablation ring(s)[361]. In an analysis of 297 patients with PAF, Pappone et al reported that 'complete vagal denervation' was associated with freedom from recurrent AF ($p=0.0002$)[362]. While a meta-analysis of 4 RCTs including 718 patients comparing PVI with PVI + GP ablation showed lower AF recurrence rates with PVI + GP ablation in PAF (60.0 vs 75.8, $p=0.001$)[363], there remain limitations to this approach. Identifying the appropriate sites to ablate remains a major challenge, as eliciting a vagal response to high frequency stimulation is relatively insensitive. Moreover, a recent randomized trial of 340 patients examining GP ablation at time of thorascopic AF surgery demonstrated significantly higher rates of sinus node

dysfunction and pacemaker implantation without any differences in AF recurrence rates with this adjunctive approach[364].

At present, atrial fibrillation does not have a "cure" and it is apparent that no single approach will guarantee rhythm control. Preventing AF recurrence requires both an individualised and multi-faceted approach that incorporates risk factor management, pharmacological therapy, cardioversion or catheter ablation. This PhD will explore novel rhythm control strategies – in particular, we examine alcohol consumption as a potentially modifiable AF risk factor (Chapters 2 – 5) and assess novel strategies to improve cardioversion success (Chapters 6 – 7) as well as improve efficacy and safety of catheter ablation (Chapters 8 – 10).

Tables and Figures

Table 1: Major Studies Examining the Impact of Alcohol Consumption on Atrial Arrhythmias

Study	Cases / patients	Male (%)	Age (y)	Follow -up (y)	Study design	AF/AFL ascertainment	Key findings
Rich et al[107] 1985	58/ 116	76	18-70	N/A	Case control	Medical records	AF patients were more likely to be heavy drinkers (>32 SDs/week) than controls (OR 3.70; 95% CI 1.70-8.05). Alcohol withdrawal was more common in those with alcohol-related AF.
Koskinen et al[365] 1987	100/ 200	82	21-64	N/A	Case control	ECG	AF patients were significantly more likely to have consumed alcohol within 2 days of AF onset than controls, with 'idiopathic AF' patients have the highest mean daily alcohol intake.
Cohen et al[366] 1988	28/ 3966	-	-	3-9	Retrospective cohort	Medical records	Heavy drinkers (42+ SDs/week) had a higher risk of developing AF (RR 2.3) and AFL (RR 3.0) than those consuming <7 SDs/week ($p<0.05$ for both).
Krahn et al[367] 1995	299/ 3983	100	18-62	44	Prospective cohort	ECG, medical report	'Alcoholism' (quantity unspecified) increased the risk of developing AF (RR 2.07; 95% CI 1.38 – 3.10)
Wilhelmsen et al[166] 2001	754/ 7495	100	47-55	25.2	Prospective cohort	Registry	'Alcohol abuse' (quantity specified) increased the risk of future AF hospitalization (OR 1.21; 95% CI 1.02-1.42)
Ruigomez et al[368] 2002	1035/ 6035	47	40-89	N/A	Nested case control	ECG, Holter, echocardiogram	Only heavy alcohol consumption increased risk of developing chronic AF (adjusted RR 2.4; 95% CI 1.4–4.1 for those consuming > 28 SDs/week)
Djousse et al[115] 2004	1055/ 4672	52	28-62	>50	Prospective cohort	ECG, medical records	Moderate alcohol intake < 21 SDs/week did not increase risk of AF/AFL, but heavier intake > 21 SDs/week increased risk by 34% (multivariate-adjusted RR 1.34; 95% CI 1.01 – 1.78)
Frost et al[369] 2004	556/ 47949	47	50-64	5.7	Prospective cohort	Registry	Increased risk of AF & AFL (HR 1.44; 95% CI 1.04-2.01) in men with moderate (~12 SDs/week) consumption.
Mukamal et al[116] 2005	1071/ 16415	46	26-75	16.3	Prospective cohort	ECG, registry, medical records	No increased AF/AFL risk with moderate consumption in men & women, heavy consumption in men (35+ SDs/wk) increased AF/AFL risk (HR 1.45;95% CI 1.02 – 2.04).
Ruigomez et al[117] 2005	70/ 418	49	40-89	2.7	Prospective observational	ECG, medical records	In patients with paroxysmal AF, alcohol consumption >14 SDs/week increased risk of progression to 'chronic AF' three-fold.
Planas et al[118] 2006	32/ 115	64	59±14	2.5	Prospective observational	ECG	In patients with prior AF, light-moderate alcohol consumption (<23 SDs/week in men, <12 SDs/week in women) significantly predicted subsequent recurrence (50% vs 24%; $p = 0.01$)
Mukamal et al[370] 2007	1232/ 5609	50	65+	9.1	Prospective cohort	ECG, registry, medical records	Habitual alcohol consumption (at all levels) in adults > 65 years did not increase risk of AF or death.
Conen et al[371] 2008	653/ 34715	0	49-60	12.4	Prospective cohort	ECG, medical records	Compared with non-drinkers, consumption ≥ 14 SDs/week in women increased AF risk (HR 1.49; 95% CI 1.05-2.11)
Marcus et al[87] 2008	74/ 260	75	59±12	N/A	Case control	Medical records	AF/AFL pts were more likely to be daily drinkers (27% vs 14%). After multivariate analysis, only AFL pts ≤ 60 years old were more likely to be daily drinkers (OR 17; 95% CI 1.6-192)
Liang et al[372] 2012	2093/ 30433	70	55+	4.7	Review of 2 anti-hypertensive RCTs	ECG, questionnaire	Light-moderate drinking (1-14 SDs/week for women; 1-21 SDs/week for men) results in higher incident AF risk in patients with cardiovascular disease (HR 1.14; 95% CI 1.04-1.26)
Larsson et al[76] 2014	6019/ 68848	62	45-83	12	Prospective cohort	Registry	Dose-dependent increase in risk of AF/AFL (RR 1.12, 1.18, 1.43 for 7-14 SDs/week, 15-21 SDs/week, >21 SDs/week respectively). Only wine & liquor (not beer) increased risk.
Qiao et al[100] 2015	40/ 122	74	55±9	1.8	Prospective observational	ECG, 3-monthly 7-day Holter	Alcohol intake post PVI predicted recurrent AF (recurrence rate 64.9% women >7 SDs/wk & men > 14 SDs/wk ; 30.8% for women 1-7 SDs /wk & men 1-14 SDs/wk ; 18.7% abstainers)

Abbreviations: AF = atrial fibrillation; AFL = atrial flutter; CI = confidence interval; ECG = electrocardiography; HR = hazard ratio; OR = odds ratio; PVI = pulmonary vein isolation; RCT = randomized controlled trial; RR = relative risk.

Table 2: Caffeine content of common commercially available caffeinated beverages

Beverage	Amount of caffeine (g)	Volume (mL)
Can of Coca Cola	32 mg	375 mL
Cup of Lipton green tea	35 mg	150 mL
Cup of Lipton black tea	55 mg	150 mL
Starbucks Café Latte – short	75 mg	236 mL
Espresso shot	106 mg	25 mL
Starbucks Café Latte – grande	150 mg	473 mL
Monster Energy drink	160 mg	473 mL
Wired X344 Energy drink	344 mg	473 mL
Fixx Energy drink	500 mg	591 mL

Table 3: Major studies examining impact of caffeinated beverages on atrial arrhythmias

Study	Cases / participants	% Male	Mean age (yrs)	Follow-up (yrs)	Study design	Key findings
Mostofsky[162] et al 2016	3415/57053	48	56.7±4.4	13.5	Population-based cohort study	• Higher coffee intake was associated with lower rate of incident AF (linear trend; p=0.02). • Compared to non-drinkers, OR 0.86 (95% CI 0.71–1.04) for 2–3 cups per day & OR 0.79 (95% CI 0.64–0.98) for 6–7 cups per day
Dixit[160] et al 2016	1388	47	71.9±5.0	N/A	Observational study (24-hr Holter)	• No correlation between atrial ectopics/hr and coffee (p=0.28) or tea intake (p=0.57). • No correlation between SVT runs and coffee (p=0.22) or tea intake (p=0.90).
Liu[180] et al 2016	401/801	56	63±1.2	-	Case control	• Green tea was protective against incident AF (multivariate OR 0.349, 95%CI 0.25-0.48) in a dose-dependent manner (p for trend = 0.001).
Larsson[373] et al 2015	7041/76475	55	61.5	12	Population-based cohort study	• No association between coffee consumption and risk of incident AF at all levels of consumption (multivariate RR 0.98 for 2-3 cups/d, RR 1.01 for ≥5 cups/d; p=0.64 for trend)
Klatsky[165] et al 2011	1512/130054	44	-	17.6	Retrospective population cohort	• Higher coffee intake was associated with lower rates of hospitalization for AF (HR 0.81; 95%CI 0.69-0.96 for ≥4 cups/d) and SVT (HR 0.63; 95%CI 0.41-0.98 for ≥4 cups/d)
Shen[374] et al 2011	296/4526	44	62±10	4	Prospective cohort	• No correlation between caffeine intake & risk of incident AF (for quartiles of intake Q1 HR 0.84; 95%CI 0.62-1.15 vs Q4 HR 0.98; 95%CI 0.7-1.39, p for trend = 0.84)
Conen[375] et al 2010	945/33638	0	53	14.4	Prospective cohort	• U-shaped relationship with lowest risk of incident AF in third quintile of intake with median 285 mg/day (HR 0.78; 95%CI 0.64-0.95; p for quadratic trend = 0.03) • None of the individual caffeine components (tea, coffee, cola, chocolate) were associated with incident AF.
Mukamal[376] et al 2009	163/1369	70	59.8	6.9-9.9	Prospective cohort	• In patients with previous myocardial infarction, coffee-drinkers in the 4 higher categories of intake had ~30% lower risk of developing AF (HR for ≥1 cups/d 0.65; 95% CI 0.40-1.05)
Frost[377] et al 2006	555/47949	47	56	5.7	Prospective cohort	• When compared to the lowest quintile, there was no association between caffeine intake & incident AF (lowest risk was 3rd quintile ~ 584 mg/day; HR 0.85 (95% CI 0.65 - 1.12).
Mattioli[378] et al 2005	116/232	74	54±7	-	Case control	• High coffee intake > 3 cups/day was associated with a lower rate of spontaneous cardioversion from AF (OR 0.3;95% CI 0.11-0.49;p=0.008).
Wilhelmsen[166] et al 2001	754/7495	100	47±55	25.2	Population-based cohort study	• Consumption of ≥5 cups/d was not associated with a higher risk of incident AF (OR 1.09; 95% CI 0.87, 1.38), although moderate consumption reached borderline significance (OR 1.24; 95% CI 1.00-1.54)

Abbreviations: AF – Atrial fibrillation; SVT – supraventricular tachycardia; HR – Hazard ratio; RR – Relative risk; OR – odds ratio; CI – Confidence Interval; N/A – not applicable.

Table 4: Major studies examining impact of caffeinated beverages on ventricular arrhythmias

Study	Cases / participants	% Male	Age (yrs)	Follow-up (yrs)	Study design	Key findings
Dixit[160] et al 2016	1388	47	71.9±5.0	N/A	Observational study (24-hr Holter)	• No correlation between VPBs/hr and coffee (p=0.86) or tea intake (p=0.32). • No correlation between VT runs and coffee (p=0.57) or tea intake (p=0.13).
Zuchinali[170] et al 2016	51	74	60.6±10.9	N/A	Randomized controlled trial	• Acute caffeine ingestion (500mg over 5 hours) vs placebo did not increase VPBs (185 vs 239; p=0.47) or non-sustained VT in patients with moderate-severe LV dysfunction.
Bertoia[379] et al 2013	239/93676	0	63.5±7.4	11	Prospective cohort study	• No association between total caffeine (p for trend = 0.52), coffee (p for trend = 0.84), caffeinated tea (p for trend = 0.30) and risk of SCD
Klatsky[165] et al 2011	323/130054	44	-	17.6	Retrospective population cohort	• Higher coffee intake was not associated with higher risk of VT (HR 1.05; 95%CI 0.98-1.12), with a trend towards lower risk of ventricular fibrillation / SCD (HR 0.88; 95%CI 0.78-1.00)
de Vreede-Swagemakers[177] et al 1999	117	84	65±7	N/A	Case control	• Only very heavy coffee consumption (>10 cups per day) was associated with a higher risk of SCD (OR 55.7; 95%CI 6.4-483), however 1-9 cups per day was not a significant predictor.
Graboys[169] et al 1989	50	76	61	N/A	Crossover trial	• In patients with structural heart disease, hourly VPB burden and non-sustained VT did not differ between the caffeine & placebo trials (despite elevated catecholamine levels in the caffeine arm)
Myers[176] et al 1987	70	79	58±2	N/A	Randomized double-blind trial	• In patients 7 days post myocardial infarction, continuous Holter monitoring did not show a difference in % patients having VPBs, nor VPB burden after 300 mg caffeine vs placebo (despite rises in blood pressure & catecholamine levels in the caffeine group).
Prineas[178] et al 1980	7311	100	37–57	N/A	Cross-sectional survey	• Compared to consumption $\leq$ 2 drinks per day, coffee ($t = 2.90$, $p < 0.005$) and tea ($t = 3.78$, $p < 0.001$) were positively associated with the presence of VPBs, with >9 cups of coffee associated with twice the risk of VPBs in healthy patients.

Abbreviations: VPB – Ventricular Premature Beats; VT – Ventricular tachycardia; SCD – sudden cardiac death; HR – Hazard ratio; RR – Relative risk; OR – odds ratio; CI – Confidence Interval; N/A – not applicable.

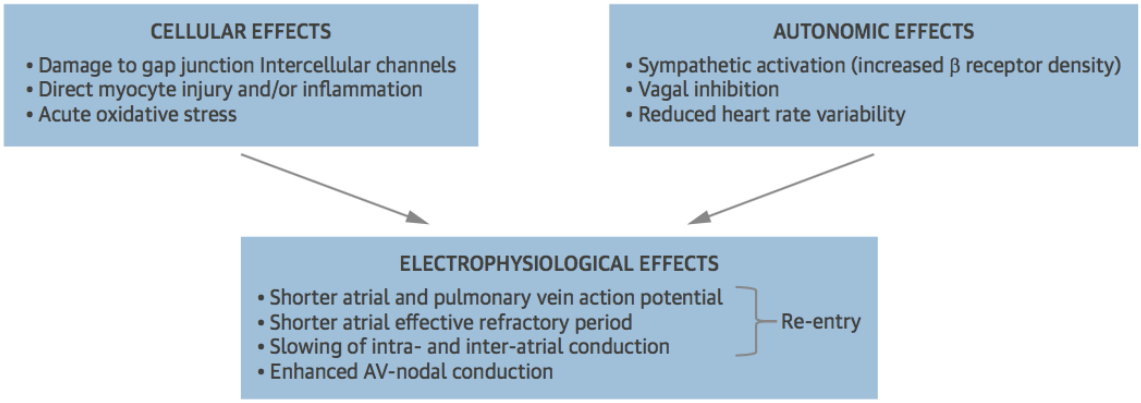
Table 5: Dietary and nutritional recommendations for prevention and management of rhythm disorders

Factor	*Effect on Arrhythmias*	*Effect on Cardiovascular Disease*
Omega-3 PUFAs	Conflicting data regarding benefit for primary & secondary AF prevention (++). Strongest evidence for reducing SCD in high-risk groups (++).	Fish intake protective against heart disease and stroke, with higher intake associated with lower rates of heart failure, stroke, sudden death and AMI. Weekly intake of 2 – 3 serves of fish (inc. oily fish) recommended. No evidence for benefit or harm for additional supplementation with omega-3 PUFA.
Mediterranean Diet	May be beneficial in primary and secondary prevention of atrial and ventricular arrhythmias (+++).	Associated with small, but significant reductions in blood pressure. No effect on lipid profile.
Nuts	Potentially protective against sudden cardiac death (++).	Higher dietary intake of α-linoleic acid (esp. walnuts, soybean oils, flaxseed, canola) beneficial for primary prevention of CVD.
Chocolate	Small amounts may be beneficial in primary prevention of AF (+) No data in the secondary prevention cohort.	Processed milk chocolate and dark chocolate are often high in saturated fat which raises LDL cholesterol and should be restricted to once a week. Consuming high polyphenol cocoa improves endothelial function and reduces blood pressure & platelet reactivity.
Saturated / Trans-fat	High intake may be pro-arrhythmic independent of effects on weight & should be minimized in those at risk of arrhythmias (++).	Minimization of saturated fat is recommended to reduce LDL cholesterol and overall cardiovascular risk.
Magnesium	No data to support routine supplementation for AF (+++). Recommend magnesium-rich diet for patients at high risk of ventricular arrhythmias and/or QTc prolongation (+++).	No evidence for harm with dietary magnesium supplementation. Recent studies suggestive of a potential benefit in prevention of coronary artery disease.
Sodium	A high salt diet should be avoided in all patients, but particularly those at risk of ventricular arrhythmias or QTc prolongation (+).	Strong evidence for blood-pressure lowering effects of a low sodium diet and possible reduction of cardiovascular events. High dietary sodium increases risk of stroke and cardiovascular disease.
Potassium	A diet replete in potassium will prevent hypokalemia, a common precipitant of both atrial and ventricular arrhythmias (++).	Weak observational data that higher dietary potassium may lower stroke risk, but no benefit seen for other cardiovascular outcomes.
Antioxidant Vitamins	A diet replete in Vitamins C and D may prevent new onset AF (++) in high-risk patients. Isolated studies suggest Vitamins C, D and E may have a role in secondary prevention of AF and ventricular arrhythmias (++).	While weak associations between Vitamin D deficiency and CVD exist, there is no data to support vitamin supplementation for CVD prevention. High doses of Vitamin E supplements may increase CVD risk.

Rating of certainty of evidence (GRADE) approach: High (++++): research provides a very good indication of the likely effect; Moderate (+++): good indication of the likely effect; Low (++): some indication of likely effect although high likelihood it may be different; Very Low (+): unreliable indication of the likely effect with very high likelihood that true effect will be substrantially different being very high.

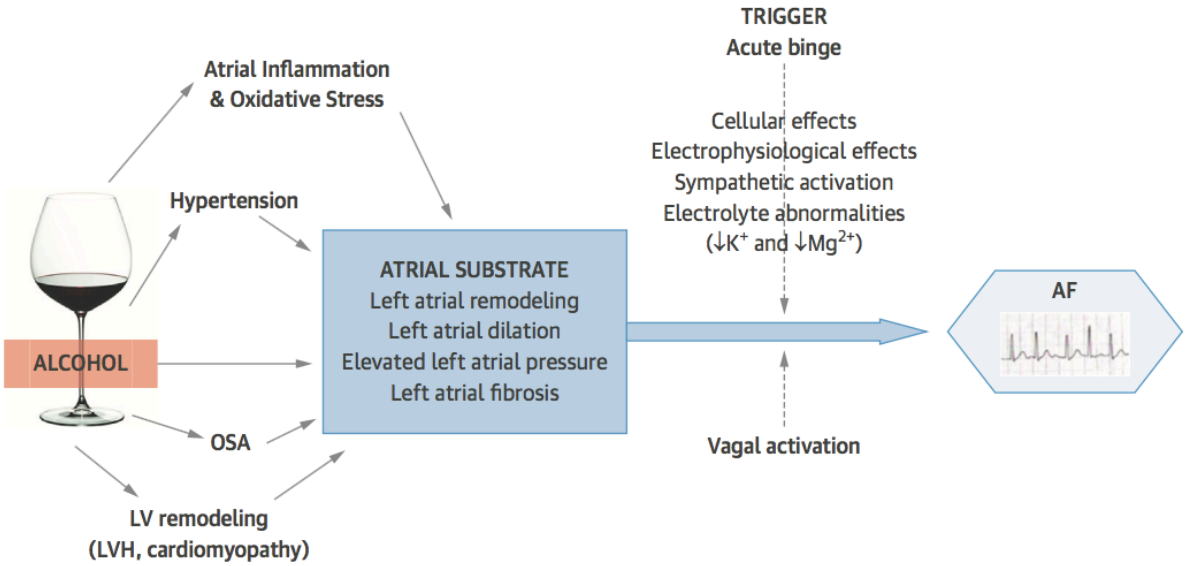
Abbreviations: PUFA: polyunsaturated fatty acids, AF: atrial fibrillation, CVD: cardiovascular disease, LDL: low density lipoprotein, AMI: acute myocardial infarction, SCD: sudden cardiac death

Figure 1: Potential Mechanisms for Acute Alcohol Consumption as a Trigger for AF



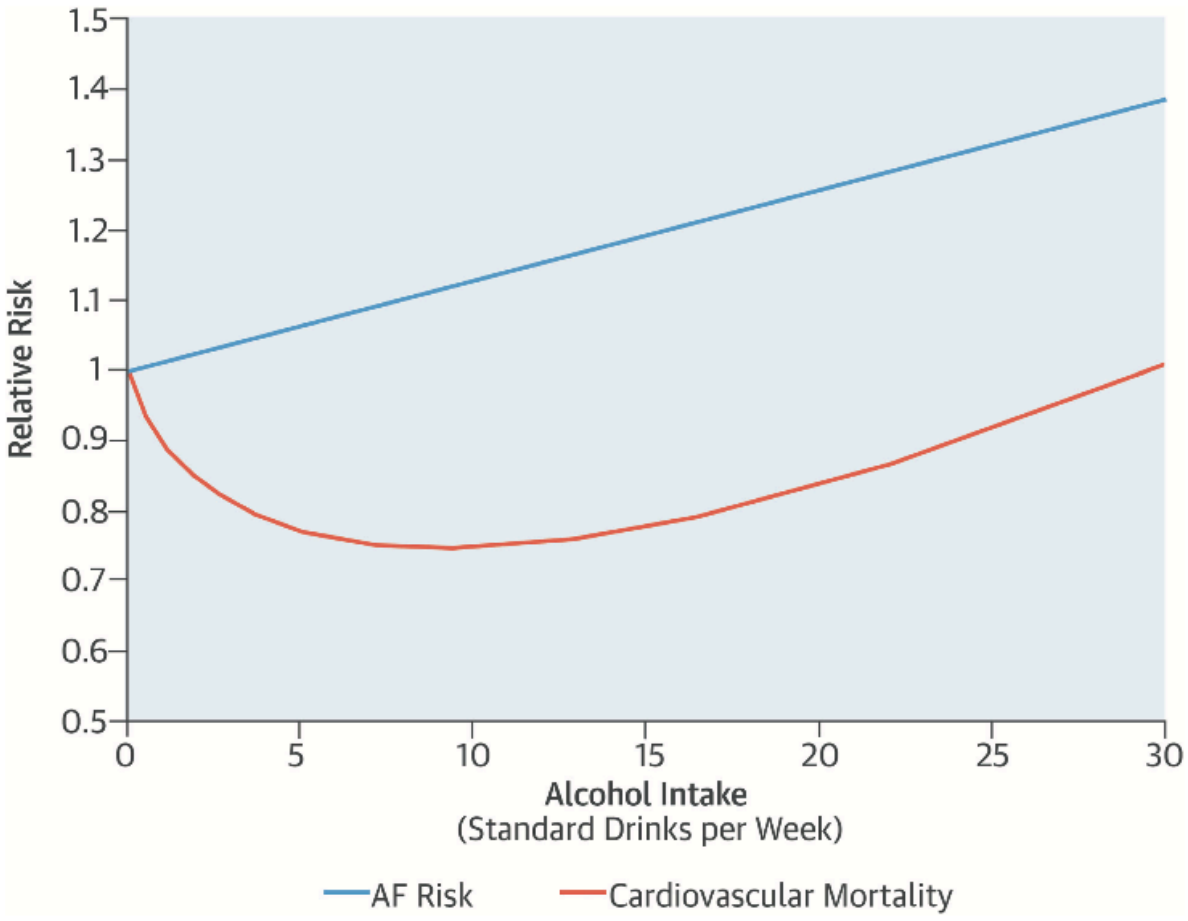
Acute alcohol consumption has direct cellular effects on atrial myocytes and influences autonomic function, forming the electrophysiological milieu for onset and maintenance of AF. AF = atrial fibrillation; AV = atrioventricular.

Figure 2: Habitual Alcohol Consumption and AF: Pathophysiology



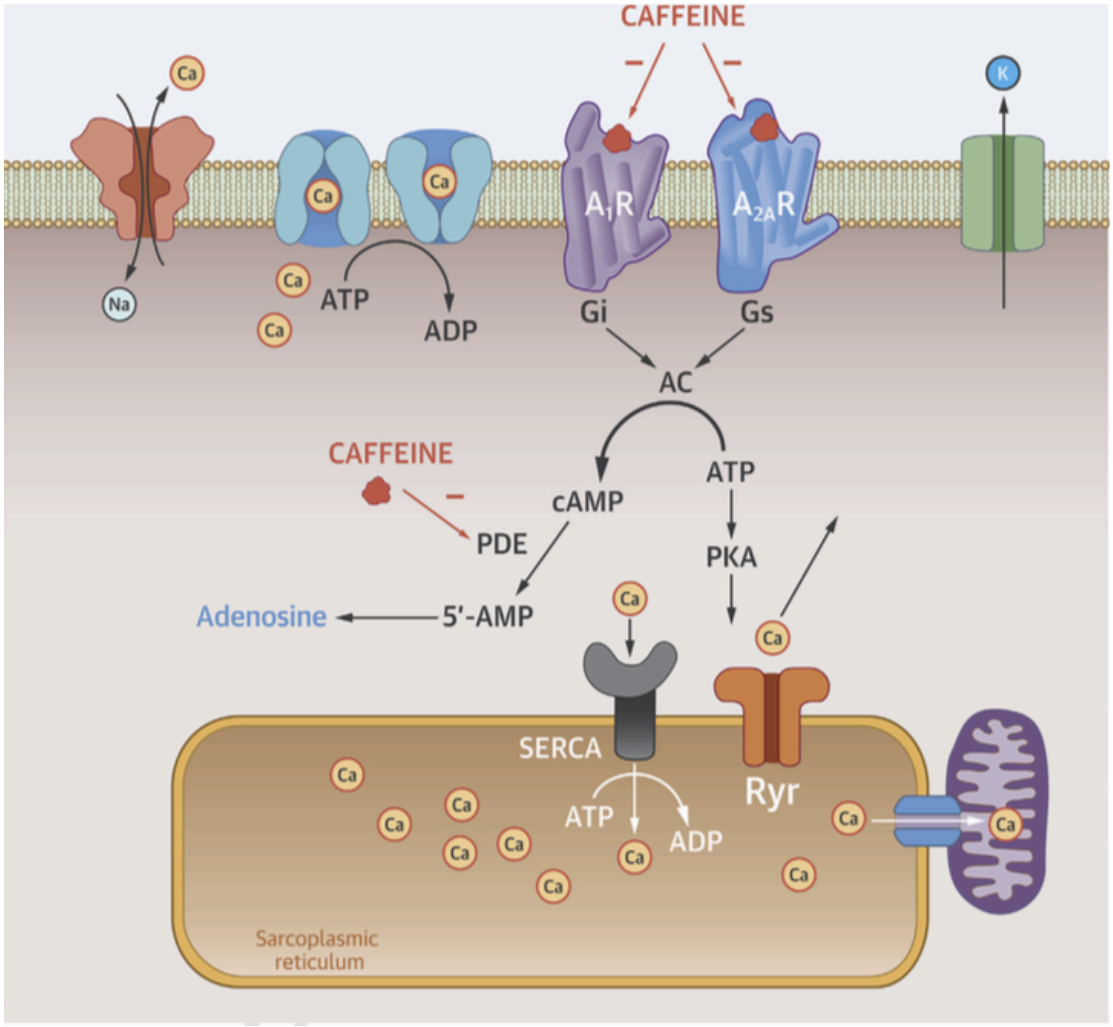
Habitual alcohol consumption predisposes to AF by direct effects on left atrial substrate and interaction with other AF risk factors, including hypertension, obstructive sleep apnea and left ventricular dysfunction. AF = atrial fibrillation; HRV = heart rate variability; K^+ = potassium; LV = left ventricle; LVH = left ventricular hypertrophy; Mg^{2+} = magnesium; OSA = obstructive sleep apnoea.

Figure 3: Habitual Alcohol Consumption: Long-term Risk of AF and Cardiovascular Mortality



Legend: Estimated long-term risk of developing AF and cardiovascular mortality in the general population with no prior history of AF on the basis of alcohol consumption in large meta-analyses. AF risk (blue line; average follow-up 12 years) adapted from Larsson et al[76] and cardiovascular mortality (red line; average follow-up 11 ± 6 years) adapted from Ronksley et al[141], with permission. AF = atrial fibrillation.

Figure 4: Cellular effects of caffeine



Abbreviations: Ca^{2+}: calcium; AR: adenosine receptor; AC: adenylate cyclase; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PDE: cyclic nucleotide phosphodiesterase; PKA: protein kinase A

Figure 5: Food Pyramid: Dietary recommendations for patients with rhythm disorders

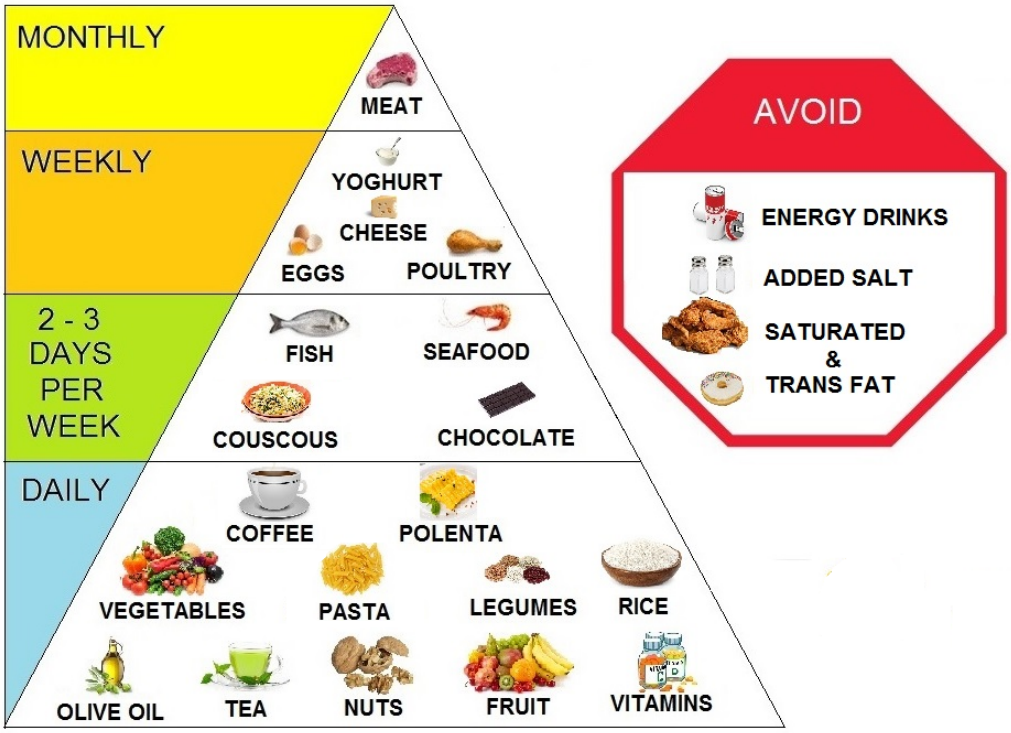
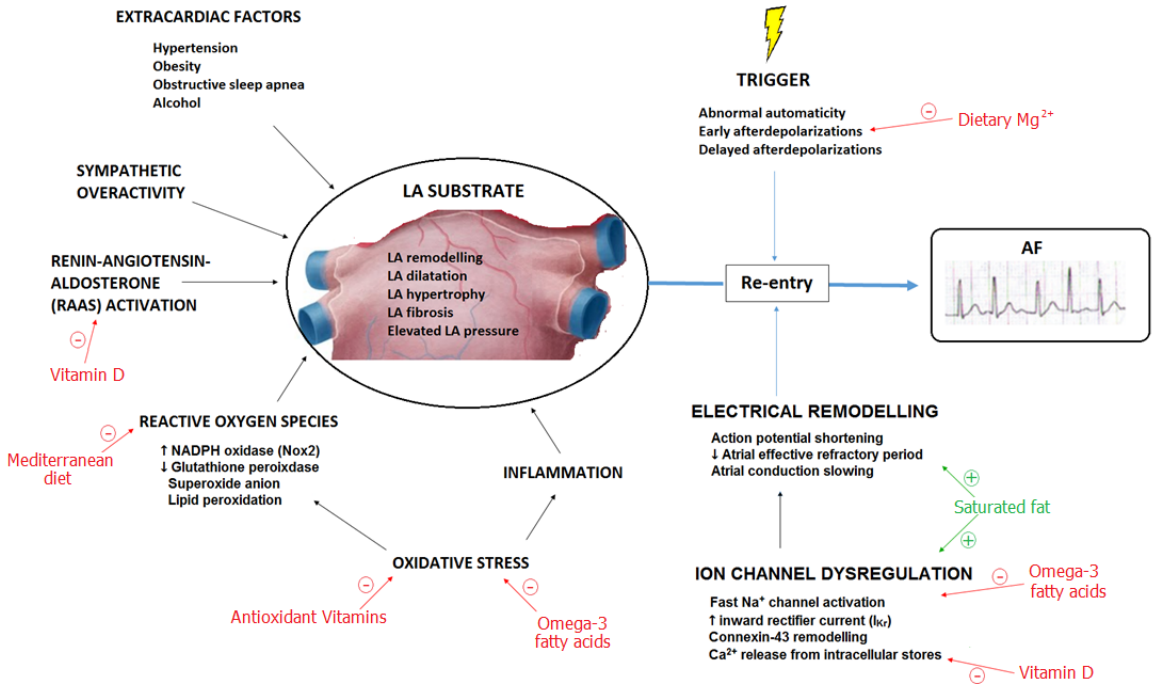


Figure 6: Impact of dietary factors on atrial fibrillation pathogenesis



Abbreviations: Mg^{2+}: magnesium; Ca^{2+}: calcium; Na^{+}: sodium; NADPH: nicotinamide adenine dinucleotide phosphate-oxidase

Chapter 2: Moderate alcohol consumption is associated with atrial electrical and structural changes – insights from high density left atrial electroanatomical mapping

Introduction

Excessive alcohol consumption has emerged as a potentially modifiable risk factor for atrial fibrillation (AF)[380]. Both binge drinking and habitual alcohol consumption have been implicated in electrical and structural changes involving the left atrium (LA). Acute electrophysiological effects of excessive alcohol include shortening of atrial refractoriness and slowing of intra-atrial conduction[83]. More recently, binge drinking has been found to activate c-Jun N-terminal kinase (JNK) leading to sarcoplasmic reticulum calcium mishandling[381] and cause contractile dysfunction related to oxidative stress, mitochondrial damage and cardiac steatosis[382], thereby increasing susceptibility to 'Holiday Heart Syndrome'.

Observational studies suggest that regular alcohol consumption, even at moderate levels may increase AF risk. A meta-analysis of seven studies involving 859,420 patients and 12,554 AF cases demonstrated an 8% increase in incident AF for each additional daily standard drink[76]. While alcoholic cardiomyopathy is well described in the ventricle for those consuming >80 grams/day for >10 years[143], the thinner walled atrium may be more susceptible to toxicity at lower doses. Compared to abstainers, those consuming even 1 drink/day have been reported to have a higher prevalence of atrial 'low voltage zones'[100]. There is a dose-related relationship between regular alcohol consumption and LA enlargement, with each additional 10g associated with a 0.16 mm increase in LA size[383].

Despite the association between regular alcohol intake and AF, detailed human electrophysiological studies describing the nature of alcohol-related atrial remodelling are lacking. We aimed to determine the impact of regular alcohol consumption on electrical and structural changes in the LA in patients with a history of AF using high-density electroanatomic mapping prior to AF ablation.

Methods

Patient population

This multi-center cross-sectional study was conducted from March 2016 to May 2018 at two hospitals. We recruited 75 patients with paroxysmal or persistent atrial fibrillation willing to consent to high-density LA mapping during initial AF ablation using the CARTO® (Biosense Webster) three-dimensional electroanatomical mapping system. The study was approved by Alfred Health and Melbourne Health Human Research Ethics Committees and all patients provided written informed consent.

Patients self-reported their average alcohol consumption in standard drinks (SDs/wk) per week (1 SD ~ 12g alcohol) over the preceding 12 months. Those consuming 2 – 7 drinks per week were considered mild drinkers, while those consuming 8 – 21 drinks per week were defined as moderate drinkers. We aimed to recruit 25 consecutive patients from each of the three drinking categories (none, mild, moderate).

Exclusion criteria included: (1) Occasional drinkers, as defined as >1 consecutive month of non-drinking during the preceding 12 months; (2) Binge drinkers, as defined by ≥5 standard drinks in a 2-hour sitting > monthly (3) Significant structural heart disease (LVEF < 40% or previous myocardial infarction); (4) Permanent AF; (5) Alcoholic liver cirrhosis; (6) Severe renal impairment; (7) Prior AF ablation.

Electroanatomical mapping protocol

Anti-arrhythmic medications were stopped at least 5 half-lives prior to AF ablation. After induction of general anesthesia, a transesophageal echocardiogram (TEE) probe was inserted to exclude LA thrombus and guide transseptal puncture. All catheters were inserted via the right femoral vein. Diagnostic catheters included a decapolar coronary sinus (CS) catheter and a quadripolar His-bundle/right ventricular catheter. Double transeptal puncture was performed using a BRK™ needle via 8F and 8.5F long SL1 sheaths (St. Jude Medical) and heparin was administered for a target ACT ~350 seconds.

A steerable circular 20-pole multipolar pulmonary vein (PV) mapping catheter (LASSO® with 2-5-2 mm electrode spacing) and a contact-force irrigated ablation catheter were then introduced into the left atrium (LA). Patients presenting in AF

underwent external cardioversion to restore sinus rhythm. After a 5 minute waiting period, voltage and activation maps were then collected using the Confidense™ algorithm during stable pacing from the distal coronary sinus (CSd) at 600msec cycle length. Patients with recurrent AF during the waiting period did not undergo research mapping and proceeded to pulmonary vein isolation. A target of 1,000 points evenly distributed across all LA regions with a mapping fill threshold of 10mm and a density acquisition filter of 1mm^2 was set and assisted with the Confidense™ software module (Figure 1A). Average point density was derived from the final point count and atrial surface area obtained from the CARTO module.

Several measures were undertaken to ensure tissue contact and accurate electrogram annotation during continuous mapping. These included use of the Tissue Proximity indicator (an impedance-based algorithm), application of an internal point filter to within 5mm of the chamber surface geometry and correlation of geometry with the contact force enabled ablation catheter.

Atrial voltage and conduction analysis

Analysis of each electrogram was performed offline. The LA was divided into anterior, posterior, septal, lateral including LA appendage, superior and inferior regions, excluding the pulmonary veins and mitral annulus. Although we collected data using the Confidense™ algorithm, all acquired points were also manually reviewed. Only points demonstrating characteristics of near-field signals were included. These signals demonstrated at least 2 sharp peaks and were consistent with anatomically adjacent signals in terms of signal quality, electrogram timing and proximity to the geometric shell. Points not fulfilling these criteria were excluded. Incorrectly collected points including artefact, atrial ectopics and far-field ventricular electrograms were deleted. Complex fractionated electrograms (CFAEs) were defined as having at least three deflections >50ms duration, while double potentials were defined as having two discrete deflections separated by an isoelectric interval. Both of these groupings were considered ‘complex signals’, representing atrial substrate. Following manual annotation of each point, maps were exported for further signal processing (MATLAB 9.1, Mathworks, MA, USA).

Bipolar voltage was defined using the peak-peak electrogram voltage. Low voltage was defined as bipolar voltage <0.5mV, however to ensure this was not an internal point it was only annotated if contiguous low voltage points were collected within a 5mm radius. Isochronal activation maps were created using the Confidense^{TM} algorithm (CARTO) during CSd pacing at 600ms. Local activation time (LAT) was annotated as per the algorithm based on bipolar and unipolar signals using the maximum negative slope (-dV/dT), compared unipolar signals with simultaneous bipolar activity in order to exclude potential far-field signals. A scar filter of 0.05mV was set and these areas were not assigned an LAT.

Mean regional conduction velocity (CV) was calculated by MATLAB using the polynomial surface method. In brief, this method assigns a fitting 'window' per region with a minimum of 20 points required. Each region is assigned subsets of coordinates in space (x,y,z) and activation time. These are fitted to a smooth polynomial surface in three-dimensional space, using a standard least squares algorithm (Figure 1B), which provides robustness against outliers. The gradient is then calculated from the fit and used to calculate velocity components, with final velocities at each point calculated from the weighted average of velocity components from every fit including that point[384-387]. Mean regional conduction velocities from the six regions were derived from the average of velocities at each point in the region, while global conduction velocity was taken as the average of the six mean regional conduction velocities. Investigators were blinded to drinking status during EGM analysis.

Follow-up

Follow-up following AF ablation included 12-lead ECG at onset of symptoms and during outpatient review at 3 months post discharge and 6 monthly thereafter. Holter monitors were performed at 6 and 12 months or for symptoms. Recurrent AF was defined as any atrial tachyarrhythmia lasting ≥ 30 seconds.

Statistical analysis

Continuous data are summarized as mean ± standard deviation or median, where appropriate. The Shapiro-Wilk test was performed to confirm normal distribution of data and a student t-test then performed for comparisons of two variables, with an ANOVA test used for three variables. Mann-Whitney U test was used for continuous

variables where normal distribution was not present. Clinical characteristics expressed as categorical variables were compared using a chi-square or Fisher exact test. Multiple linear regression was performed to identify multivariate predictors of low voltage, conduction velocity and complex signals, with each of these used as a continuous dependent variable. Clinical parameters with a univariate p value <0.15 were included in multivariate analysis. Logistic regression was used to identify electrophysiologic predictors of post-ablation recurrence. Statistical Package for the Social Sciences for Windows (SPSS version 23, IBM) was used to perform data analysis. P values < 0.05 were considered statistically significant.

Results

Patient characteristics

Prior to AF ablation, 75 patients (male 69%, mean age 58.7±9.1 years and median CHA_2DS_2-VASc score = 1) underwent high-density LA mapping during CS pacing. There were 25 lifelong non-drinkers, 25 mild drinkers (4.4±2.3 drinks/week) and 25 moderate drinkers (14.0±4.2 drinks/week). Representative voltage and propagation maps for the three groups are shown in Figure 2.

Baseline characteristics for all three groups are shown in Table 1. The three groups had a similar profile with respect to age, gender, AF phenotype and medical comorbidities. Moderate drinkers had significantly larger left atrial size than non-drinkers (28.0±4.7 vs 22.7±3.8 cm^2; p=0.008).

Electroanatomic mapping

The mean global LA voltage, global conduction velocity and %complex potentials are shown in Figures 2, 3A and 3B respectively. The mean mapping time was 15±5 minutes with 1016±445 points collected per patient following filtering and manual annotation. There was no significant difference in the number of points between groups (p=0.71), nor point density between groups (average point density for non-drinkers 7.2 points/cm^2 vs mild drinkers 8.1 points/cm^2 vs moderate drinkers 5.9 points/cm^2; p=0.46).

Atrial voltage

Moderate drinkers had significantly lower mean global bipolar voltages (1.53±0.62mV) compared with non-drinkers (1.89±0.45mV; p=0.02), as shown in Figure 3. However,

mean global bipolar voltages did not significantly differ between mild drinkers (1.77±0.51mV; p=0.41) and non-drinkers. There was a significantly greater proportion of low voltage electrograms in moderate drinkers (30.6±24.3%; p=0.02) but not mild drinkers (23.2±15.1%; p=0.12) compared with non-drinkers (18.0±6.9%). Scar (% points with bipolar voltage < 0.1mV) was more prevalent in moderate drinkers (3.2±4.9%), compared with mild drinkers (2.4±2.2%) and non-drinkers (1.6±1.8%), although this was non-significant (p=0.23).

Regional differences in mean voltage and % low voltage regions are shown in Figures 4A and 4B respectively. Of note, mild drinkers had significantly lower mean voltages in the septal region compared with non-drinkers (1.3 ± 0.4 vs 1.6 ± 0.6 mV; p=0.03), while there were no significant differences in other regions. Mild drinkers also had significantly more areas of low voltage in the septal (20.7 ± 13.5 vs 31.5 ± 17.3%; p=0.02) and lateral regions (38.4 ± 27.7 vs 24.8 ± 17.2%; p=0.046) compared to lifelong non-drinkers.

Univariate and multivariate clinical predictors of low global voltage are shown in Table 2. In addition to age and gender, moderate alcohol consumption (8 – 21 drinks per week), but not mild consumption, was a significant multivariate predictor of atrial low voltage (p = 0.04). Overall, women had lower mean global voltage (1.56±0.27mV vs 1.80±0.62; p=0.04) and no significant difference in conduction velocity compared to men (34.9±11.9 vs 41.1±13.8 cm/sec; p=0.10).

Atrial conduction

Moderate drinkers had significantly slower CV (33.5±14.4 vs 41.7±12.1 cm/sec; p=0.04), and a higher proportion of complex potentials (7.8±4.7 vs 4.5±2.7%; p=0.004) compared to non-drinkers (Figures 5A and 5B respectively). These %complex potentials encompassed CFAEs (moderate drinkers 5.7±3.2 vs non-drinkers 3.6±2.4%; p=0.02) and double potentials (2.1±2.5 vs 0.9±0.9%; p=0.05). The proportion of complex potentials was significantly greater in mild drinkers (6.6±4.6%) compared with non-drinkers (4.5±2.7%; p =0.047). There was no significant difference in mean conduction velocity between mild and non-drinkers.

Regional analysis of conduction velocity and %complex potentials is shown in Figures 6A and 6B respectively. Moderate alcohol consumption was associated with reductions in regional tissue voltage reaching statistical significance in the anterior (30.8±18.5 vs 45.6±25.2 cm/sec; p = 0.04) and superior regions (33.6±21.0 vs 55.1±25.1 cm/sec; p = 0.003) compared to non-drinkers. The anterior region was also the most common site for observed differences in complex potentials (moderate drinkers 7.8±9.2 vs non-drinkers 2.7±3.5; p=0.01), particularly CFAE (6.4±7.4 vs 2.4±3.2; p=0.03). Regional differences in % CFAEs and % double potentials are shown in Figure 7.

A modest positive correlation was observed between mean bipolar voltage and conduction velocity in 5 of 6 regions: anterior (r=0.44; p<0.001), posterior (r=0.43; p<0.001), superior (r=0.43; p<0.001), inferior (r=0.38; p=0.001), septal (r=0.35; p=0.004), lateral (r=0.07; p=0.55). Analyses for independent predictors of atrial conduction abnormalities are shown in Table 3. Significant univariate predictors of conduction slowing were female gender (p=0.05), moderate alcohol consumption (p=0.01) and anti-arrhythmic therapy (p=0.04), however only moderate alcohol consumption (p=0.01) and female gender (p=0.03) were multivariate predictors. Univariate predictors of complex signals (CFAE and double potentials) were persistent AF (p=0.01), AF duration (p=0.05) and moderate alcohol consumption (p=0.04), but only AF duration was a significant multivariate predictor (p=0.02). Mild alcohol consumption did not predict low voltage, conduction slowing or presence complex signals on univariate or multivariate analysis (p>0.05).

Follow-up

After 18.7 ± 5.4 months of follow-up from initial AF ablation, 28/75 (37%) patients developed recurrent AF and 9/75 (12%) underwent repeat ablation. Logistic regression was performed to determine univariate electrophysiological predictors of recurrence post AF ablation. Lower mean global voltage (OR 0.30; 95% CI 0.11–0.83), higher proportion of low voltage (<0.5 mV) electrograms (OR 1.05; 95% CI 1.01–1.10) and % complex potentials (OR 1.16; 95% CI 1.03–1.31) were all significant predictors of outcome. Mean global conduction velocity (OR 0.98; 95% CI 0.95–1.02), % double potentials (OR 1.22; 95% CI 0.97–1.54), %CFAE (OR 1.15; 95% 0.99–1.35) did not reach significance.

Discussion

This cross-sectional study of patients with a history of AF and relatively low prevalence of other comorbidities reports the electrical and structural changes in the atrium associated with long-term alcohol consumption. The key findings are:

(1) Regular moderate drinkers (average ~14 drinks/week) had significantly lower global atrial voltage, proportion of low voltage and slower conduction velocities.

(2) Moderate alcohol consumption, together with older age and female gender was a stronger multivariate predictor of lower voltage than other AF risk factors, such as obesity and hypertension.

(3) Milder drinkers (≤7 drinks/week) did not demonstrate significant differences in global voltage and conduction velocities compared with non-drinkers suggesting a safe threshold for alcohol consumption.

Alcohol and Atrial Fibrillation

Attention to lifestyle has emerged as an important aspect of AF management. While many studies have focussed on weight loss[126], less data exists regarding the impact of regular alcohol consumption, ubiquitous in Western culture. Although binge drinking is a well-recognized AF precipitant[105], habitual consumption even at low-moderate levels may represent an important modifiable risk factor. The majority of middle-aged American adults diagnosed with AF for the first time consume alcohol at mild to moderate levels[388]. In fact, meta analyses report as little as 1 drink per day is associated with heightened AF risk[76,77]. The mechanisms by which alcohol consumption causes myocardial injury include alterations in sodium and calcium current densities[99], oxidative stress[389], apoptosis[390], inflammation, mitochondrial dysfunction, accelerated protein degradation and abnormal fatty acid metabolism[391].

While it is well-described that self-reported consumption underestimates true intake[392], the present study supports this 'relatively low' cut-off as the threshold for potential alcohol-related atrial toxicity. Significant electrophysiological and structural changes in atrial substrate were demonstrated in patients consuming 8–21 drinks/week. Atrial remodelling was not significantly different for most indices in those consuming 1–7

drinks/week compared to non-drinkers which may support a potentially *safe* threshold for alcohol consumption in the AF population although this is speculative.

Alcohol and Atrial substrate

The presence of low voltage with the electrophysiological sequelae of conduction slowing and fractionation has been shown to correlate with histological fibrosis[253] and late gadolinium enhancement on cardiac MRI[393]. These findings have important implications for prognosis. Verma et al demonstrated a significant increase in recurrent AF following catheter ablation in patients with pre-existent left atrial scarring[394]. In 122 patients undergoing ablation for paroxysmal AF, lifelong non-drinkers had the highest success rates (81%), followed by 'moderate' drinkers consuming 1–14 drinks/week for men & 1–7 drinks/week for women (69%), then heavy drinkers (35%)[100].

Our findings provide insights into the pathophysiologic mechanism responsible for this clinical observation. Excessive alcohol consumption may also be an under-appreciated factor resulting in AF progression. In a large cohort study, moderate-heavy alcohol consumption portended a three-fold higher risk of progression from paroxysmal to persistent AF, while more 'traditional' risk factors such obesity, hypertension and diabetes did not reach significance[117]. Regular alcohol consumption is associated with an increase in atrial size independent of AF burden. Our group recently reported progressive impairment in LA mechanical function on cardiac MRI with increasing alcohol intake[395], supporting the results of earlier echocardiographic studies[383]. Subtle abnormalities in echocardiographic LA strain have been reported with as little as 1–6 drinks/week[396].

The presence of LA fibrosis is independently associated with heightened risk of stroke and transient ischaemic attack[397]. Recent cohort studies have highlighted the association between excessive alcohol intake and risk of stroke in the AF population[398]. In the present study lower atrial voltages and conduction slowing demonstrated in moderate drinkers may result in atrial myopathy and impaired LA appendage emptying velocities which may in part explain this clinical observation[399].

Limitations

One of the major limitations of our CV calculation methodology is that it assumes that wavefront propagation is restricted to the endocardial surface and does not include epicardial mapping. We assume that the tissue between mapped points is both structurally and electrically homogenous. In particular, we have not taken into account the effects of transmural conduction or the effects of structural and functional heterogeneities that exist in a three-dimensional atrial substrate in the calculation of CVs. While pacing from the coronary sinus enabled a stable and reproducible reference, we acknowledge that wavefront propagation in regions furthest away from the pacing site are less uniform than regions in closer proximity such as the posterior wall.

Due to the observational study design, there is the possibility for confounding due to unmeasured factors, such as sleep disordered breathing and medication compliance. The relatively small sample size may be underpowered to detect more subtle differences in atrial substrate and ablation outcomes between non-drinkers and mild-drinkers. The categorisation of alcohol consumption into mild vs moderate was determined by patient reporting and may be unreliable although the observed biologic dose response effect was consistent. The findings in the present study are confined to patients with a history of AF undergoing ablation and does not necessarily address the relationship between alcohol consumption and incident AF in the general population. Although the present study demonstrates an association between increasing amounts of alcohol consumption and atrial substrate, further studies are needed to determine the impact of abstinence from alcohol on AF burden and whether reverse remodelling occurs.

Conclusion

Regular moderate alcohol consumption, but not mild consumption is associated with lower atrial voltage and conduction slowing. These electrical and structural changes may in part explain the propensity to atrial fibrillation in regular drinkers and may represent an important modifiable risk factor for AF.

Table 1 – Baseline Characteristics

Parameter	Non-drinkers (n=25)	Mild drinkers (n=25)	Moderate drinkers (n=25)	p-value
Age	57±9	58±10	62±7	0.29
Gender (female, %)	7 (28%)	10 (40%)	6 (24%)	0.58
Hypertension (%)	7 (28%)	7 (28%)	9 (36%)	0.65
Diabetes Mellitus (%)	1 (4%)	1 (4%)	1 (4%)	1.0
Dyslipidaemia (%)	9 (36%)	6 (24%)	5 (20%)	0.36
TIA / Stroke	2 (8%)	0 (0%)	2 (8%)	0.36
CHA_2DS_2-VASc Score	1.0±1.2	1.0±0.9	1.2±1.2	0.87
Paroxysmal AF (%)	12 (48%)	14 (56%)	11 (44%)	0.70
Cardioversion to SR	7 (28%)	5 (20%)	7 (28%)	0.64
Time since AF diagnosis (months)	57±54	54±48	72±66	0.56
% Anglo-Saxon	22 (88%)	24 (96%)	23 (92%)	0.59
Weight (kgs)	88±14	89±12	92±14	0.61
Body mass index	29±4	29±3	30±7	0.59
Anti-arrhythmic therapy	19 (76%)	17 (68%)	15 (60%)	0.19
Flecainide	9 (36%)	6 (24%)	4 (16%)	
Sotalol	7 (28%)	9 (36%)	9 (36%)	
Amiodarone	3 (12%)	2 (8%)	2 (8%)	
Alcohol intake (SDs/week)	0	4.4±2.3	14.0±4.2	<0.001
Echocardiographic parameters				
LVEF(%)	56±3	58±5	57±5	0.45
LVEDD (mm)	50±5	51±5	50±4	0.90
LA area (cm^2)	22.7±3.8	24.7±4.9	28.0±4.7	0.008

Abbreviations: TIA – transient ischaemic attack, AF – Atrial Fibrillation, LVEF – Left ventricular ejection fraction, LVEDD – Left Ventricular End Diastolic Diameter.

Table 2: Multivariate predictors of low global voltage

Parameter	Univariate p value	Multivariate analysis			
		Standardized β-coefficient	95% CI for β	t	p value
Voltage					
Age	0.001	-0.348	(-0.037, -0.008)	-3.059	0.003
Gender	0.02	-0.251	(-0.522, -0.030)	-2.247	0.03
Moderate ETOH*	0.02	-0.230	(-0.526, -0.001)	-2.013	0.04
AF duration	0.07	-0.168	(-0.004, 0.001)	-1.507	0.14
Hypertension	0.14	-0.034	(-0.287, 0.212)	-0.303	0.76
AF type	0.23	-			
Mild ETOH*	0.51	-			
Body mass index	0.90	-			
Dyslipidemia	0.91	-			
AAD therapy	0.95	-			
Diabetes	0.98	-			

*Compared with all other groups

Abbreviations: AAD: Antiarrhythmic drug, ETOH: alcohol, CI: Confidence Interval

Table 3: Multivariate predictors of atrial conduction abnormalities

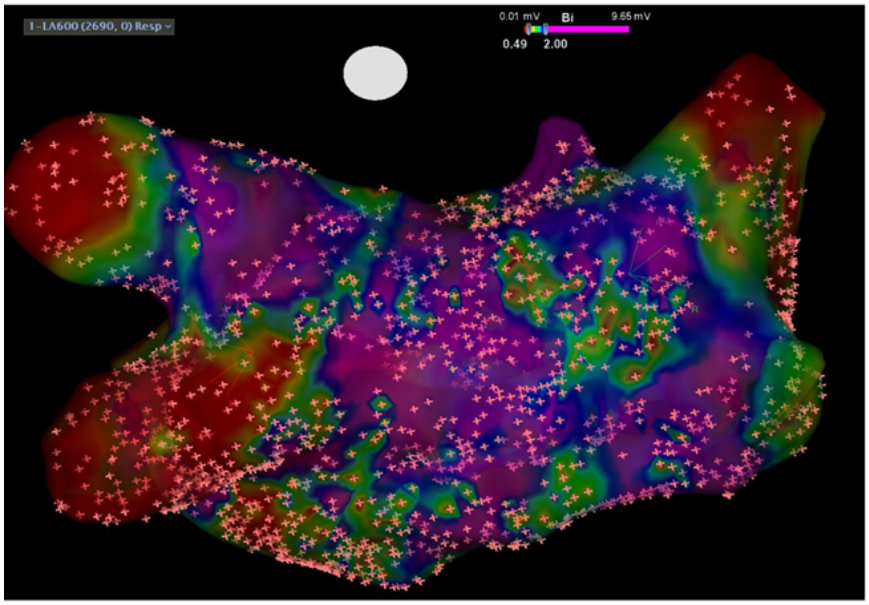
Parameter	Univariate p value	Multivariate analysis			
		Standardized β-coefficient	95% CI for β	t	p value
Conduction Velocity					
Gender	0.05	-0.290	(-14.237,-1.203)	-2.377	0.02
Moderate ETOH*	0.01	-0.281	(-15.571,-0.054)	-2.021	0.04
AF duration	0.09	-0.174	(-0.094,0.015)	-0.174	0.16
AAD therapy	0.04	0.134	(-2.904,9.710)	1.083	0.28
Mild ETOH*	0.14	0.113	(-4.219,10.240)	0.836	0.41
Age	0.39	-			
Dyslipidemia	0.41	-			
Body mass index	0.70	-			
Hypertension	0.77	-			
AF type	0.94	-			
Diabetes	0.95	-			
% Complex signals					
AF duration	0.05	0.341	(0.002, 0.026)	2.385	0.02
AF type	0.01	-0.260	(-2.543, 0.146)	-1.802	0.08
Hypertension	0.06	0.100	(-0.880, 1.842)	0.715	0.48
Moderate ETOH*	0.04	0.020	(-1.448, 1.663)	0.139	0.89
Body mass index	0.11	-			
Dyslipidemia	0.18	-			
Gender	0.35	-			
AAD therapy	0.43	-			
Mild ETOH*	0.62				
Diabetes	0.64	-			
Age	0.98	-			

*Compared with all other groups

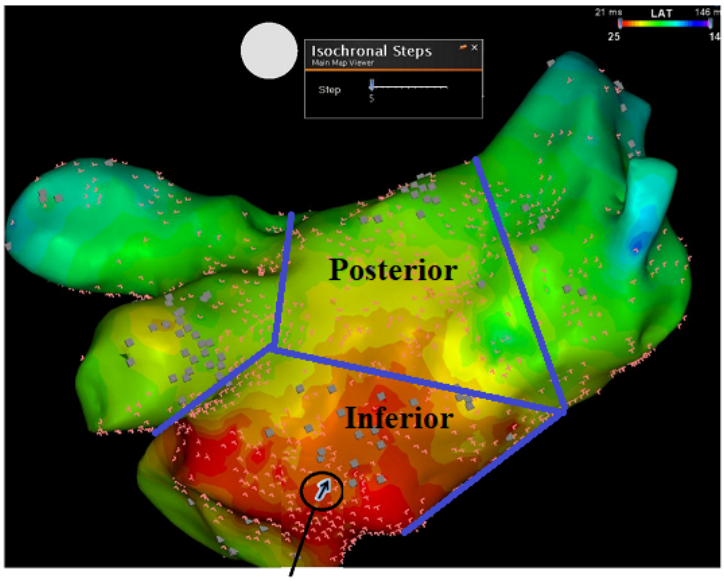
Abbreviations: AAD: Antiarrhythmic drug, ETOH: alcohol, CI: Confidence Interval

Figure 1: Representative high density left atrial electroanatomical maps demonstrating: A. Bipolar voltage and B. Propagation map with calculation of conduction velocity maps using the polynomial surface method

A



B



$$t_i(x, y, z) = ax^2 + by^2 + cz^2 + dxy + exz + fyz + gx + hy + iz + j$$

$$\frac{dx}{dt} = \frac{\partial x}{\partial t} + \frac{\partial x}{\partial y}\frac{dy}{dt} + \frac{\partial x}{\partial z}\frac{dz}{dt}$$
$$\frac{dy}{dt} = \frac{\partial y}{\partial t} + \frac{\partial y}{\partial x}\frac{dx}{dt} + \frac{\partial y}{\partial z}\frac{dz}{dt}$$
$$\frac{dz}{dt} = \frac{\partial z}{\partial t} + \frac{\partial z}{\partial x}\frac{dx}{dt} + \frac{\partial z}{\partial y}\frac{dy}{dt}$$

Figure 2: Representative high-density voltage (top panel) and propagation maps (bottom panel) of the posterior left atrium for non-drinkers, mild drinkers, and moderate drinkers

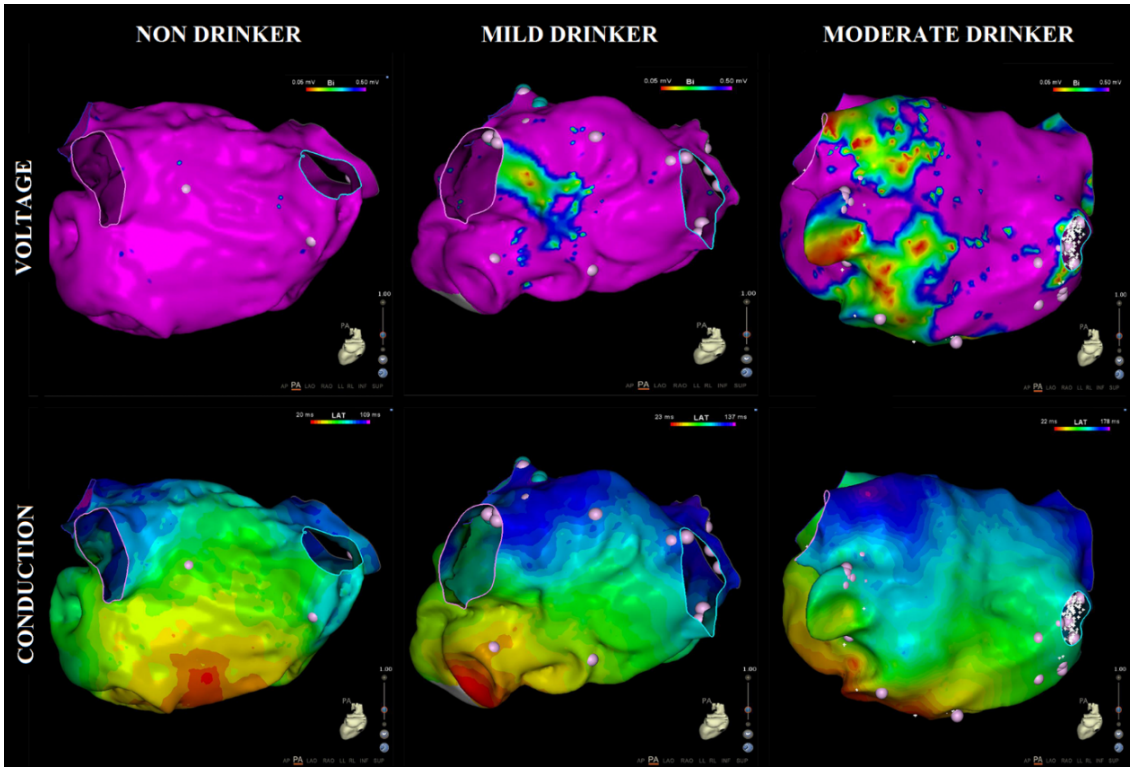


Figure 3: Mean global left atrial voltage by alcohol consumption category

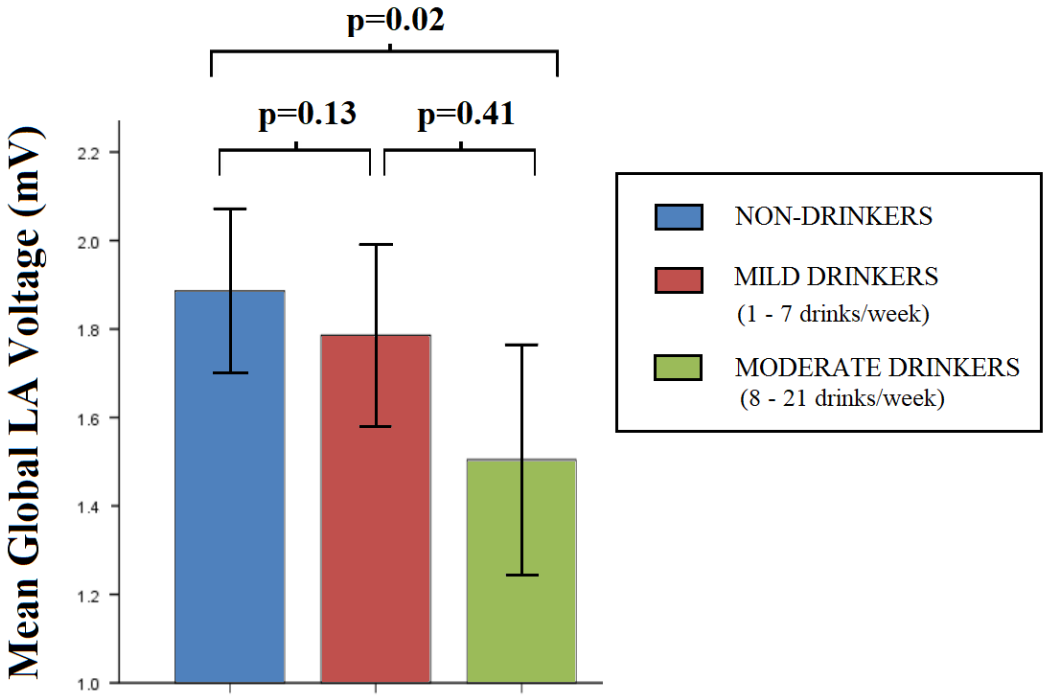


Figure 4: A. Mean global left atrial conduction velocity; B. Global % of Complex Potentials by alcohol consumption category

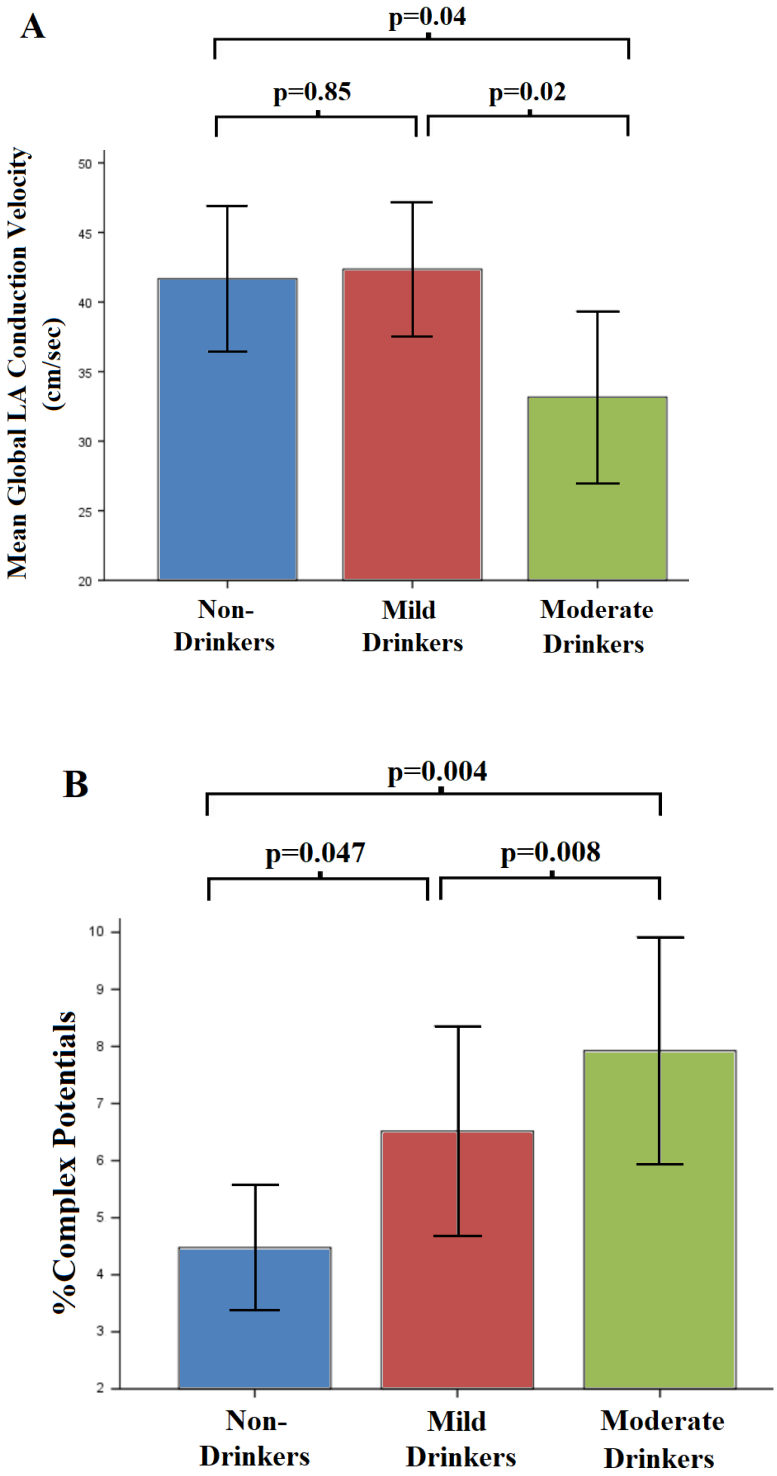


Figure 5: A. Regional mean voltage distribution; B. Regional % Low Voltage regions by alcohol consumption category

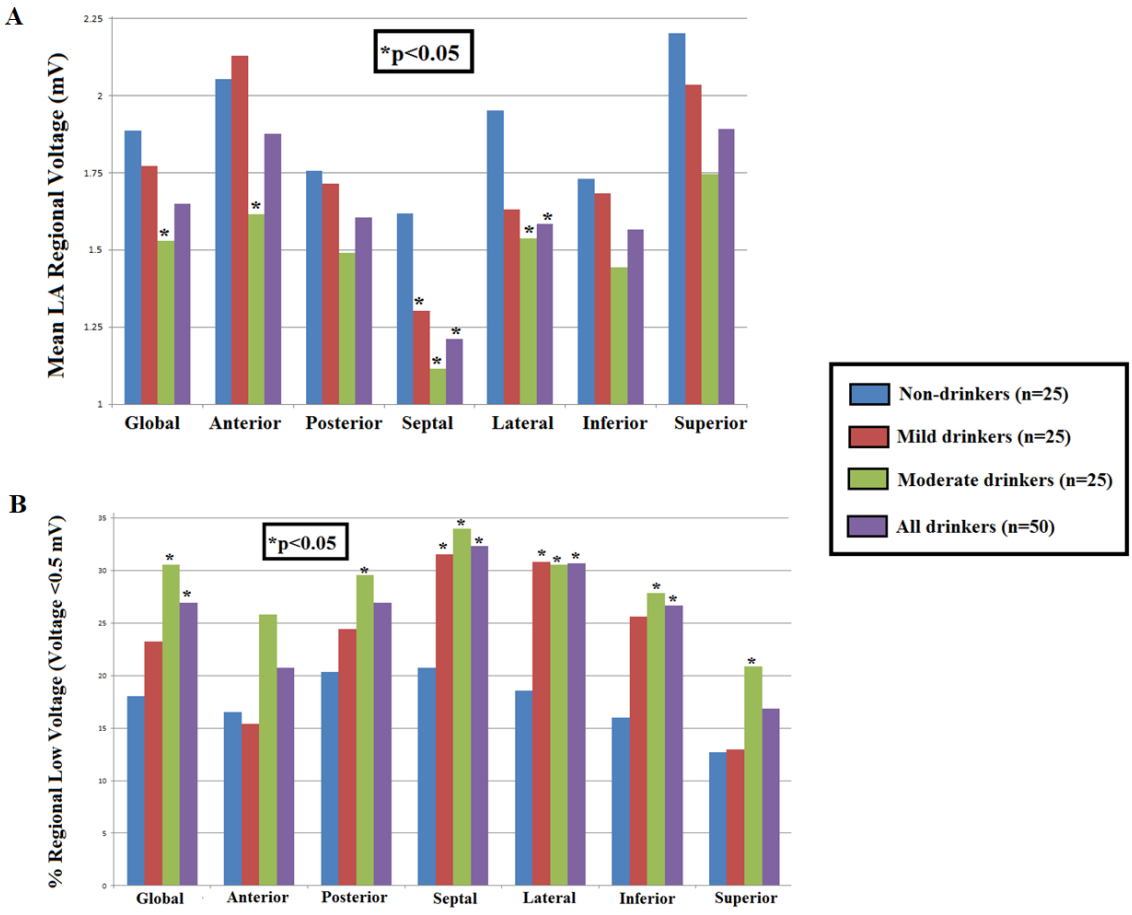


*Figure Legend: *p<0.05 for comparisons with non-drinkers*

Figure 6: A. Regional mean conduction velocity distribution; B. Regional %Complex Potentials by alcohol consumption category

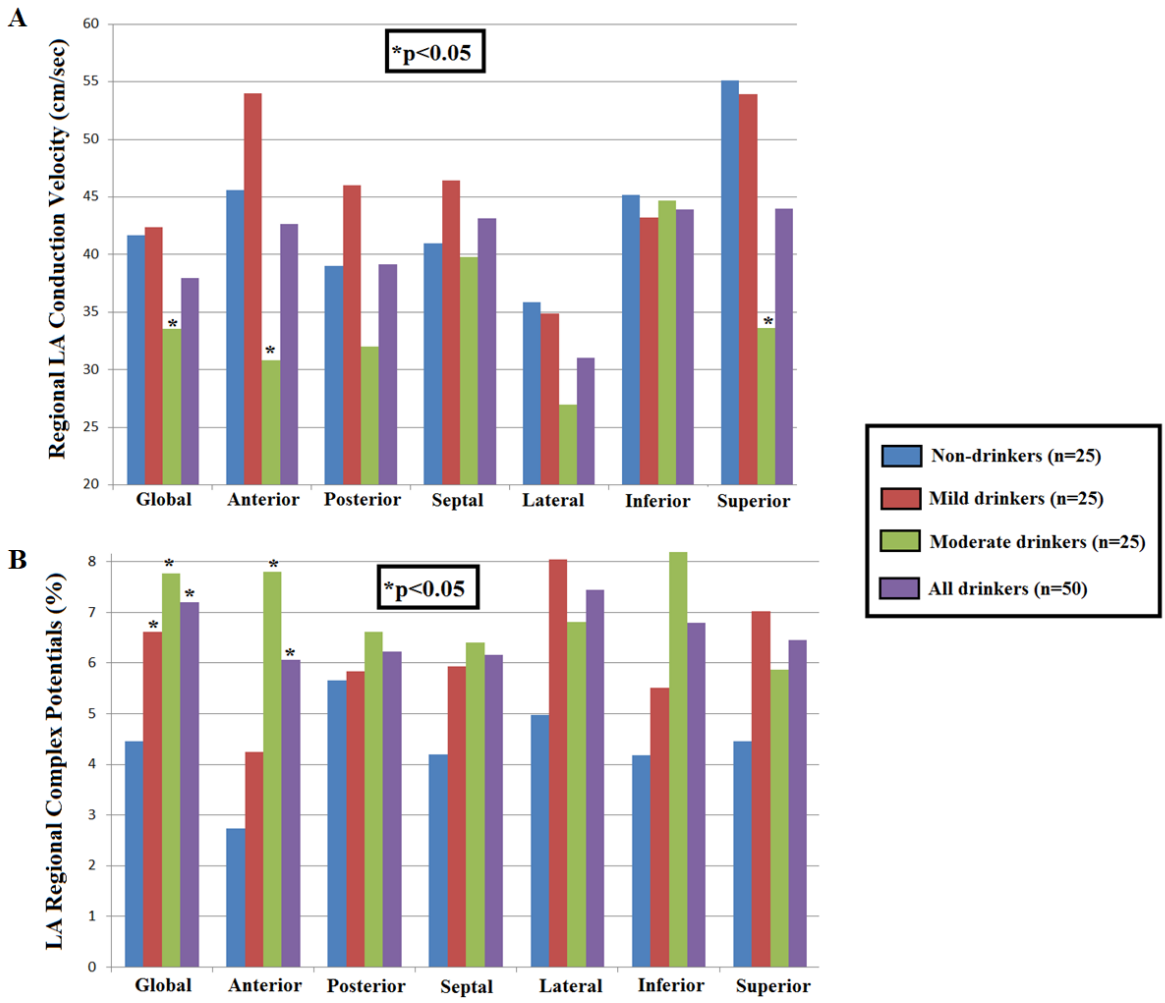
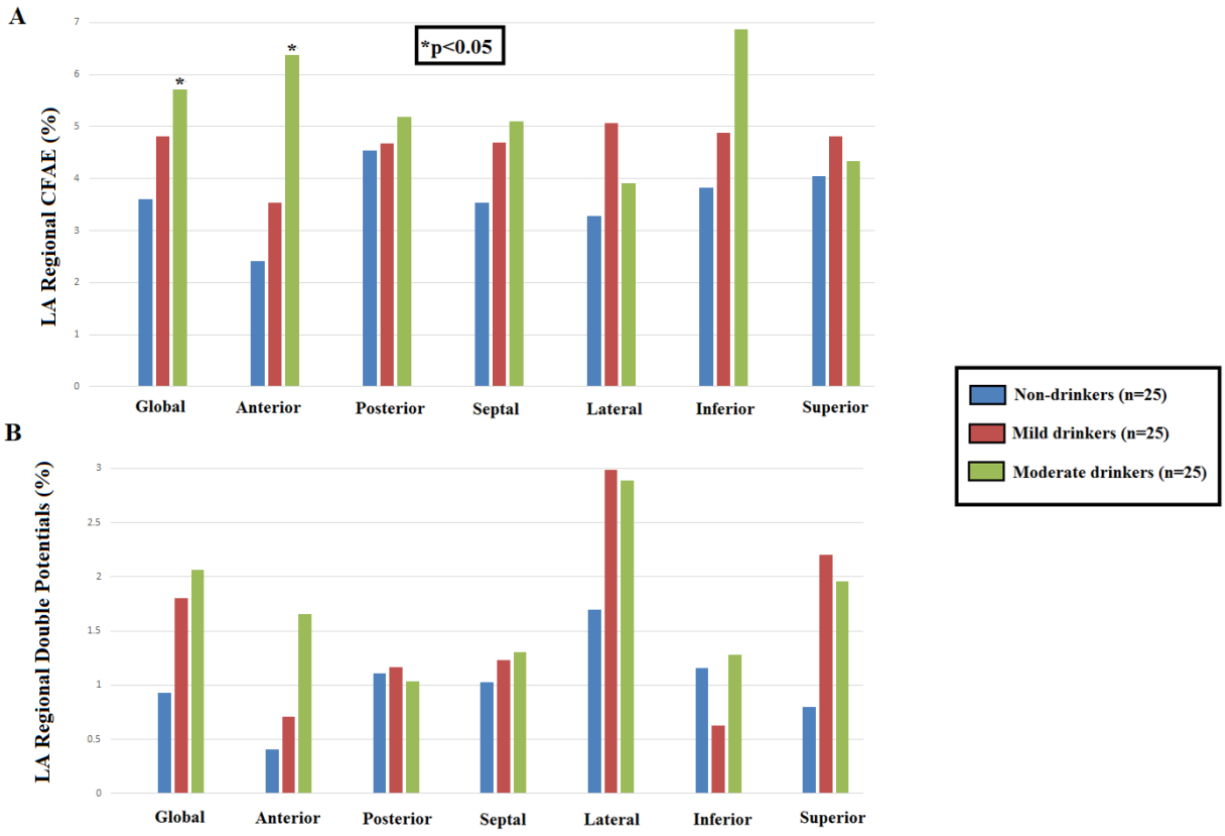


*Figure Legend: *p<0.05 for comparisons with non-drinkers*

Figure 7: Regional differences in % CFAEs and % double potentials



Chapter 3: Regular alcohol consumption is associated with impaired atrial mechanical function in the atrial fibrillation population: a cross-sectional MRI-based study

Introduction

Alcohol consumption has emerged as an important risk factor for AF[380]. In a meta-analysis of 7 studies involving 859,420 patients and 12,554 AF cases, AF incidence increased by 8% for each additional standard drink per day[76]. Population based studies have demonstrated an association between regular alcohol consumption and left atrial (LA) enlargement in a dose-related manner[400]. Left atrial size is a well-established determinant of AF recurrence. The direct contribution of alcohol to LA dilatation and AF risk has been estimated to be ~ 24% however the contribution of AF itself and associated conditions such as hypertension, obesity and sleep apnoea can be difficult to untangle[383]. Daily drinking has been linked with atrial fibrosis in a dose-dependent manner[100].

Moreover, excessive alcohol consumption is a well-established cause of dilated cardiomyopathy. The putative mechanisms responsible for alcohol mediated cardiac chamber enlargement include oxidative stress, inflammation and apoptosis[401]. We hypothesised that the thinner-walled atrium may be more vulnerable than then ventricle to the potentially deleterious effects of 'moderate' alcohol consumption and an important factor in AF pathogenesis. Moreover, atrial mechanical dysfunction on echocardiography has been correlated with a higher risk of left atrial thrombus formation[402] and may provide incremental diagnostic information over CHA_2DS_2-VASc score for predicting stroke risk in patients with AF[403]. To date there have been limited studies evaluating the effect of regular alcohol consumption on atrial mechanical function. We sought to evaluate the impact of alcohol consumption on left atrial size and mechanical function using 3T cardiac MRI (CMR) in the AF population.

Methods

Patient selection & study design

This is a single centre observational study conducted from April 2016 to May 2018. We aimed to prospectively recruit 160 outpatients with paroxysmal or persistent atrial fibrillation and a rhythm-control strategy to undergo 3 Tesla (3T) CMR in sinus rhythm. AF type (paroxysmal or persistent) and burden were based on the patients' AF profile and % time spent in AF respectively in the 12 months prior to MRI. Patients self-reported their average alcohol consumption in standard drinks (~12g alcohol) per week (SDs/wk) over the preceding 12 months, and those consuming ≥3 SDs/week were categorized as regular drinkers. Patients also categorized their beverage of choice as either wine, beer or spirits. Regular drinkers were sub-divided into 3 groups based on quantity consumed as either: Mild (3 – 10 SDs/wk), Moderate (11 – 20 SDs/wk) or Heavy (>20 SDs/wk) drinkers. Lifelong non-drinkers were used as controls. We aimed to recruit 40 consecutive patients in each of the four groups.

Exclusion criteria included: (1) Occasional drinkers defined as >1 consecutive month of non-drinking during the preceding 12 months [102] Former drinkers; (3) Permanent AF; (4) Alcoholic liver cirrhosis; (5) Significant renal impairment (eGFR < 30 mL/min); (6) Significant known structural heart disease (LVEF < 40% or previous myocardial infarction with regional wall motion abnormality).

CMR protocol

Our CMR scanning and analysis protocol has been described previously[404]. All CMR examinations were performed on a 3T scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). All post-processing of images was performed using a dedicated CMR analysis workflow of the Syngo.via software package (Siemens Healthineers, Erlangen, Germany).

Cine sequences were acquired in the four-chamber, two-chamber, three-chamber and short-axis views using an ECG-gated balanced steady-state free precision (SSFP) sequence in expiration, extending from the pulmonary veins to the LV apex (4-mm slice thickness, no gap). LV mass, end-diastolic volume, end-systolic volume, and LVEF were analyzed on commercially available post processing software with LV volumetric analysis performed using the summation of disks method. Papillary muscles

were regarded as part of the ventricular cavity. Measurements were indexed to body surface area.

As the focus of the scan was the left atrium, radiographers optimized the scan to minimize LA foreshortening where possible and image the LA length perpendicular to the mitral annular plane. Maximum (LA_{max}) and minimum (LA_{min}) LA volumes were measured in sinus rhythm using the biplane area-length method, as shown in Figure 1, with pulmonary veins and left atrial appendage carefully excluded at their junctions with the LA. LA length was measured from the mid-point of the mitral annulus to the mid-point of the superior LA wall. Global LA emptying fraction (LAEF) was (LAmax – LAmin)/LAmax. LA reservoir function was (LAmax – LAmin)/LAmin.

CMR measurements were performed by two cardiologists, and interobserver variability for 100 consecutive atrial measurements was calculated using Pearson's Correlation coefficient, with $r = 0.841$.

Statistics

The primary outcome measure was a comparison of LAEF between drinkers and non-drinkers, with LAVI and LA reservoir function used as secondary endpoints. Based on prior studies looking at comparisons of electrical remodelling between drinkers and non-drinkers, we calculated that to detect a minimum absolute difference of 10%, we would need to enrol ~ 100 patients to provide a power of 0.8 at an alpha value of 0.05. The Shapiro-Wilk test was performed to confirm normal distribution of data and a student t-test then performed. All continuous data are summarized as mean ± standard deviation or median, where appropriate. Comparisons of the clinical characteristics between groups were performed using a chi-square or Fisher exact test. Mann-Whitney U test was used for continuous variables where normal distribution was not present.

Multiple linear regression was performed to determine multivariate clinical predictors of atrial mechanical dysfunction, using LAEF as a continuous dependent variable. Data analysis was performed using Statistical Package for the Social Sciences for Windows (SPSS version 23, IBM). P values < 0.05 were considered statistically significant. The study was prospectively approved by Alfred Health Human Research Ethics Committee

and all patients provided written informed consent to undergo cardiac MRI for the purposes of this research study.

Results

In total 160 participants with a history of AF underwent cardiac MRI in sinus rhythm between April 2016 and May 2018. Baseline characteristics of lifelong non-drinkers (n=40) and regular drinkers (n=120) are shown in Table 1. Patients in both groups were predominantly males and did not differ significantly with respect to age, AF type and duration, weight and medical co-morbidities. Mean and median alcohol intake was 15.8 ± 6.9 and 15 standard drinks per week (~180g) respectively for 25.1 ± 10.3 years.

Regular drinkers were classified as either Mild (3 – 10 SDs/wk; n=40), Moderate (11 – 20 SDs/wk; n=40) or Heavy (>20 SDs/wk; n=40), as shown in Table 2. The majority of patients in both groups were wine or beer drinkers, and a significant proportion consumed both beverage types on a regular basis. A small proportion in both groups were frequent binge drinkers (as defined by ≥5 standard drinks in a 2-hour sitting > monthly).

Cardiac MRI findings are presented in Table 3. The majority of patients had preserved left ventricular systolic function, with normal LV volumes and mass. However, regular long-standing drinkers had significantly larger atria (RA area 25.3 ± 5.9 cm^2 vs 22.7 ± 4.8cm^2 (p=0.02); LAVI 50±13 mL/m^2 vs 43±12 mL/m^2; p=0.005, with impaired mechanical function (LAEF in sinus rhythm 40±14 vs 52±15; p<0.001) and reservoir function (77±48 vs 119±63; p<0.001) compared with lifelong non-drinkers.

There was a significant dose-related reduction of both LAEF (mild 45.4±13.5% vs moderate 39.1±14.7% vs heavy drinkers 35.6±12.6%; p<0.01) and reservoir function (mild 95.8±55.6 vs moderate 74.8±47.1 vs heavy drinkers 61.7±34.4%; p<0.01), as shown in Figure 2. LAVI was not significantly different between moderate and heavy drinkers (50.5±15.6 mL/m^2 vs 51.2±9.8; p = 0.82) although both of these groups had significantly larger atria compared with non-drinkers (42.9±12.0 mL/m^2) as shown in Figure 3. Type of alcoholic beverage consumed (beer, wine, and/or spirits) did not significantly affect LAVI (p=0.637), LAEF (p=0.335) or reservoir function (p=0.234).

Multiple linear regression was undertaken to determine multivariate clinical predictors of atrial mechanical dysfunction (based on LAEF). Significant predictors included number of standard drinks per week (p=0.001), older age (p=0.018) and persistent AF (p=0.016). Gender (p=0.105), hypertension (p=0.363), diabetes mellitus (p=0.140), history of binge drinking (p=0.195), time since first AF episode (p=0.549), LVEF (p=0.240) and CHA_2DS_2-VASc score (p=0.121) were not statistically significant.

Discussion

This cross-sectional observational study of 160 patients with a history of AF aimed to determine the impact of regular alcohol consumption on atrial and ventricular parameters using high-definition cardiac MRI. The main findings were:

(1) Regular alcohol drinkers had significantly larger right and left atria with impaired mechanical and reservoir function compared to non-drinkers, despite similar ventricular parameters;

(2) A dose-related effect of alcohol consumption was demonstrated with more severe atrial mechanical dysfunction associated with higher alcohol intake;

(3) Habitual regular alcohol consumption, but not binge drinking or alcohol beverage type, was associated with atrial mechanical dysfunction;

(4) Regular alcohol consumption, even at mild levels was a significant predictor of impaired LA emptying fraction.

As a burgeoning epidemic in Western countries, AF is increasingly seen as a lifestyle-related condition. While binge drinking is a well-recognized acute precipitant of acute AF ('holiday heart syndrome'[105]), long-term habitual alcohol consumption is increasingly appreciated as a risk factor for incident AF[405], even at levels as low as 1 standard drink per day[76,77]. In the present study, even 'mild' drinkers (average intake ~7 drinks/week) had impaired mechanical function while 'moderate' alcohol drinkers (average ~16 drinks/week) also had significantly dilated atria compared with non-drinkers. The putative mechanisms are beyond the scope of this clinical study but may include direct myopathic and fibrotic effects on the thinner-walled atria. Consistent with previous studies, lower levels of alcohol intake are less likely to affect ventricular

size and function, with 'alcoholic cardiomyopathy' predominantly described in those consuming >80 g/day (~45 drinks/week)[406].

The deleterious downstream structural effects of heavy alcohol consumption on the ventricle are well established however low to moderate alcohol intake is generally considered cardioprotective in patients with dyslipidemia and coronary disease[407,408]. The impact of alcohol on the atrium are only beginning to emerge. In a population-based echocardiographic study, McManus et al observed a 0.16mm (95% CI 0.10-0.21) increase in LA dimension for each 10g alcohol intake per day, estimating that 24% of the incident AF risk was related to alcohol mediated LA enlargement[383]. Singh et al similarly reported an increase in echocardiographic left atrial volume index with relatively modest levels of alcohol intake (adjusted OR 1.81; 95% CI 1.13 – 2.90, p=0.01)[409]. The present study utilized high-definition 3T cardiac MRI volumetric analysis to determine dose-related effects of regular alcohol intake on atrial dysfunction.

Mechanisms of alcohol toxicity on cardiac function

Postulated mechanisms for direct cardiotoxic effects of alcohol include inflammation, oxidative stress[389], apoptosis[390], mitochondrial dysfunction[410], deranged fatty acid metabolism[411] and accelerated protein degradation[391,412]. While these effects have been predominantly studied in the ventricle, recent studies suggest that the much thinner walled atria may be more vulnerable to myopathic effects at moderate doses sustained over a long period. Animal studies suggest that even 1 week of excessive alcohol consumption may cause a significant reduction in sodium and calcium atrial current densities[79]. Adverse atrial electrical remodelling ensues with increasing consumption, culminating in fibrosis. In those undergoing AF ablation, degree of atrial fibrosis as characterized by regional low voltage increased by 10% in the left atrium for each standard drink consumed[100]. In patients with a history of atrial flutter undergoing electrophysiology study, atrial effective refractory periods were significantly shorter in drinkers (≥1 drink/day) compared with non-drinkers[87].

Clinical implications

As the most commonly consumed 'drug' in the United States[413], alcohol's effects on the atrium in the ever-growing AF population have important implications for

prognosis. In a study of 122 patients undergoing pulmonary vein isolation for paroxysmal AF, non-drinkers had the lowest recurrence rates (81%), followed by moderate (69%) then heavy drinkers (35%)[100]. Our findings of impaired atrial mechanical function and larger LA size in regular drinkers may also explain why alcohol consumption in the AF population was associated with higher stroke rates in a large cohort study[139], even after adjustment for established clinical risk factors.

Recent studies suggest that eradication of 'alcohol abuse' may result in 73,000 fewer AF cases in the United States[414]. While alcohol abstinence may be appropriate in the AF population, there is insufficient evidence to recommend complete abstinence in the broader cardiac population. While some studies suggest a U-shaped relationship between alcohol consumption and all-cause mortality[415], others argue that beneficial associations of low intensity alcohol are largely attributable to inappropriate reference group selection and poor adjustment for confounders[416]. Nevertheless, in the AF population, a reduction in alcohol intake to < 3 standard drinks/week, amongst other cardiometabolic risk factor reduction measures, has been shown to reduce AF recurrence rates[126]. This study supports the notion that regular alcohol intake at even modest doses may be associated with adverse LA mechanical remodelling which may explain the vulnerability to AF recurrence in this population.

Limitations

This study has several limitations. As an observational study, we are only able to demonstrate association, rather than causation. Moreover, atrial parameters prior to the development of AF were unavailable in these patients. Alcohol intake was self-reported, and actual amount consumed may be higher and subject to recall and misclassification bias. While regular drinkers had evidence of atrial mechanical dysfunction compared with lifelong non-drinkers, the clinical significance of these changes with respect to clinical endpoints such as stroke or mortality are unknown. Further studies are needed to determine whether these changes are reversible with abstinence from alcohol.

Conclusion

In patients with AF, moderate alcohol consumption is associated with significantly increased LA size and impaired atrial mechanical function. This may in part explain the propensity for AF recurrence and stroke risk in patients with atrial fibrillation who regularly consume moderate amounts of alcohol.

Table 1: Baseline characteristics

Parameter	Non-drinkers (n=40)	Regular drinkers (n=120)	p-value
Age	60.4 ± 10.6	61.6 ± 10.4	0.60
Gender (male, %)	74%	77%	0.71
Hypertension (%)	42%	45%	0.78
Diabetes Mellitus (%)	10%	6%	0.53
Dyslipidaemia (%)	17%	16%	0.90
CHA_2DS_2-VASc Score	1.5 ± 1.6	1.4 ± 1.1	0.59
Type of AF (% Paroxysmal / Persistent)	56% / 44%	58% / 42%	0.85
Time since AF diagnosis (years)	6.4 ± 5.3	5.5 ± 7.0	0.62
AF burden (%)	7.2 ± 9.5%	8.7 ± 15.3%	0.74
Class I/III antiarrhythmic	78%	81%	0.82
Ethnicity (% Anglo-Saxon)	82%	86%	0.56
Weight (kgs)	89 ± 13	88 ± 16	0.90
Body mass index	28.6 ± 4.4	28.0 ± 4.8	0.51
Apnoea Hypopnea Index (AHI)	16.1 ± 20.5	10.7 ± 16.9	0.62
Alcohol intake (standard drinks/week)	0	15.8 ± 6.9	<0.001
Duration of alcohol intake (years)	0	25.5 ± 10.0	<0.001

Table 2: Alcohol intake details (n = 120 regular drinkers)

Parameter	Mild (n=40)	Moderate (n=40)	Heavy (n=40)
Alcohol intake (drinks/wk)	7.8± 2.9	15.7 ± 2.4	23.5 ± 2.6
Duration of regular alcohol intake (yrs)	22.3 ± 10.2 yrs	25.2 ± 10.8 yrs	25.7 ± 8.9 yrs
Beverage consumed			
Beer (%)	45%	53%	53%
Wine (%)	63%	73%	78%
Spirits (%)	13%	19%	13%
>1 beverage consumed (%)	15%	45%	34%
Binge drinking > 1/month	26%	19%	35%

Table 3: Cardiac MRI: drinkers vs non-drinkers

Parameter	Non-drinkers (n=40)	Drinkers (n=120)	p-value
LVEDV (mL)	173 ± 35	178 ± 43	0.61
LVESV (mL)	68 ± 19	76 ± 24	0.09
Stroke volume (mL)	106 ± 23	102 ±27	0.48
LVEDV / BSA	81 ±14	81 ± 16	0.26
LVEF (%)	61.0 ±7.2	58.0 ± 8.5	0.06
LV mass (g)	136 ±36	137 ± 39	0.91
LV mass / BSA	69 ± 12	65 ± 16	0.26
RVEDV (mL)	176 ± 43	167 ± 38	0.49
RVESV (mL)	68 ± 15	70 ± 21	0.746
RA area (cm^2)	22.7 ± 4.8	25.3 ± 5.9	0.02
LA area (cm^2)	24.6 ± 4.5	27.9 ± 6.2	0.003
LA volume (mL)	88.7 ± 23.9	104.0 ± 29.7	0.004
LAVI (mL/m^2)	42.9 ± 12.0	50.1 ± 13.4	0.005
LAEF (%)	52.0 ± 14.6	39.8 ± 14.1	<0.001
LA reservoir function (%)	118.6 ± 62.7	76.6 ± 47.7	<0.001

Abbreviations: LVEDV – left ventricular end-diastolic volume, LVESV – left ventricular end-systolic volume, LV – left ventricle, BSA – body surface area, RV – right ventricle, RA – right atrium, LA – left atrium, LA – left atrial volume indexed, LAEF – left atrial emptying fraction.

Figure 1: Volumetric assessment of left atrial volumes using the biplane area-length method.

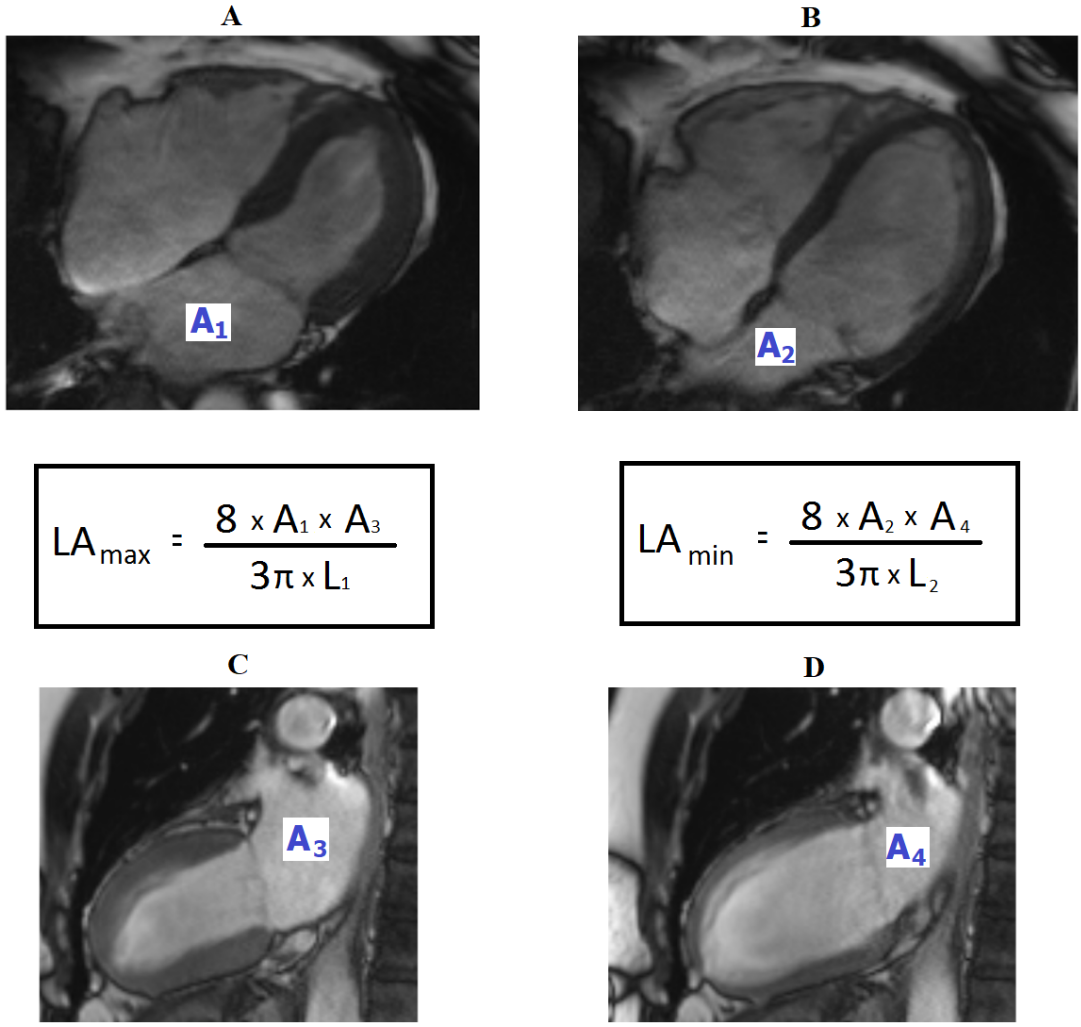
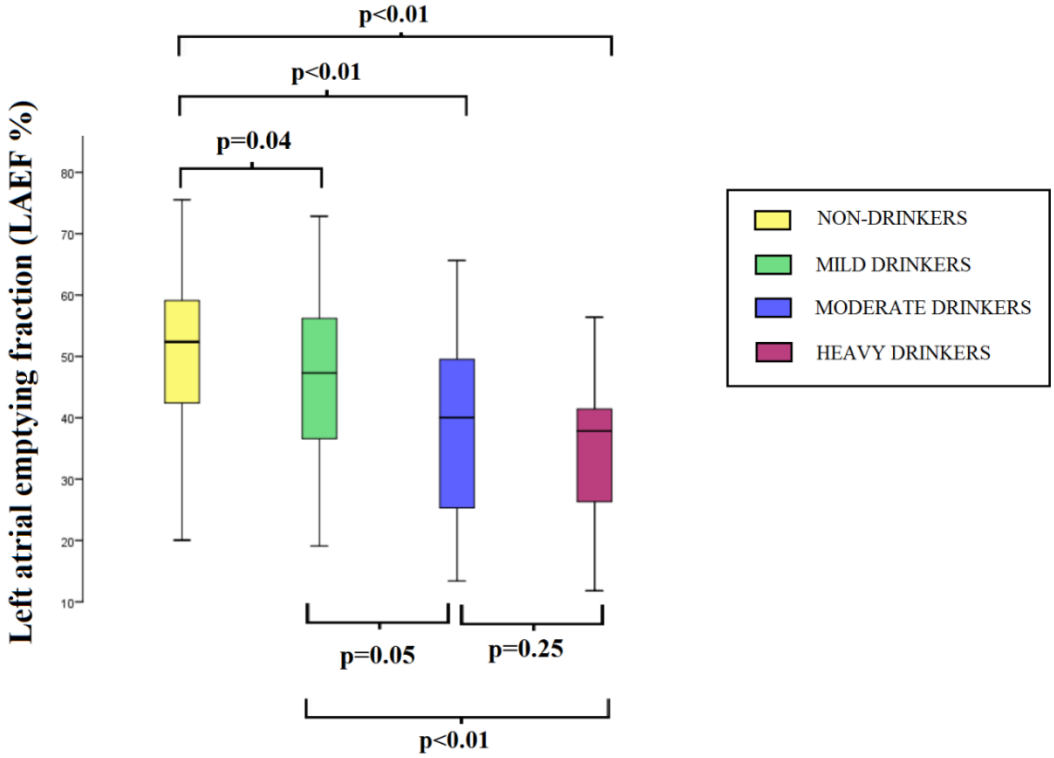


Figure Legend: A: Four-Chamber view, A_1=maximum LA area; B. Four-Chamber view, A_2=minimum LA area; C: Two-Chamber view, A3 = maximum LA area; D: Two-chamber view, A4 = minimum LA area.

Figure 2: Dose-related impairments in left atrial function



Abbreviations: LAEF: Left atrial emptying fraction; SDs/wk: standard drinks per week (1 SD ~ 12g alcohol).

Figure 3: Relationship between and alcohol intake by grade and left atrial volume index (LAVI)

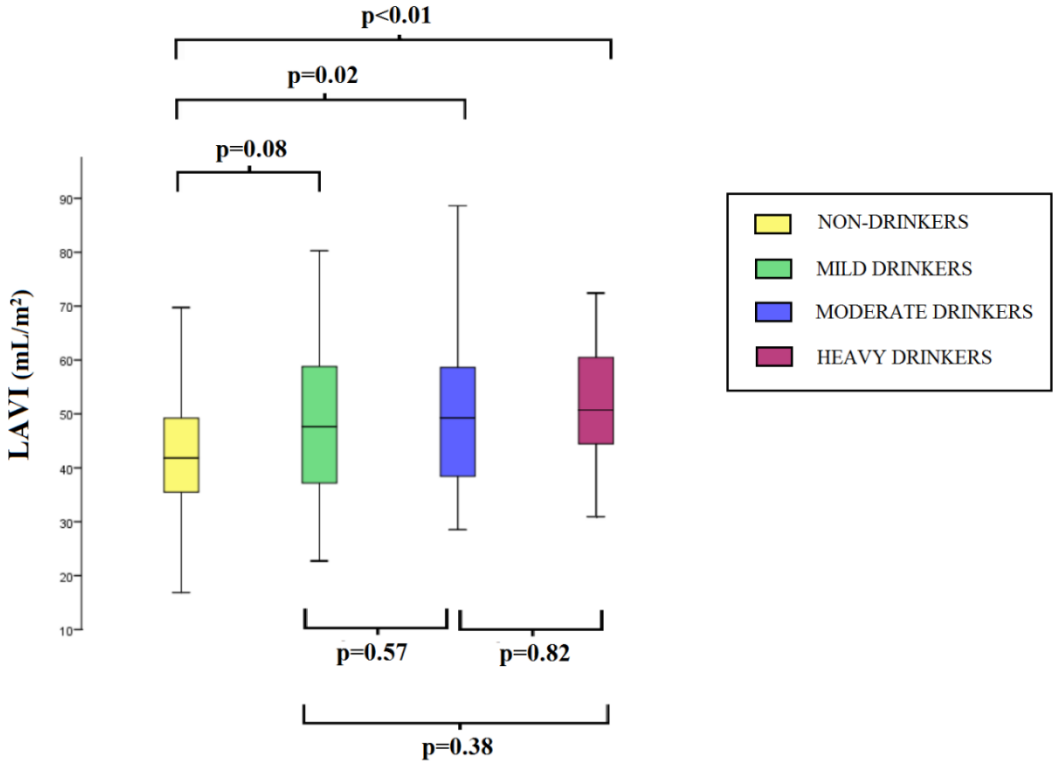
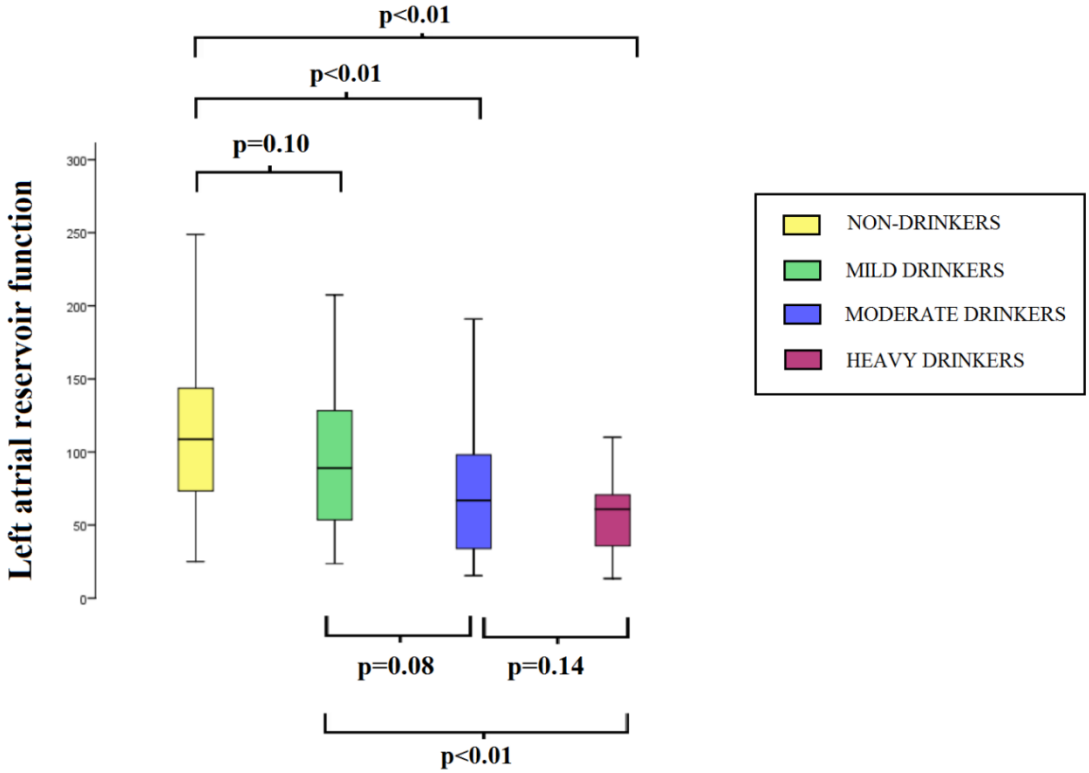


Figure 4: Relationship between and alcohol intake by grade and left atrial reservoir function



Chapter 4: Impact of Alcohol Abstinence in Moderate Drinkers with Atrial Fibrillation: Results from the Alcohol-AF Randomized Controlled Trial

Introduction

Atrial fibrillation affects over 33 million people worldwide and is the leading cause of stroke in the older population[1]. Alcohol is ingrained in Western culture, with 53% of Americans regularly consuming alcohol. Population based studies demonstrate an association between alcohol consumption and atrial fibrillation. Observational studies indicate a dose-response relationship between degree of alcohol intake and risk of incident AF, left atrial dilatation, development of atrial fibrosis and recurrence following ablation. These adverse effects have been reported even in those consuming 7–14 drinks per week, suggesting the atrium is perhaps more vulnerable than the ventricle to the toxic effects of alcohol. Moreover, alcohol is causally linked with other recognized AF risk factors, including hypertension, sleep apnoea, obesity and left ventricular dysfunction[380].

Attention to lifestyle-related factors in the AF population has received significant attention in recent years, with observed benefits including reduction in arrhythmia burden and reverse atrial remodelling. These studies focussed primarily on structured weight loss and mandated a consumption of < 3 standard drinks per week[126,258,259]. We undertook a randomized controlled trial evaluating the intervention of abstinence from alcohol among habitual drinkers with a history of AF.

Methods

Study design

This was a prospective open-label multi-centre randomized clinical trial. Patients were recruited from six tertiary hospitals in Australia (Alfred Hospital, Royal Melbourne Hospital, Cabrini Hospital, Melbourne Private Hospital, Western Health and Monash Medical Centre). Ethics committee approval was sought and obtained at each participating centre. The trial was prospectively registered with the Australian New

Zealand Clinical Trials Registry (ANZCTR: ACTRN 12616000256471) and the study protocol is available online via the ANZCTR website.

Study Population

Patients meeting the inclusion criteria at participating institutions were invited to participate in the study. Inclusion criteria were: (1) Age 18 – 85 years; [102] Symptomatic paroxysmal AF (minimum 2 episodes over the preceding 6 months) or symptomatic persistent AF with a rhythm control strategy (3) Mild-moderate alcohol consumption (minimum 10 standard drinks or ~120 grams per week). As per study protocol all patients at randomization were required to be in sinus rhythm and medically stable on current anti-arrhythmic therapy with no planned ablation during the 6-month follow up period.

Exclusion criteria included: (1) Evidence of alcohol dependence or alcohol abuse (as determined by CAGE & AUDIT-C questionnaires); [102] Severe left ventricular systolic dysfunction, as defined by left ventricular ejection fraction < 35%; (3) Significant comorbid non-cardiac illness, including liver cirrhosis and end-stage renal disease; (4) Psychiatric comorbidity or inability to comply with follow-up. All participants provided written informed consent to partake in the study.

Run-in-phase and randomization

After written patient consent was obtained, patients underwent a four week run-in period prior to randomization. The purpose of this run-in period was to confirm inclusion criteria were met with respect to alcohol intake, exclude permanent or 'unstable' AF, and assess compliance. During this period patients kept an alcohol diary and rhythm was monitored using the AliveCor® mobile phone app and/or Holter monitoring or pre-existing implantable devices.

Following the run-in phase, eligible participants were randomized in a 1:1 fashion to either the Abstinence or Control group. A computerized central randomization scheme was generated using block randomization and sets of randomly selected blocks were provided to investigating sites.

Abstinence group

All patients in this group were encouraged to abstain completely from all forms of alcohol for a minimum 6-month period. They were provided verbal and written advice to assist them and received monthly verbal and electronic contact from study investigators to assess compliance and provide positive reinforcement. Random urine testing for Ethyl Glucuronide (EtG), an alcohol metabolite present for 4 days following consumption, was also performed to assess compliance. 'Compliance' was defined as average alcohol intake ≤2 standard drinks/week.

Control group

Patients in this control group were advised that they could continue their usual alcohol consumption. It was emphasised that they were not required to increase alcohol consumption as part of the study. Patients in both groups were asked to keep a weekly alcohol intake diary and this was reviewed during monthly contact with investigators.

Rhythm monitoring

All patients underwent comprehensive rhythm monitoring throughout the course of the study. Time to recurrence and AF burden were determined using either cardiac rhythm management devices (pre-existing pacemaker or implantable loop recorder) or through the AliveCor® mobile phone app in conjunction with Holter monitoring. Patients were asked to email twice daily AliveCor® 30 second electrocardiogram (EKG) trace regardless of symptoms and then additional traces in the event of symptoms. Cardiac rhythm management devices were either interrogated at clinic visits or via remote monitoring. Final endpoint analysis with respect to AF recurrence was performed by two cardiologists blinded to the patient's allocated group.

Primary and secondary endpoints

Pre-specified co-primary endpoints using an intention-to-treat analysis were: (1) Time to AF recurrence, defined by any atrial tachyarrhythmia lasting ≥ 30 seconds (after a 2-week blanking period) and [102] AF burden, defined as percentage of time in AF during the entire 6-month follow-up period. This was calculated based on the time-weighted average of the proportion of EKGs during the six months which indicated the presence of AF. While the study was initially planned to proceed for 12 months, this was

modified to 6 months during the course of the study by the steering committee due to challenges with recruitment, in particular unwillingness by many potential participants to undertake 12 months of abstinence.

Secondary endpoints were pre-specified and compared between and within groups at baseline and 6 months, including weight, blood pressure and AF symptoms using the modified European Heart Rhythm Association score[417]. Echocardiographic and cardiac magnetic resonance (CMR) measurements were performed according to standard guidelines[418] by experienced cardiologists blinded to randomization.

All CMR examinations were performed on a 3T scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany) with image post-processing performed using a dedicated CMR analysis workflow of the Syngo.via software package (Siemens Healthineers, Erlangen, Germany). Cine sequences using an ECG-gated balanced steady-state free precision (SSFP) sequence were acquired in the four-chamber, two-chamber, three-chamber long axis views, as well as a short-axis stack extending from the pulmonary veins to the LV apex (4-mm slice thickness, no gap). LA volumes were measured in sinus rhythm using the biplane area-length method, with pulmonary veins and left atrial appendage carefully excluded at their junctions with the LA. LA length was measured from the mid-point of the mitral annulus to the mid-point of the superior LA wall. Global LA emptying fraction (LAEF) was (LAmax – LAmin)/LAmax.

Statistical analysis

The sample size calculation for the primary endpoint of time to AF recurrence assumed a recurrence rate of 30% based on preliminary data. To detect a minimum absolute difference in recurrence of 20% between groups, we enrolled 70 patients in each group to provide a power of 0.8 at an alpha value of 0.05.

For continuous variables, including AF burden, the Shapiro-Wilk test was first performed to confirm that the data were consistent with a normal distribution. A student t-test was performed if data were normally distributed; otherwise a Mann-Whitney test was utilized. For between-group comparisons, the chi-square test for categorical variables, and the Wilcoxon rank-sum or student's t-test for continuous variables, were used as appropriate. A paired t-test or Wilcoxon signed-rank test was used for within

group comparisons. All continuous data were summarized as mean ± standard deviation or median, as appropriate while categorical variables were summarized as count (proportion).

Time-to-event analyses for AF recurrence were performed with Kaplan-Meier plots and the log-rank test. Univariate and multivariate analyses were performed using Cox's proportional hazards accounting for co-variates. Data analysis was performed using Statistical Package for the Social Sciences for Windows (SPSS version 23, IBM) with statisticians analysing data masked to group allocation. *P*-values < 0.05 were considered statistically significant.

Results

Patient population

Of 697 patients screened for participation who met all inclusion criteria (Figure 1), 140 patients agreed to be randomized into the Abstinence (n=70) and Control (n=70) groups. A large proportion of screened patients (n=491, 70.4%) were not willing to consider abstinence. Baseline clinical characteristics (Table 1) were well balanced between the groups, in particular AF phenotype and method of AF monitoring. Wine and beer were the predominant beverages consumed. The majority of patients were not binge drinkers and had no biochemical evidence of alcohol excess. Fifty patients (36%) had continuous rhythm monitoring (loop recorder or pacemaker). Adherence to Alivecor® recordings in the remainder was satisfactory (median 257 traces per patient during follow-up, IQR 124-382). A total of 137/140 (97.9%) completed the 6-month follow up and 3 patients were lost to follow-up.

Alcohol intake

Patients in the Abstinence group reduced their alcohol intake from 16.8±7.7 to 2.1±3.7 SDs/week (87.5% reduction; mean difference 14.7, 95% CI 12.7–16.7, p<0.001). Complete abstinence was achieved by 43/70 (61.4%) patients in the Abstinence group, with < 2 SDs/week achieved by 53/70 (75.7%) and 60/70 (85.7%) reducing their alcohol intake to ≥ 70% of baseline. Positive urine ETG was observed in 15.8% undergoing testing in the Abstinence group. A small reduction in alcohol intake

(19.5%) was observed in the Control group from 16.4±6.9 to 13.2±6.5 SDs/week (mean difference 3.2, 95% CI 1.9–4.4, p<0.001).

Primary endpoints

At 6-months, a documented AF recurrence > 30 seconds had occurred in 37 (52.9%) patients in the Abstinence group and 51 (72.9%) patients in the Control group (p=0.014). AF-free survival (Figure 2) was longer in the Abstinence group (log-rank p=0.004). Overall median AF burden was lower in the Abstinence group 0.46% (IQR 0–3.7%) compared with the Control group 1.20% (IQR 0.0–10.45%); p=0.016 (Figure 3).

Secondary endpoints

AF-related hospitalizations occurred in 6 (9%) of Abstinence patients and 14 (20%) Controls (p=0.053). There was a significant reduction in weight in the Abstinence group (Δ weight -2.7±3.3 vs +0.8±3.0 kg; p<0.01) as well as BMI ((Δ weight -0.86±1.08 vs +0.30±0.97;p<0.01). Those in the Abstinence group had a significant reduction in systolic BP (-12.4±12.8 vs -1.0±12.5 mmHg; p=0.02), but not in diastolic or mean BP (Table 2).

Differences in AF-related symptoms at Baseline and Follow-up are shown in Figure 3. Alcohol abstinence was associated with a significant reduction in moderate or severe symptoms compared to Controls (10.1 vs 32.4%; p=0.002) at 6-month follow-up. Baseline and follow-up MRI parameters are shown in Table 2. In the Abstinence group there was a significant improvement in left atrial mechanical function (LAEF 42±14 baseline vs 50±8% at follow-up; p=0.02) and reduction in left atrial dimensions (LA area 29.5±4.9 vs 27.1±4.5 cm^2; p<0.01 and LAVI 56.7±11.9 vs 53.7±6.4; p=0.09). In addition there was a significant reduction in epicardial fat (Δ area -0.42±1.34 vs 1.26±3.07 cm^2; p=0.03) in the alcohol abstinence group.

Multivariate Cox proportional hazard regression analysis (Table 3) demonstrated that abstinence from alcohol (HR 0.52; 95%CI 0.30-0.89) was associated with freedom from AF. Neither change in weight (p=0.85) nor change in systolic blood pressure (p=0.64) were multivariate predictors of AF recurrence. Subgroup analysis by AF type

(Figure 5) demonstrates that Abstinence appeared to reduce recurrence risk in paroxysmal AF (log-rank p=0.015) with a trend towards reduction in persistent AF (log-rank p=0.053).

Those who were able to achieve complete abstinence (n=43) over 6 months had a significantly lower risk of recurrence than those reducing intake to 1 – 9 drinks/week (n=40, HR 2.1; 95% CI 1.2 – 3.7, p=0.014) and those consuming ≥10 drinks/week (n=57, HR 2.3; 95% CI 1.3 – 4.0, p=0.003).

Discussion

This is the first randomized trial to examine the impact of abstinence in symptomatic patients with AF who consume moderate quantities of alcohol. The key benefits observed with alcohol abstinence include:

(1) Reduction in arrhythmia recurrence rates and AF burden, with associated improvement in AF-related symptom scores.
(2) Favourable left atrial remodelling with small, but significant improvements in left atrial mechanical function.
(3) Reduction in total body weight and epicardial fat on CMR.
(4) Reduction in blood pressure, particularly systolic BP.

Earlier meta-analyses report a heightened dose-related risk of incident AF compared to non-drinkers, with differences even observed in mild drinkers consuming as little as 7 SDs/week (RR 1.08; 95%CI 1.06-1.10)[76]. Our study, with an average habitual alcohol intake of ~16 SDs/week and low rate of binge drinking (~25%), demonstrates that moderate habitual consumption is contributory to AF episodes and symptoms.

The mechanisms by which moderate habitual consumption reduces arrhythmia burden are likely multi-factorial. Early differences in AF recurrence rates between the two groups (<60 days) and stronger difference in paroxysmal AF in this study suggests amelioration of arrhythmia triggers due to abstinence. Abstinence may negate previously observed short-term autonomic effects of alcohol consumption, including reduction in heart rate variability[91,419], sympathetic modulation[89] and vagal

stimulation[94]. Moreover, cessation of 'binge drinking' may avoid acute cardiac inflammation observed in cardiac MRI studies[104].

Mild-moderate habitual alcohol consumption has been associated with dose-related increases in left atrial size[383] and impairments in atrial mechanical and reservoir function[420]. Moreover, 'moderate drinkers' display evidence of adverse electrical remodelling compared with non-drinkers with slower left atrial conduction, more complex fractionated potentials[421] and lower voltages, with the clinical consequence of higher AF recurrence following ablation in observational studies[100]. In the present study, observed improvements in left atrial mechanical function and size in the abstinence group at follow-up may in part be explained by a reduction in atrial inflammation and/or 'stunning', regression of fibrosis or reverse remodelling owing to reduced AF burden.

With an energy content of 29kJ per gram of alcohol, excessive alcohol consumption can contribute to weight gain[129]. In the present study alcohol abstinence resulted in small but significant reductions in both total body weight and epicardial fat without specific additional weight loss measures employed as part of the intervention. Epicardial fat has emerged as an important predictor of AF burden with putative mechanisms including pro-inflammatory and pro-fibrotic paracrine effects and adipocyte infiltration[422,423]. Risk factor or life style management has been adopted as the fourth pillar of AF management guidelines[424] with goal-directed weight management demonstrated to reduce AF burden[126,258,259.] The combined impact of alcohol abstinence in epicardial fat reduction and weight loss may also have contributed to AF reduction.

Alcohol has been causally linked with hypertension (especially systolic), with proposed mechanisms including activation of the renin-angiotensin system, increased vascular reactivity and inhibition of endothelial nitric oxide production[425]. A recent meta-analysis showed significant dose-dependent risk of hypertension particularly in men, even at intake as low as 1–2 drinks per day[426]. Our study's findings are consistent with a systematic review of 36 trials demonstrating reduction in blood pressure with amelioration of alcohol intake, particular in those consuming >14 drinks/week[427]. Management of hypertension, particularly with renin-angiotensin-aldosterone

blockade, has been shown to be beneficial in the secondary prevention of AF[428] and may also have contributed to observed reductions in arrhythmia recurrence.

Limitations

This study comprised a heterogeneous patient population of both paroxysmal and persistent AF patients with different mechanisms of AF detection, although these were well-balanced between the groups minimizing related bias. The clinical applicability of alcohol abstinence requires separate attention as only a minority of patients screened were agreeable to potential abstinence. This is an important public health issue as current trends demonstrate a rise in alcohol consumption amongst adults over 60, in concert with higher rates of AF in this demographic.

Despite rigorous selection of motivated patients, close follow-up and urine testing, self-reporting of alcohol intake may be subject to recall and misclassification bias. Sleep-disordered breathing may be a confounding factor and sleep studies were not routinely performed in all patients. There are conflicting epidemiological data that mild-moderate alcohol consumption may be associated with lower risk of cardiovascular disease, and this study was underpowered to determine the impact of abstinence on endpoints such as heart failure, stroke or mortality.

Conclusion

Moderate habitual alcohol consumption is a potentially modifiable risk factor in AF, with abstinence associated with a reduction in AF burden, symptomatology and favourable LA remodelling, weight loss and improved blood pressure control in a motivated AF cohort. A significant reduction in alcohol consumption should be considered part of the lifestyle intervention in the management of atrial fibrillation.

Table 1: Baseline Characteristics for the Alcohol-AF trial

Parameter	Abstinence group (n=70)	Control group (n=70)
Age (years)	61.6±9.4	62.8±8.6
Gender (% male)	61 (87.1%)	58 (82.9%)
Weight (kg)	89.9±16.0	89.3±13.3
Body mass index (BMI)	28.4±4.4	28.5±4.5
Hypertension (%)	31 (44.3%)	26 (37.1%)
Diabetes mellitus (%)	5 (7.1%)	6 (8.6%)
TIA / stroke	7 (10.0%)	5 (7.1%)
Dyslipidemia	11 (15.7%)	18 (25.7%)
Previous / current smoker	13 (18.6%)	11 (15.7%)
Obstructive sleep apnea	12 (17.1%)	16 (22.9%)
Coronary artery disease	10 (14.3%)	5 (7.1%)
Previous heart failure	6 (8.6%)	6 (8.6%)
CHA_2DS_2-VASc score	1.5±1.2	1.3±1.1
Time from first AF diagnosis (yrs)	6.9±7.2	5.0±5.3
AF type (paroxysmal / persistent)	45/25 (64.3% / 35.7%)	43 / 27 (61.4% / 38.6%)
Previous AF ablation	20 (28.6%)	25 (35.7%)
Pacemaker or loop recorder	23 (32.9%)	27 (38.6%)
Antiarrhythmic therapy	44 (62.9%)	49 (70.0%)
Amiodarone	6 (8.6%)	4 (5.7%)
Sotalol	20 (28.6%)	23 (32.9%)
Flecainide	18 (25.7%)	22 (31.4%)
Alcohol intake (SDs/week)	16.8±7.7	16.4±6.9
Beverages consumed		
Wine	48 (68.6%)	47 (67.1%)
Beer	34 (48.6%)	34 (48.6%)
Spirits	13 (18.6%)	9 (12.9%)
Binge drinking	20 (28.6%)	16 (22.9%)
MCV (fL)	91±3	93±5
GGT (U/L)	41±29	47±26
TTE measurements		
LA area (cm^2)	27.3±8.3	26.8±6.8
LAVI (mL/m^2)	44.4±10.7	43.4±11.2
LVEDD (mm)	49±10	50±6
LVEF (%)	57±8	57±11
LV mass index (g/m^2)	100.0±23.2	94.9±23.4
E/E’	10.9±9	9.0±3

Abbreviations: SDs/week – standard drinks per week, TIA – transient ischemic attack, MCV – mean corpuscular volume , GGT – Gamma-glutamyl transferase, AF – atrial fibrillation.

Table 2: Secondary endpoints at baseline and follow-up

	Abstinence			Control			
	Baseline	**Follow-up**	**p value***	**Baseline**	**Follow-up**	**p value***	**p value†**
Blood pressure							
Systolic BP (mmHg)	137.6±15.6	125.5±16.6	<0.001	133.2±17.3	131.4±14.9	0.40	0.09
Diastolic BP (mmHg)	77.7±10.0	74.5±11.5	0.03	77.2±10.0	76.3±10.8	0.62	0.47
Mean BP (mmHg)	97.7±10.4	91.5±12.4	<0.001	95.9±11.4	94.7±10.2	0.48	0.21
Weight (kg)	89.9±16.0	87.3±13.9	<0.001	89.3±13.3	90.7±14.4	0.04	0.19
CMR measurements							
LA area (cm^2)	29.5±4.9	27.1±4.5	<0.01	31.7±6.0	31.9±7.2	0.84	0.01
LAVI (mL/m^2)	56.7±11.9	53.7±6.4	0.09	56.0±16.7	50.0±4.4	0.40	0.98
LAEF (%)	42±14	50±8	0.02	38±11	41±5	0.27	0.09
Epicardial fat area (cm^2)	4.3±2.4	3.9±1.8	0.19	4.3±3.7	5.5±3.0	0.07	0.04

Abbreviations: p value* - within group comparison, p value† - between group comparison at follow-up, LA – left atrial, LAVI – left atrial volume indexed, LVEDD – left ventricular end diastolic dimension, LVEF – left ventricular ejection fraction, LAEF – left atrial emptying fraction.

Table 3: Multivariate analysis using Cox Proportional Hazards model for time to AF recurrence

Covariate	β-Coefficient	p-value	HR	95.0% CI	
				Lower	Upper
Abstinence arm	-.654	.018	.520	.303	.893
Monitoring type	-.012	.965	.988	.590	1.656
Age	-.007	.677	.993	.960	1.027
Female gender	.042	.904	1.043	.522	2.085
Δ weight	.008	.853	1.008	.924	1.101
Δ systolic BP	.004	.635	1.004	.989	1.019
Previous AF ablation	-.079	.764	.924	.550	1.552
AF type	.523	.082	1.686	.935	3.040
AF duration	.034	.106	1.035	.993	1.078

Figure 1: CONSORT diagram of patients entering the study

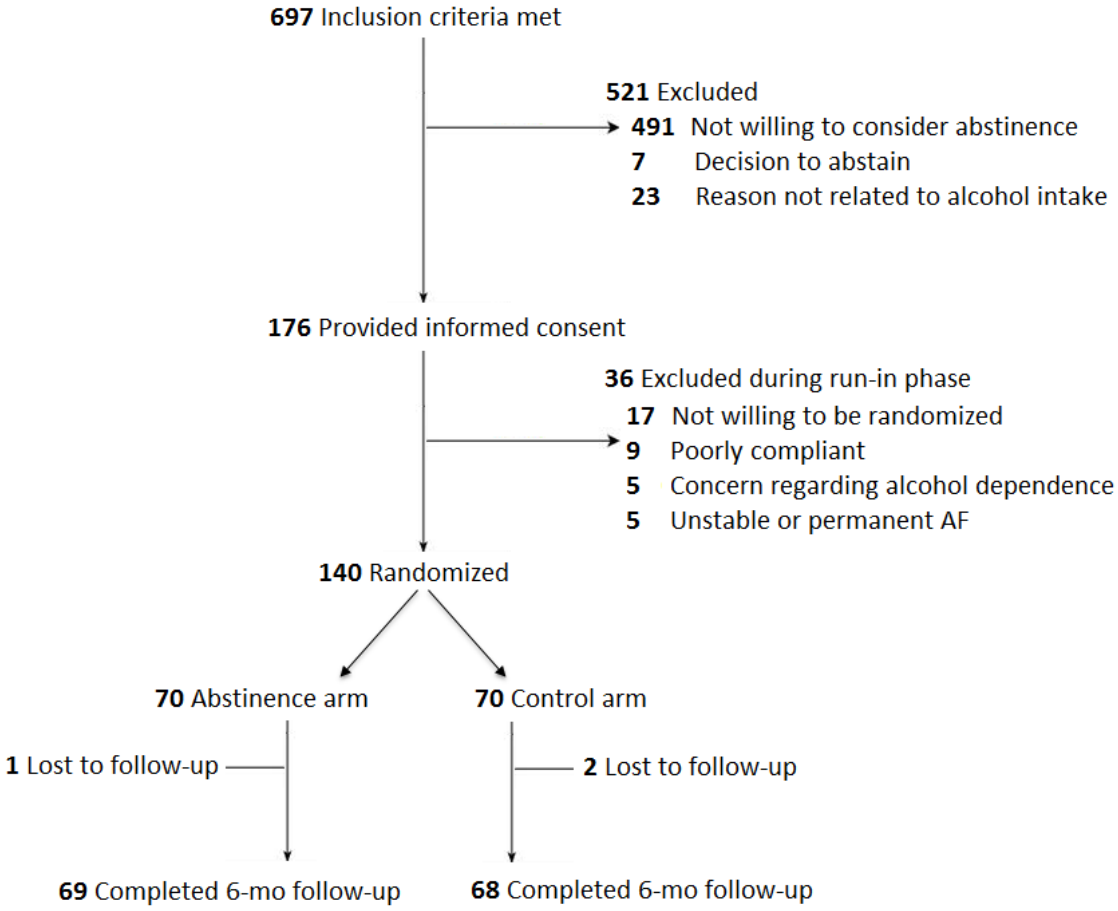


Figure 2: Time to AF recurrence

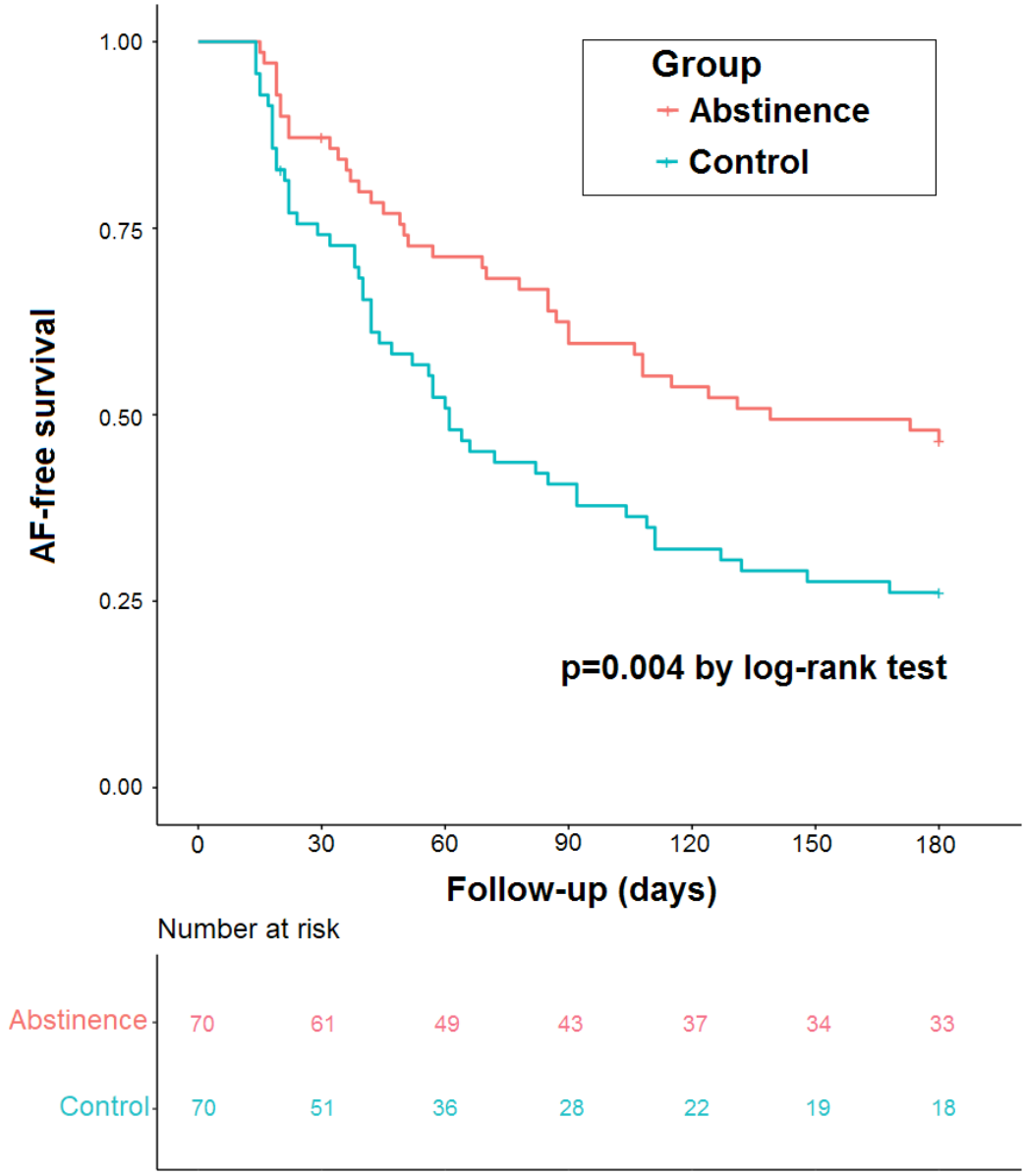


Figure 3: Comparison of AF burden between Abstinence and Control groups

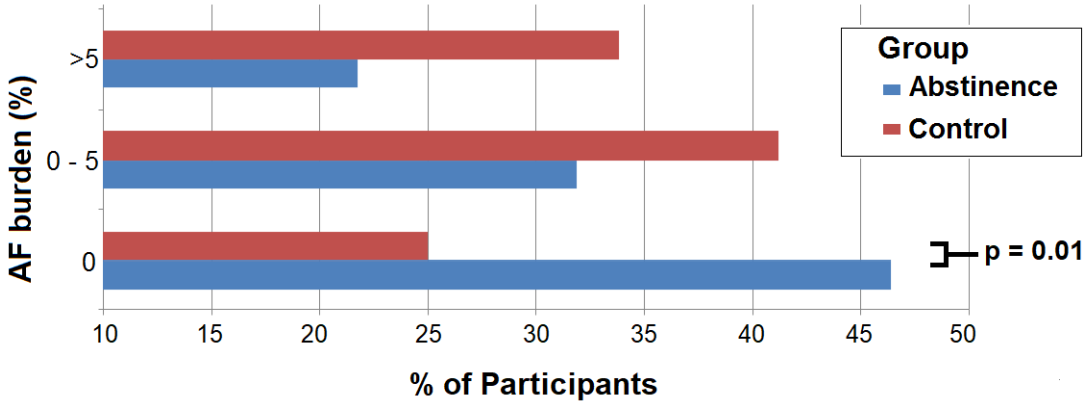


Figure 4: Changes in AF symptom scores between Abstinence and Control groups

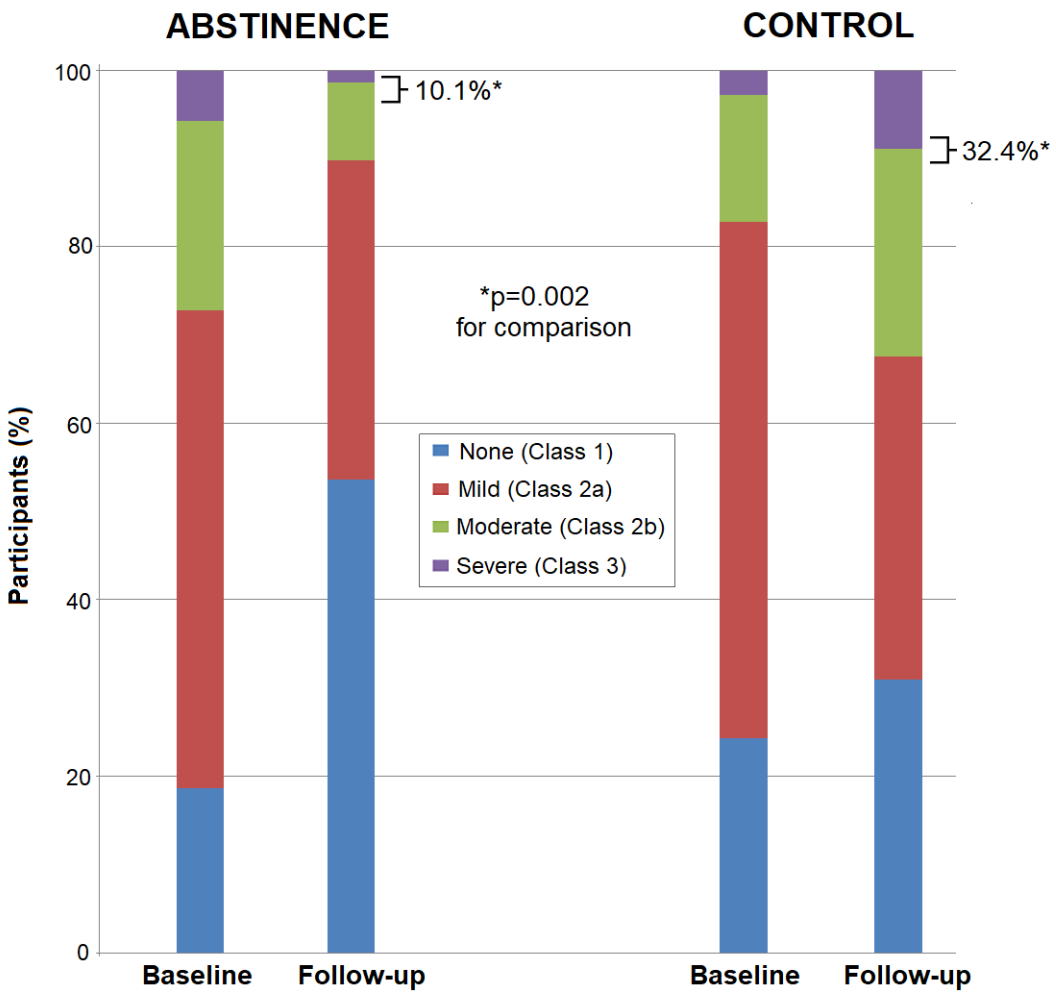
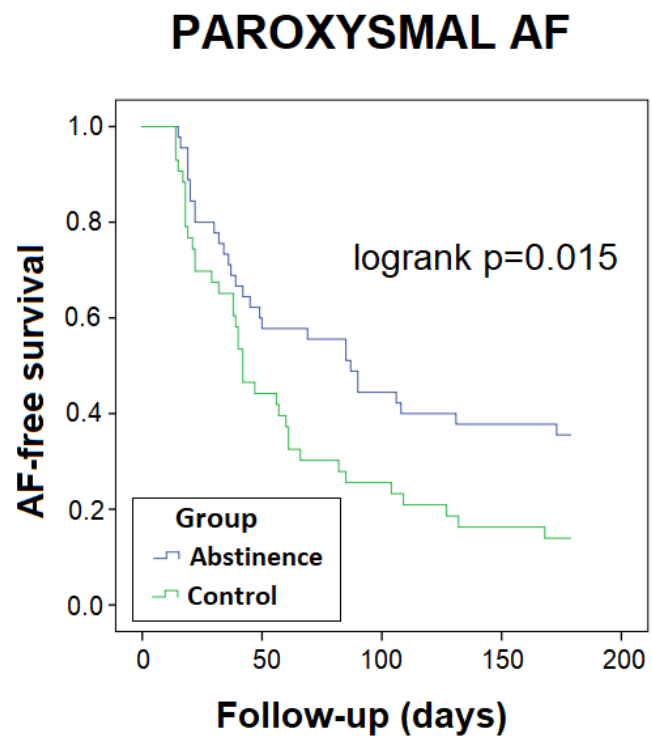
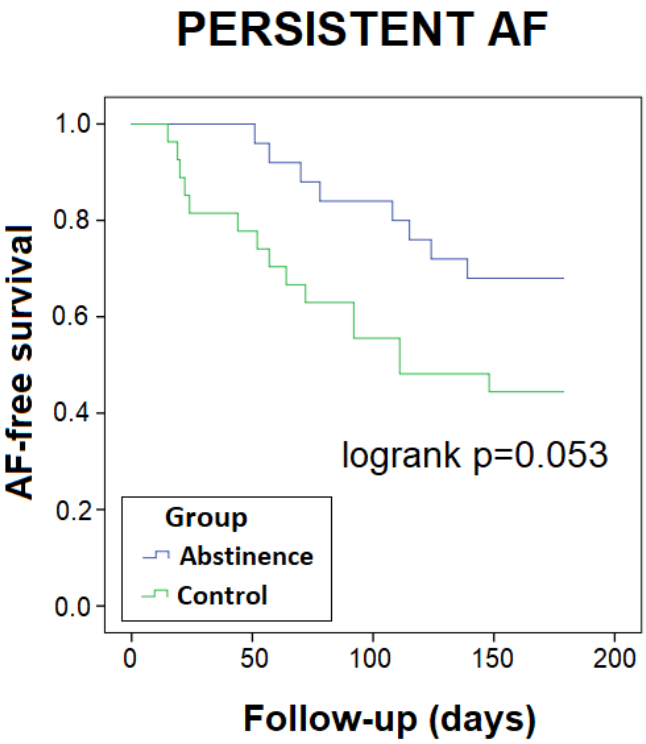


Figure 5: Subgroup analysis by AF type (paroxysmal and persistent AF) – time to AF recurrence





Chapter 5: Relation of Alcohol Consumption to Left Ventricular Fibrosis Using Cardiac Magnetic Resonance Imaging

Introduction

A U-shaped relationship is well described between alcohol consumption and cardiovascular mortality. Population studies suggest increased survival in light-to-moderate regular drinkers[407,408] compared with abstainers and heavy drinkers[414]. Proposed mechanisms include anti-oxidant & anti-inflammatory effects[429], which may explain observed reductions in heart failure[430,431] independent of coronary artery disease[432]. Ventricular T1 mapping using cardiac magnetic resonance imaging (CMR) has emerged as a validated non-invasive tool for quantifying fibrosis from collagen accumulation within the interstitium, and is also useful for characterization of infiltrative pathologies and acute myocardial injury[433]. In particular, the native T1 time is particularly sensitive to myocardial oedema and fibrosis[434]. We hypothesized that light-to-moderate alcohol consumption may have favourable effects on the ventricular myocardium, and sought to examine the relationship between alcohol consumption and markers of diffuse ventricular fibrosis on CMR.

Methods

This is a single centre observational study performed at Baker Heart and Diabetes Institute, Melbourne, Australia between August 2015 and May 2018. We aimed to prospectively recruit 165 participants to undergo 3T CMR with ventricular T1 mapping. Participants were healthy volunteers whom underwent CMR solely for the purpose of research. An alcohol intake history was taken to estimate average alcohol consumption in standard drinks per week (SDs/week) over the preceding 12 months, where 1 SD ~ 12g alcohol which is equivalent to 100mL glass of 13% red wine, 375mL can of mid-strength (3.5%) beer and 30mL of 40% spirits. Consumption over the preceding month was assessed to exclude recent binge drinkers & the potential impact of acute inflammation.

Regular light-to-moderate drinkers (7–28 SDs/week for > 12 months) and lifelong non-drinkers as controls were recruited consecutively, with a frequency-matching study design used to match for age & gender. Exclusion criteria included: (1) Infrequent alcohol intake defined as 1 – 6 SDs/week; [102] Heavy alcohol intake > 28 SDs/week; (3) Frequent (> monthly) or recent (last 1 month) binge drinking, as defined as >5 SDs over a 2 hour period ; (4) Alcoholic liver cirrhosis; (5) Significant renal impairment (eGFR < 30 mL/min); (6) Significant known structural heart disease (LVEF < 40% or previous myocardial infarction with regional wall motion abnormality).

Our CMR scanning and analysis protocol has been described previously[404]. CMR examinations were performed on a 3T scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). Post-processing of images was performed using a dedicated CMR analysis workflow of the Syngo.via software package (Siemens Healthineers, Erlangen, Germany). After acquisition of scout images, cine sequences were acquired in the 4-chamber, 2-chamber, 3-chamber and short-axis views extending from the mitral valve annulus to the LV apex (8-mm slice thickness, no gap) using an ECG-gated balanced steady-state free precision (SSFP) sequence in expiration. LV mass and LV volumetric analysis (summation of disk method) were analyzed on commercially available post-processing software and indexed to body surface area. Papillary muscles were considered part of the ventricular cavity. Myocardial T1 times were derived using the ShMOLLI sequence (Siemens Healthineers, Erlangen, Germany) which automatically generated pixel maps of T1 times. These were used during post-processing with a motion correction algorithm applied to the raw images, as shown in Figure 1. Post-contrast sequences were analysed 10 min following intravenous bolus injection of gadolinium-diethylene triamine penta-acetic acid (DTPA) (0.2 mmol/kg BW, Magnevist, Schering, Germany).

Each sequence was acquired within an end-expiration breath-hold using an ECG-triggered single-shot acquisition with a balanced steady-state free precession readout in a single mid-LV short-axis slice. Native T1 (pre-contrast) and post contrast T1 times were measured in the myocardium and left ventricular blood pool using a region of interest [435] on the T1 pixel map, T1 measurements were taken at the mid SAX level,

both by including the entire myocardium (excluding artefact) and by taking a region within the septum. The myocardial extracellular volume (ECV) was calculated from the dynamic steady state concentration of extracellular contrast in the myocardium relative to the blood pool, incorporating the participant's haematocrit (Hct), as previously described[436]. CMR measurements and T1 mapping were performed by two experienced CMR cardiologists (CMR fellowship trained, > 1000 cases experience) in accordance with recommendations stipulated by the Society for Cardiovascular Magnetic Resonance position statement[433]. Both cardiologists were blinded to the drinking status of each patient.

The primary outcome measure was a comparison of T1 mapping parameters (native ventricular T1 time, post-contrast T1 time & ECV) between regular drinkers & lifelong non-drinkers. We estimated we would need to enrol 96 patients to detect a 5% absolute difference in the native T1 time between both groups to provide a power of 0.8 at an alpha value of 0.05. The Shapiro-Wilk test was performed to confirm normal data distribution and a student t-test then performed. Continuous data are summarized as mean ± standard deviation or median, as appropriate. Between-group comparisons were performed using a Chi-square or Fisher exact test. Complete-case analysis was performed using Statistical Package for the Social Sciences for Windows (SPSS version 23, IBM). P values < 0.05 were considered statistically significant. The study was approved by Alfred Health Human Research Ethics Committee.

Results

In total 165 participants were recruited between August 2015 and June 2018, comprising 120 regular light-to-moderate drinkers (7–28 standard drinks per week for > 12 months) and 45 age-matched non-drinkers. Baseline clinical characteristics did not differ significantly between the groups as shown in Table 1. Patients in both groups were mostly male (69.5%), 'middle-aged' (mean age 59±12 years) and Anglo-Saxon (86%), with a relatively low prevalence of medical comorbidities (35% hypertension, 7% diabetes mellitus).

Alcohol consumption patterns are summarized in Table 2. The majority of patients consumed approximately 1 – 3 standard drinks per day (mean intake 16.3 SDs/week)

for a large portion of their adult life (26.1 ± 10.5 yrs duration). Wine was the most common (55%) alcoholic beverage consumed followed by beer (35%). Cardiac MRI characteristics are shown in Table 3. Regular alcohol consumption (mean alcohol intake 16±6 SDs/week) was associated with lower markers of diffuse ventricular fibrosis with respect to all three T1 mapping parameters (as shown in Figure 2):

- Native T1 time 1140±47 vs 1173±39ms in non-drinkers; p<0.001,
- Post-contrast T1 time 470±47 vs 445±43ms in non-drinkers; p =0.01, and
- ECV 25.0±2.7% vs 27.0±2.8% in non-drinkers; p=0.003.

As shown in Table 3, regular drinkers had similar indexed LV size, LV systolic function and LV mass compared with non-drinkers. Delayed Gadolinium Enhancement (DGE) was infrequently observed and minor when present, occurring in 3 (6.7%) non-drinkers (2 subtle linear midwall, 1 subendocardial DGE) and 5 (2.4%) of regular drinkers (4 subtle linear midwall, 1 subendocardial DGE). All three T1 mapping parameters were compared with respect to quantity of alcohol intake and type of beverage consumed (beer, wine, spirits), as summarized in Table 4. There were no dose-related or beverage-specific effects observed with respect to any of the T1 parameters (p>0.05). Nevertheless, all drinking groups had less ventricular fibrosis than lifelong non-drinkers.

Multiple linear regression was performed looking at the impact of patient factors (i.e. gender, age, cardiovascular risk factors) & imaging variables (LV systolic function, LV mass) on native T1 time (dependent variable) in our cohort (Table 5). Regular moderate alcohol consumption was identified as a significant independent predictor of shorter native T1 time (Standardized Beta coefficient = -0.255; p=0.008). There was no statistical interaction of the gender (p=0.51) & age (p=0.09) with alcohol consumption & fibrosis.

Discussion

Mild to moderate levels of alcohol consumption are associated with reductions in heart failure, all-cause mortality and sudden death in observational studies. The present study is hypothesis-generating and provides some preliminary insights into a possible mechanism for the observed U-shaped relationship, namely reduction in diffuse

ventricular fibrosis. Heavy drinkers are at higher risk of sudden cardiac death (>42 drinks per week)[437,438] and may develop alcoholic cardiomyopathy (>50 drinks per week for >10 years)[143]. Histological changes include myocytolysis, cytoplasmic lipid droplet formation, myofibrillatory disarray, interstitial fibrosis and myocyte apoptosis[439].

T1 mapping has been validated in human studies as a reliable non-invasive measure of interstitial fibrosis. Bull et al demonstrated a strong correlation between collagen volume fraction (CVF) and native T1 time in 19 patients with aortic stenosis[440]. In 44 patients undergoing cardiac biopsy, CVF correlated more closely with native T1 time, followed by ECV. Iles et al demonstrated a strong correlation between post-contrast myocardial T1 times and histological diffuse myocardial fibrosis[441]. A further study in 19 heart failure and hypertrophic cardiomyopathy patients found that degree of myocardial interstitial fibrosis measured at explant / myectomy correlated significantly with post-contrast T1 times[442]. In a study of 117 diastolic heart failure patients, CMR ECV correlated with histological ECV on myocardial biopsy, brain natriuretic peptide levels, exercise capacity and hospitalizations[443].

The myocardial extracellular collagen network, comprising type I and III fibrillary collagen, functions to preserve tissue architecture, tensile strength, and maintain chamber geometry in all individuals. Collagen turnover is dynamic and influenced by numerous homeostatic mechanisms[444], and collagen concentrations and inter-molecular cross-linking increase with age[445]. Beneficial anti-inflammatory and anti-oxidant effects of mild-moderate alcohol consumption have been well-described, and may prevent excessive accumulation of collagen resulting in a reduction in collagen volume fraction (CVF).

Light to moderate regular alcohol consumption is associated with reductions in inflammatory markers. In a population-based study of 840 women, Oliveira et al found a U-shaped relationship between hs-CRP and alcohol intake, with those consuming up to 30g/day having lower levels than non-drinkers[446]. Imhof et al demonstrated a U-shaped relationship for both alpha1-globulins ($p=0.0006$) and CRP ($p=0.048$) and an inverse U-shaped relationship between negative acute-phase reactants albumin ($p=0.006$) and alcohol consumption in 781 males[447]. In 6793 healthy adults, intake of

either beer or wine (up to 40 g/day) was associated with lower CRP, fibrinogen and white cell count compared to heavy and non-drinkers. A crossover study of healthy men found significant reductions in hs-CRP, intercellular adhesion molecule-1, interleukin-6, and monocyte chemoattractant protein-1 after 30 g/day wine intake for 1 month[448]. In a randomized study, moderate beer consumption (4 glasses/day in men, 3 glasses/day in women) for just 3 weeks was associated with a reduction in CRP and fibrinogen compared with non-alcoholic placebo[449]. Collagen turnover is subject to the effects of various inflammatory mediators[450]. In the present study mild-moderate alcohol consumption over many years is associated with a reduction in diffuse ventricular fibrosis.

A reduction in ventricular fibrosis may in part explain a reported reduction in heart failure in a large dose-response meta-analysis involving 202,378 individuals and 6,211 incident cases of heart failure[451]. Di Castelnuovo et al recently demonstrated that consumption of 7–28 SDs/week (as in our cohort) reduced the risk of new-onset HF by 22% over 8 years compared to never drinkers[452]. In 6,797 patients with severe systolic dysfunction, light-to-moderate drinking up to 14 SDs/week reduced all-cause mortality (7.2 vs 9.4 deaths/100 person years)[101]. These findings were consistent in ischemic and dilated cardiomyopathy.

This hypothesis-generating observational study posits a mechanistic explanation linking the observed beneficial effects of mild-moderate alcohol consumption on ventricular fibrosis and heart failure, mortality and sudden death outcomes. It adds to the growing body of evidence that suggests that mild-moderate amounts of alcohol are not detrimental to the ventricle, and on the contrary, may reduce the markers of ventricular fibrosis. These preliminary findings may have potential clinical implications as many physicians continue to counsel patients with cardiomyopathy to abstain from alcohol entirely[453].

This study has several limitations. While T1 mapping has been widely validated histologically, it remains a relatively novel technique and the clinical significance of small but statistically significant differences are unclear. Lack of histological and biochemical validation are potential limitations. The benefits of alcohol observed may be related to unknown confounders, such as associated diet or socioeconomic status.

Thus the negative association between alcohol and ventricular fibrosis does not imply 'causation'. Alcohol intake was self-reported and hence may be inaccurate, potentially explaining the absence of a dose-response relationship. While reduction in native T1 time observed in the drinking group can relate to fat deposition, the findings of the post-contrast and ECV do not support this. It should also be noted that ECV has correlates significantly ($p<0.05$) with native T1 and post-contrast T1 ($r=0.31$ and $r=-0.57$ respectively), hence the findings in all three T1 mapping parameters are not entirely independent.

Conclusion

Regular light-to-moderate or "social" alcohol consumption is associated with a reduction in the markers of diffuse ventricular fibrosis as determined by CMR. These preliminary findings may potentially explain the association between modest alcohol intake and reduction in sudden death and heart failure.

Table 1: Baseline clinical characteristics

	Alcohol Drinkers		
Parameter	**No (n=45)**	**Yes (n=120)**	**p-value**
Age (years)	58±14	60±11	0.22
Men	67%	72%	0.56
Hypertension	36%	34%	0.89
Diabetes Mellitus	7%	9%	0.63
Dyslipidemia	20%	17%	0.61
Smoker	8%	12%	0.49
Anglo-Saxon	84%	87%	0.60
Body mass index (kg/m^2)	27±5	27±5	0.93
Weight (kg)	83±15	86±17	0.44
Medications			
ACE inhibitors / ARBs	13%	16%	0.71
Beta Blockers	25%	27%	0.88
Statins	16%	13%	0.73

Definition(s): dyslipidemia: LDL ≥130 mg/dl, HDL <40 mg/dl, total cholesterol ≥200 mg/dl, or triglycerides ≥150 mg/dl

Table 2: Alcohol intake details (n=120)

Parameter	Value
Alcohol intake (SDs/wk)	16.3 ± 6.4
Duration of regular alcohol intake (yrs)	26.1 ± 10.5
Beverage consumed	
Beer	34.5%
Wine	55.1%
Spirits	10.9%

*Values are provided as mean ± standard deviation.

Definition(s): SDs/wk – standard drinks per week, where 1 SD ~ 12g alcohol.

Table 3: Cardiac MRI parameters

Parameter	Non-drinkers (n=45)	Drinkers (n=120)	p-value
Stroke volume (mL)	100±23	102±27	0.77
Left ventricular ejection fraction (%)	60±12	58±10	0.35
Left ventricular end diastolic volume (mL)	163±36	176±42	0.15
Right ventricular end diastolic volume (mL)	160±36	166±39	0.75
Left ventricular mass (g)	122±39	135±42	0.16
Left ventricular end diastolic volume indexed (mL/BSA)	79±13	81±16	0.55
Left ventricular mass indexed (g/BSA)	63±15	64±18	0.78
Native T1 time (msec)	1173±39	1140±47	<0.001
Post-contrast T1 time (msec)	445±43	470±47	0.01
Extracellular volume	27.0±2.8%	25.0±2.7%	0.003

Table 4: T1 mapping parameters by quantity of alcohol intake and beverage

Drinking category	Native T1 time (ms)	Post contrast T1 time (ms)	ECV (%)
Non-drinkers	1173±39	445±43	27.0±2.8%
7 – 14 SDs/week	1139±48	480±46	25.0±2.6%
14.1 – 21 SDs/week	1143±50	457±53	25.5±2.8%
21.1 – 28 SDs/week	1138±42	472±35	24.4±2.6%
Beer	1144±50	480±46	25.2±2.7%
Wine	1137±47	468±45	25.0±2.8±
Spirits	1136±53	460±38	24.5±3.0%

Table 5: Multivariate analysis of predictors of shorter native T1 time in our cohort

Independent Variable	Standardized Beta coefficient	Significance
Age	.092	0.365
Alcohol consumption	-.255	0.008
Gender	-.114	0.277
Hypertension	.115	0.271
Diabetes mellitus	-.022	0.813
LV ejection fraction	-.086	0.354
LV mass	.173	0.116

Figure 1: Pixel map images using ShMOLLI technique for Native T1 and Post Contrast T1 Mapping

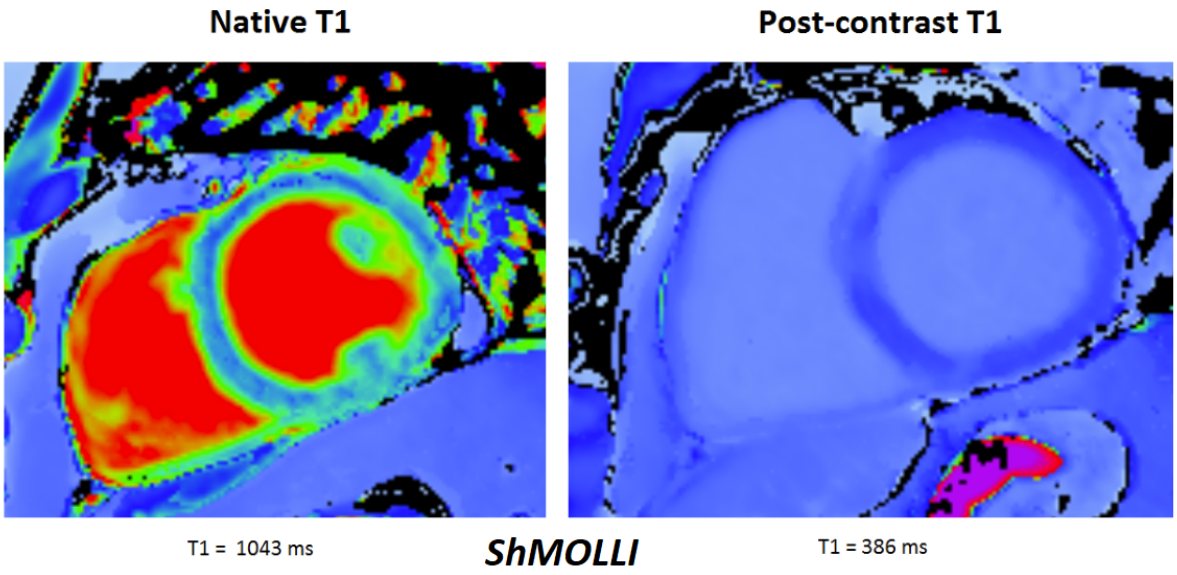
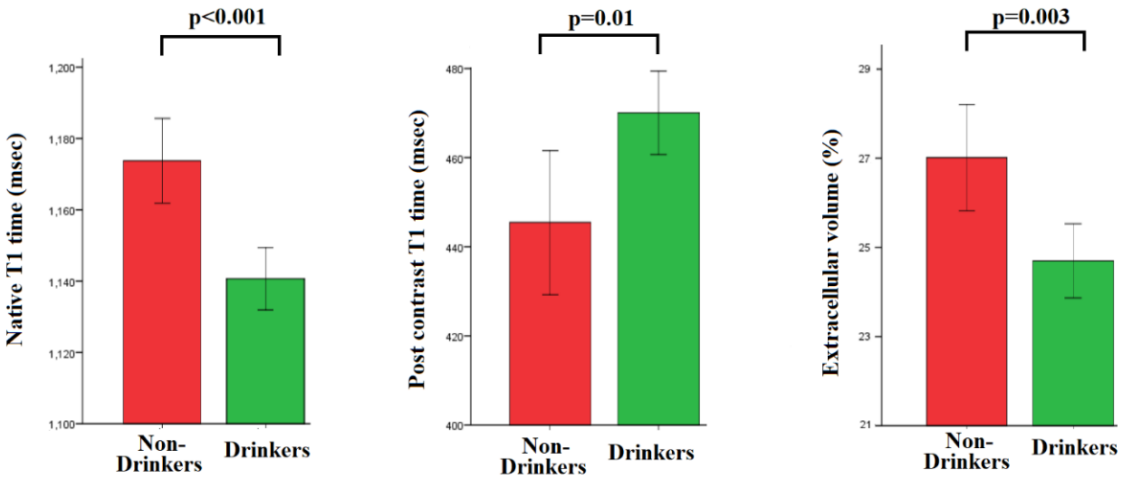


Figure 2: Comparison between mild-moderate regular drinkers and lifelong non-drinkers with respect to T1 mapping parameters



Chapter 6: Cardioversion of Atrial Fibrillation in Obese Patients: Results from the Cardioversion-BMI Randomized Controlled Trial

Introduction

With burgeoning rates of both obesity and AF in Western countries, increasing numbers of patients are being referred for direct electrical cardioversion (ECV) as part of a rhythm control strategy. Success rates range from 50 – 93%[454,455] and depend on several factors including left atrial size, AF duration and transthoracic impedance (TTI). Body mass index (BMI) is a key determinant of TTI and therefore cardioversion failure is more frequent in obese patients[456].

A recent large meta-analysis did not demonstrate a difference in cardioversion success rates for different electrode positions (anteroposterior vs anteroapical) in most patients[323], however this did not specifically electrode positions in obese patients. Moreover, the modality used appears to be an important factor. In a randomized trial of 201 patients, hand-held paddles successfully cardioverted 98% of patients, compared to 86% with adhesive patches ($p = 0.001$)[322]. This is likely explained by a lower TTI conveyed by hand-held paddles and hence more efficient energy delivery to the left atrium[457,458]. Again this study did not pre specify the impact of intervention in obese patients. We hypothesized that an even greater difference would be observed with paddles in obese patients.

For ease of use and workplace safety many centers routinely use patches for ECV with a reduction in the availability of hand held paddles. There are no randomized trials to date looking at cardioversion in obesity. We performed a randomized controlled trial to determine the optimum modality and shock vector for ECV of obese patients (BMI ≥ 30) with persistent AF. In particular, we hypothesized that hand-held paddles would be more effective than adhesive patches. We also performed an additional observational sub-study in morbidly obese patients to test the safety and efficacy of Manual Pressure Augmentation in those with refractory ECV to 200J.

Methods

Cardioversion-BMI randomised controlled trial

We prospectively recruited 125 patients between 7/2016 – 3/2018 at four hospitals in Melbourne, Australia. Patients were included if they were undergoing a clinically-indicated external cardioversion for persistent atrial fibrillation and had a body mass index ≥ 30. Atrial flutter was an exclusion criteria.

A computerized central randomization scheme was generated using block randomization and sets of randomly selected blocks were provided to the investigating sites. Randomization occurred prior to ECV to enable appropriate patient positioning prior to administration of sedation. Thus, operators were not blinded to group allocation.

Patients were randomized in a 1:1:1:1 fashion into 1 of 4 arms based on modality (adhesive patch or hand-held paddles) and shock vector (anteroposterior [AP] or anteroapical [AA]). All shocks were biphasic and synchronized. If the first two shocks (100J, then 200J) failed then patients crossed over to a 200J shock using the alternative modality (patch or paddle), as shown in Figure 1. Each subsequent shock was delivered at least 3 minutes after the previous failed shock and electrode location and vector remained constant for all three shocks.

For anteroapical (AA) shocks, anterior electrodes (paddle or patch) were placed just to the right of the upper sternal border below the clavicle and the apical electrodes were placed to the left of the nipple with the center of the electrode in the mid-axillary line with the patient supine. For anteroposterior (AP) shocks, the anterior electrode was placed in the right parasternal region, and the posterior electrode was placed in the left infrascapular region with the patient positioned on their side (Figure 1).

To improve efficacy and safety of all cardioversions, body hair was shaved and electrodes were applied to dry, clean skin free of abrasions. For paddle shocks, a coupling agent (defibrillation paste or gel pad) was used to cover the metal electrode surfaces. Firm paddle pressure was encouraged, and use of in-built sensors to assess paddle-to-patient contact were encouraged (if available) to maximize energy delivery. Propofol was the main agent used to provide deep sedation.

Successful cardioversion was defined as two consecutive sinus beats uninterrupted by AF occurring immediately after cardioversion. The pre-specified primary endpoints for comparison between the Patch and Paddle arms were (1) rate of successful cardioversion with either 1st or 2nd shock (i.e. up to 200J biphasic) and [102] rate of successful cardioversion by modality (i.e. patch vs paddle). Secondary endpoints were comparisons between AA and AP shock vectors, average energy use (J) by modality and rates of successful cardioversion with 1st shock (100J).

Statistics

A power calculation determined that to detect a minimum absolute difference in the primary endpoint of 20% between both groups, ~58 patients needed to be enrolled in each group (i.e. paddle / patch) to provide a power of 0.8 at an alpha value of 0.05.

The primary endpoints were assessed using a 2 x 2 contingency table and χ^2 test. All continuous data are summarized as mean ± standard deviation or median, where appropriate. The Shapiro-Wilk test was performed to confirm normal distribution of data and a student t-test then performed. Mann-Whitney U test was used for continuous variables where normal distribution was not present. Comparisons of the clinical characteristics between groups were performed using a χ^2 or Fisher exact test. A logistic regression analysis was performed to determine multivariate predictors of successful external cardioversion using the primary endpoint (1st or 2nd shock success) as the dependent variable and BMI, age, ejection fraction, continuous AF duration and LA size as covariates. Data analysis was performed using Statistical Package for the Social Sciences for Windows (SPSS version 23, IBM). P values < 0.05 were considered statistically significant.

All patients provided informed written consent to the study protocol. The trial was approved by the Alfred, Melbourne, Cabrini and Western Health Human Research Ethics Committees and complies with the Declaration of Helsinki. The trial (Cardioversion-BMI) was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR: 12616000302459).

Observational sub-study using Manual pressure augmentation

During the course of the Cardioversion-BMI randomized trial, we concurrently ran an observational sub-study to assess the safety and efficacy of Manual Pressure Augmentation (MPA) in morbidly obese patients (BMI ≥ 35) with PeAF who failed shocks up to 200J with both patches and paddles. Patients from the Cardioversion-BMI randomized trial who failed all three shocks with patches and paddles were allowed to be included in the study (and enrolled at the time of the initial cardioversion), as were additional patients who were not in the randomized study.

Manual pressure was delivered during the expiratory phase of respiration, with either one or two operators wearing latex gloves providing manual pressure augmentation on each patch with either one or two hands (Figure 3) while another clinician charged and delivered energy through the defibrillator. Initial energy used was mandated at 200J biphasic using this approach, however if a 360J biphasic defibrillator was available, an additional shock at 360J using MPA was delivered. Shock vector remained unchanged throughout the study.

Results

Cardioversion-BMI Randomized Controlled Trial

In total 125 patients were randomized into either Patch (n=63) or Paddle (n=62) arms, with patients also split between AA (n=64) and AP (n=61) shock vectors. Of these, 120 (96.0%) were recruited from elective ECV lists while 5 (4.0%) were acute inpatients. A Flow Diagram of the study and success rates by modality are shown in Figure 2. Baseline characteristics of patients in both Paddle and Patch arms are shown in Table 1. Patients were well-matched between the groups and were predominantly male, markedly obese (mean BMI 35) with dilated atria (mean LA area 28 cm^2) and prolonged duration of continuous AF (> 3 months in 55% of patients).

Primary and secondary endpoints are summarized in Table 2. Success from 1st or 2nd shock was 43/63 (68.2%) for patches & 56/62 (90.3%) for paddles (p=0.002). There were 20 crossovers from patches to paddles (12/20 third shock success with paddles) & 6 crossovers from paddles to patches (3/6 third shock success with patches). Paddles

successfully cardioverted 68/82 patients compared with 46/69 using patches (82.9% vs 66.7%; p=0.02).

Success with 100J was significantly higher in the Paddle group (50%) compared to the Patch group (27%, p=0.01). Average energy requirement was significantly lower in the Paddle arm (150±50 vs 173±45 J in the Patches group; p=0.01). 1st or 2nd shock success was 27/30 (90%) for AP Paddles, 23/31 (74%) for AP Patches, 29/32 (91%) for AA Paddles, 20/32 (63%) for AA Patches. Shock vector did not influence 1st or 2nd shock success rates (82.0% AP vs 76.6% AA; p=0.46).

In the subgroup of 22 patients with morbid obesity (defined as BMI > 40) included in the study (mean BMI 44.5±4.0), 6/22 (27%) were successfully cardioverted with 100J while 17/22 (77%) were successfully cardioverted with up to 200J. After inclusion of crossovers successful cardioversion was achieved with paddles in 9/16 patients (56%) compared to 8/15 (53%) with patches (p=0.87). Shock vector did not affect final success (AA 75% vs AP 79%; p=0.86) in this subgroup.

Patients who failed all three shocks (n=11) were more likely to be heavier (weight 119±18 vs 106±19kg; p=0.03), have LV dysfunction (LVEF 44.5±11.4 vs 53.0±10.4%; p=0.02) and have a longer continuous AF duration (11.0±12.7 vs 4.8±7.2 months; p=0.04). Antiarrhythmic therapy (82% vs 62%; p=0.20), LA area (30.4±8.1 vs 27.4±7.7 cm2; p=0.27) and previous cardioversion attempts (64 vs 68%; p=0.78) were not significantly different.

A logistic regression analysis was performed to determine multivariate predictors of successful external cardioversion. Lower body mass index (OR 0.92; 95% CI 0.85-0.98; p=0.025) was a significant predictor of successful ECV. Left ventricular systolic dysfunction (p=0.23), age (p=0.22), LA size (p=0.84) and continuous AF duration (p=0.81) were not statistically significant. There were no safety issues or complications throughout the course of the study.

Manual pressure augmentation observational sub-study

In total 20 patients underwent MPA, including 11 patients from the randomized trial who failed all three shocks (200J using both patches and paddles). Shock vector

remained unchanged for all shocks, and was anteroapical in 10/20 (50%) and anteroposterior in 10/20 (50%). Most patients were male (17/20) and morbidly obese (BMI 39±6). Mean LVEF was 44±12%, LA area 30±8 cm^2 and continuous AF duration was 5.6± 4.4 months.

All patients had failed shocks with 200J with patches and paddles. MPA at 200J was successful in 10/20 (50%) of these patients and MPA at 360J was attempted in 7/10 remaining patients, with 6/7 (86%) being successful. Two operators were used to deliver MPA in 5 instances. Hence MPA was successful in 16/20 (80%) of patients who failed both patches and paddles at 200J, despite the shock vector remaining unchanged for all shocks. No complications were reported for patient or operator(s) with this technique.

Discussion

Atrial fibrillation is an emerging epidemic which is in part related to the increasing prevalence of obesity. Electrical cardioversion is a first line rhythm control strategy however is less effective in obese patients. A higher failure rate of ECV in an ever-growing obese AF population may in part be explained by the current trend of replacing hand-held paddles with disposable adhesive patches to enable easy-to-use 'hands-free' therapy. In the first randomized study looking at optimizing ECV success in obesity there were several important findings:

(1) Current standard practice in many centers of using patches with 200J capable defibrillators leads to a failure rate of ~ 30% in obese patients with AF.

(2) Hand-held paddles significantly improve success rates over adhesive patches at the same energy.

(3) Shock vector was not an important factor in determining success rates.

(4) Use of a starting energy below 200J in obese patients is unsuccessful in the majority.

(5) Manual pressure applied over adhesive patches using gloved hand(s) is likely to improve efficacy further, and can be applied safely without risk to patient or operator up to 360J biphasic.

(6) Availability of 360J capable defibrillators may improve success rates in morbidly obese patients, although this was not systematically tested in this study.

Factors which may explain the reduction in the success of ECV for atrial fibrillation in obesity include higher transthoracic impedance, greater inter-electrode distance and decreased transthoracic current flow due to dissipation of current. In addition to greater chest circumference, obese patients have higher volumes of pericardial fat, intrathoracic fat and visceral adipose tissue that may impact ECV success[459].
Several earlier studies suggested superiority of paddles over adhesive pads in patients with a range of BMIs and included atrial fibrillation and flutter[460-462]. Many centers (including all four participating sites in the current study) routinely use adhesive pads only for ECV. The present study underscores the importance of maintaining the availability of hand-held paddles in overweight and obese patients.

Proposed mechanisms for superiority of paddles include paddle force resulting in lower transthoracic impedance[463], more uniform and effective electrode-skin contact[464], improved emptying of the lungs and resultant shorter distance between electrodes and atrium with higher transthoracic current flow[318]. Excessive current delivery resulting in myocardial necrosis is rare[465], and the use of 360J biphasic capable defibrillators may improve success further. Internal cardioversion is successful in obese patients who fail ECV[466] with a direct relationship between BMI and defibrillation threshold, however is invasive and more expensive than external cardioversion.

Importantly, there is significant heterogeneity between operators with respect to force delivered using paddles, and this may explain the cross-over rates observed. In a study of 54 clinicians applying paddle force to mannequins during standard defibrillation, sternal paddle forces ranged from 26.1-132.8N while apical paddle force ranged from 18.6-118.5 N. These findings may explain the variable success in crossovers from paddles to pads, and vice versa, observed in the present study[467]. Moreover, the learning curve associated with using paddles may curtail widespread adoption. In our experience, the Manual Pressure Augmentation technique described (and safely used at our institution for >100 patients to date) is easy to learn and enables consistent application of force. The conformation of the patch to the chest wall while applying pressure (which does not occur with more rigid paddles) and ease-of-use with two operators may shorten inter-electrode distance further and enable more efficient energy transfer accounting for the high efficacy of this technique in the observational sub-study.

The successful defibrillation of AF in obese patients may be of limited durability with each 5 kg/m^2 BMI increase associated with a ~10% higher risk of AF recurrence at follow-up[468]. Achieving weight loss, and addressing associated comorbid conditions such as sleep apnea, hypertension, diabetes and excessive alcohol consumption remain critical. These measures, while difficult to achieve in many, are most likely to be effective at reducing AF recurrence rates, reversing remodelling of AF substrate and improving long-term outcomes[258].

Clinical implications

Cardioversion attempts should not be abandoned in obese AF patients if adhesive patches are unsuccessful at 200J. We propose either the routine use or availability of hand-held paddles to improve the likelihood of successful cardioversion. This may require education of health care workers to ensure cardioversion by hand-held paddles can be delivered safely. Additional strategies that may improve success include Manual Pressure Augmentation and escalation to 360J. These findings may have additional implications for resuscitation of other cardiac arrhythmias, including shock-refractory ventricular tachycardia or fibrillation, particularly in obese patients.

Limitations

There is a learning curve associated with use of hand-held paddles, and we did not assess operator experience or transthoracic impedance to determine whether this was a significant contributor to unsuccessful paddle shocks. Body fat distribution (i.e. chest circumference, abdominal adiposity) rather than BMI may be a predictor of success and was not determined. It is possible that shock efficacy using the AP vector may be different between patients positioned on their side as opposed to supine (not assessed in this study), whereby a morbidly obese patient's weight may exert considerable force on the posterior patch. The relatively small number of patients and observational nature of the non-randomized sub-study limits the ability to draw definitive conclusions regarding safety and efficacy of manual pressure augmentation and higher voltages.

Conclusion

Routine use of adhesive patches with defibrillation up to 200J is inadequate for AF in many obese patients. Hand-held paddles improve ECV success rates and should be

considered for electrical cardioversion of atrial fibrillation in obesity. Manual pressure over patches and availability of 360J capable defibrillators may improve success further.

Table 1: Baseline Characteristics for the Cardioversion-BMI Randomized Trial

Parameter	Patch arm (n=63)	Paddle arm (n=62)	p-value
Age (years)	61±11	60±10	0.76
Gender (% male)	75%	71%	0.65
Weight (kg)	109±20	106±17	0.50
Body mass index (BMI)	35±6	35±5	0.86
Hypertension (%)	41%	50%	0.51
Diabetes mellitus (%)	25%	38%	0.45
Continuous AF duration (months)	4±9	5±5	0.61
Antiarrhythmic therapy at ECV	71%	57%	0.48
Amiodarone	32%	23%	
Sotalol	21%	23%	
Flecainide	18%	11%	
Echocardiographic data			
Left atrial area (cm^2)	28±8	28±9	0.99
LVEF (%)	50±12	53±10	0.34
Mean E/E'	9±6	11±3	0.53

Abbreviations: ECV – direct cardioversion, LVEF – Left ventricular ejection fraction.

Table 2: Comparison between Patch and Paddle arms (first three shocks)

Parameter	Patch arm (n=63)	Paddle arm (n=62)	p-value
Primary endpoint 1: Success (1st or 2nd shock)	43/63 (68.2%)	56/62 (90.3%)	0.002
Primary endpoint 2: Success by modality	46/69 (66.7%)	68/82 (82.9%)	0.02
Average energy use (Joules)	173±45	150±50	0.01
1st shock (100J) success	17/63 (27%)	31/62 (50%)	0.01

Figure 1: Cardioversion-BMI Trial Protocol, including electrode position by shock vector

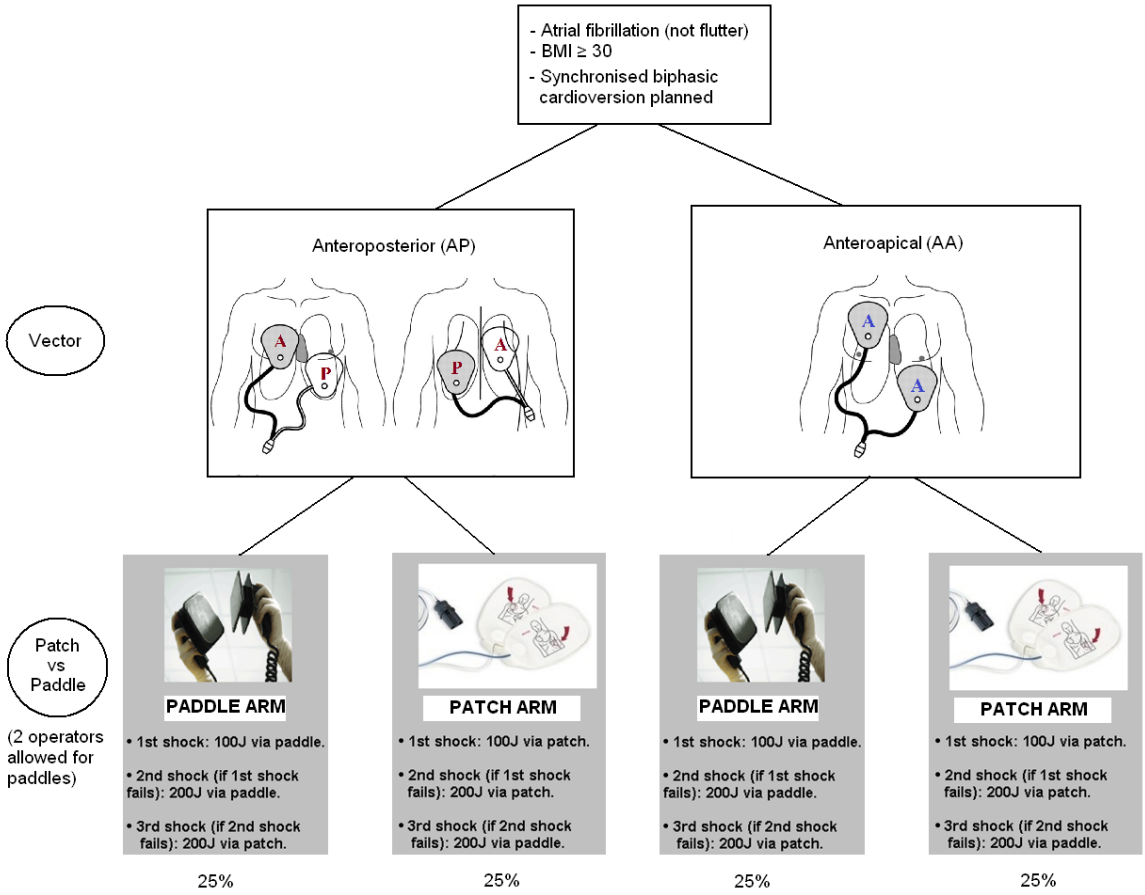


Figure 2: Study Flow Diagram and Success Rates by Modality in the Cardioversion-BMI Randomized Trial

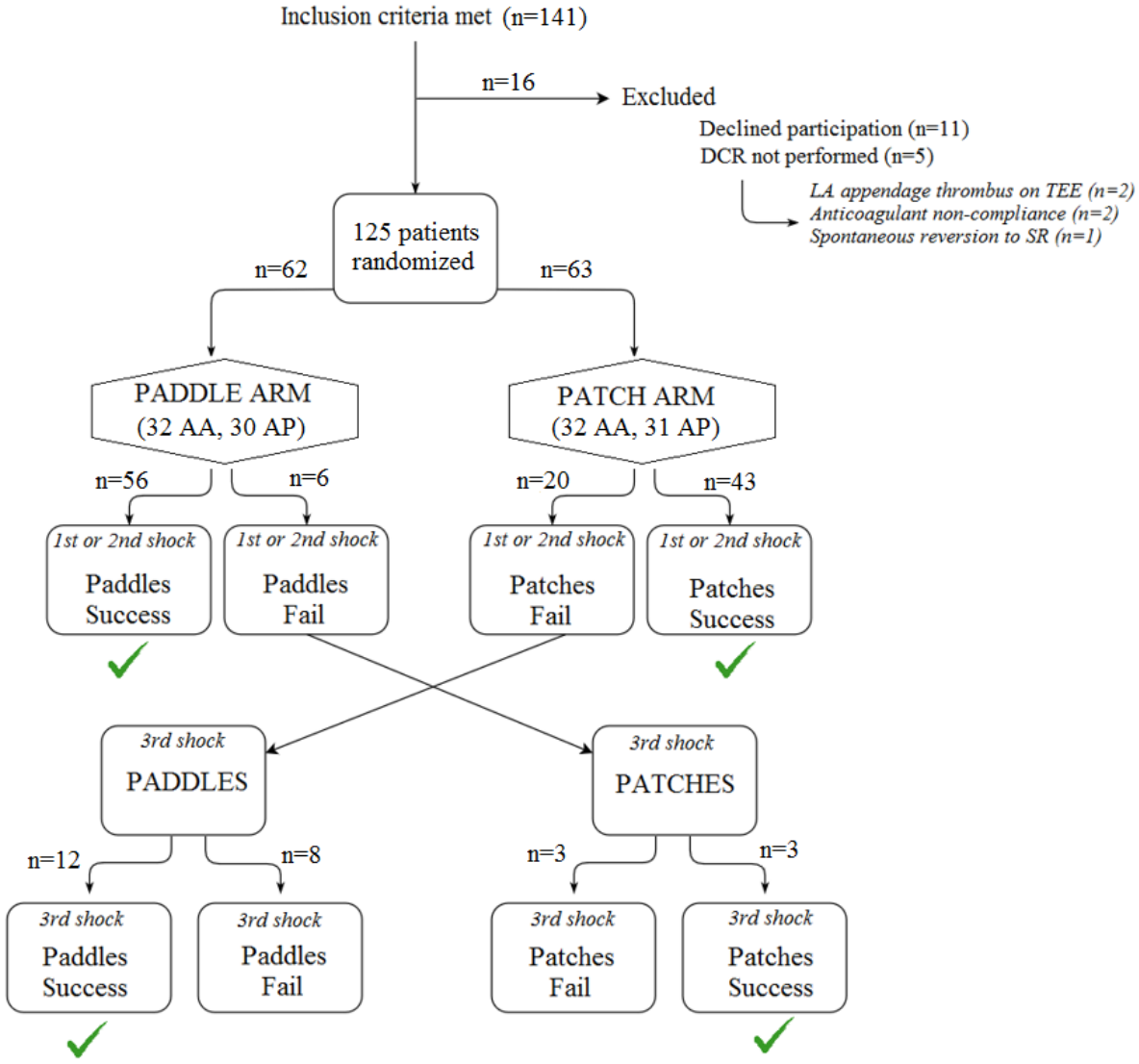
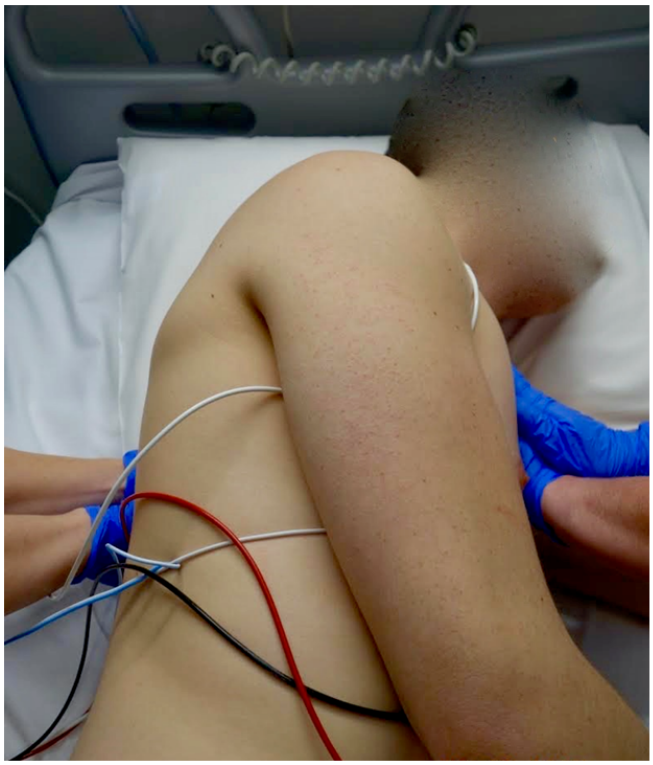


Figure Legend – DCR: direct cardioversion, TEE: transesophageal echocardiogram, AA: anteroapical, AP: anteroposterior, SR: sinus rhythm, LA: left atrial.

Figure 3: Example of Manual Pressure Augmentation using two operators in the anteroposterior position



Chapter 7: A comparison of early versus delayed elective electrical cardioversion for recurrent episodes of persistent atrial fibrillation: a multi-center study

Introduction

As an emerging epidemic of cardiovascular disease, increasing numbers of patients are utilizing electrical cardioversion (CV) for treatment of symptomatic persistent atrial fibrillation (PeAF). The timing of CV following AF recurrence is dictated by a combination of factors, including patient symptoms, physician preference and resource availability. In addition to adverse effects on quality of life from prolonged AF duration, progressive adverse electrical and structural changes occur in the atria at different time points following arrhythmia onset[469]. The clinical implications of delayed CV for intermittent PeAF are not well categorized, although some studies suggest these patients are at higher risk of AF recurrence[470]. Due to barriers to accessing early elective cardioversion, including time taken to see a family physician, obtain specialist referral and wait for a scheduled CV, we adopted a policy of instructing patients to present directly to the Emergency department for early cardioversion.

We sought to compare a strategy of early 'Emergency' CV versus delayed 'Elective' CV for treatment of intermittent PeAF. We hypothesized that benefits of early CV may extend beyond symptoms, including prevention of adverse remodelling, reduction in recurrence risk and potentially lower utilization of AF ablation.

Methods

Study design

In this observational retrospective cohort study, we evaluated 150 patients presenting with symptomatic PeAF presenting to two centres in metropolitan Melbourne between 2/2014 – 7/2017. All included patients had a history of persistent AF, as defined by a previous or current episode of AF lasting longer than 7 days. We sought to compare two patient groups – those treated with Emergency vs Elective cardioversion strategies and included 75 consecutive patients from each group. Follow-up occurred over 12 months.

Exclusion criteria included: (1) Persistent AF with prior early re-initiation of AF within 1 month[102]; Paroxysmal AF, with a prior history of spontaneous reversion within 7 days or chemical reversion; (3) Atrial flutter as the only documented rhythm; (4) Permanent AF, where sinus rhythm was unable to be restored; (5) Asymptomatic or minimally symptomatic patients as they are frequently unsure of time of symptom onset; (6) Previous AF ablation; (7) Decompensated heart failure.

Emergency cardioversion (ED-CV) group

Patients with a past history of CV for symptomatic PeAF were provided an AF action plan during their outpatient visit to follow in the event of recurrent symptoms. Patients were advised to document time of symptom onset and present to the emergency department within 36 hours, and fast for 6 hours prior to arrival. Consistent with guidelines, CV is routinely performed in un-anticoagulated patients within 48 hours of symptom onset without transesophageal echocardiography guidance or if anticoagulation is uninterrupted in those with AF onset > 48 hours. An emergency department physician assessed each patient and propofol was administered for sedation during CV. Additional antiarrhythmics were advised at clinician discretion. Patients with unclear onset of AF who were not consistently anticoagulated for the preceding 4 weeks were not cardioverted due to potential risk of left atrial appendage thrombus, as transesophageal echocardiography is not routinely available in the emergency department.

Elective cardioversion (EL-CV) group

Patients in this group were managed in an elective fashion consistent with usual care. This included new or repeat referral to a cardiologist, outpatient review, followed by placement on an elective hospital waiting list.

Anticoagulation

Anticoagulation was managed according to CHA_2DS_2-VASc score as per guidelines[144]. All those with AF> 48 hours in the elective group required a minimum of 4 weeks oral anticoagulant (AC) prior or a pre-cardioversion TEE. All in this group also required a minimum of 4 weeks AC post DCR if they were not already on long-term oral AC.

Patients with a CHA_2DS_2-VASc score of ≥ 2 (or = 1 at physicians discretion) were on long term oral anticoagulants.

Follow-up and endpoints

Follow up for 12 months following cardioversion included 12-lead ECG at onset of symptoms and during outpatient review at 3 months post discharge and 6 monthly thereafter. Holter monitors were performed at 6 and 12 months or for symptoms. Referral for AF ablation was routinely initiated for symptomatic AF despite 1 – 2 antiarrhythmic agents. Medical records, including specialist and family physician visits, emergency and inpatient discharge summaries were reviewed for recurrences and subsequent referrals for AF ablation.

The primary endpoint was time to persistent AF recurrence. Secondary endpoints included AF duration prior to CV, changes in left atrial (LA) size on echocardiography from baseline to follow-up, modified European Heart Rhythm Association [471] score at 12 months and time to referral for AF ablation.

Statistical analysis

Baseline characteristics and outcome measures are summarized as mean ± standard deviation or median, where appropriate. The Shapiro-Wilk test was performed to confirm normal distribution of data. The chi-square test was used to compare categorical variables, and Wilcoxon rank-sum test or Student's t-tests used for continuous variables. With respect to analysis of 'time to AF recurrence' and 'time to referral for AF ablation', these were performed using time-to-event methods with outcomes in the two study groups to be compared with the use of hazard ratios and 95% confidence intervals using a Cox proportional-hazards regression model. Multiple linear regression analysis was performed to determine independent clinical predictors of AF-free survival at follow-up. Duration of AF-free survival was used as the continuous dependent variable.

Data analysis was performed using Statistical Package for the Social Sciences for Windows (SPSS version 23, IBM). P values < 0.05 were considered statistically significant. The study was approved by the Alfred and Melbourne Health Human Research Committees and complies with the Declaration of Helsinki. The study was

registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12618001425280).

Results

A total of 150 patients were included from two public hospitals in Melbourne, Australia with all undergoing CV for intermittent PeAF between 1/2014 – 7/2017. A CONSORT flow diagram for included patients is shown in Figure 1. Baseline characteristics for 75 consecutive Early and 75 consecutive Elective CV are presented in Table 1. Patients were similar with respect to age, gender, co-morbidities and baseline left atrial size. However, the ED-CV cohort had a longer history of AF and more prior cardioversions. As expected, the ED-CV patients had a markedly shorter median AF duration prior to CV: median 1 day (IQR 1-3 days) vs 3 months (IQR 2-7 months; p<0.001). Two ED-CV patients were hypotensive on presentation and required emergent cardioversion.

A transesophageal echocardiogram (TEE) was performed in 25/75 (33.3%) prior to CV in the EL-CV group. There were no complications from CV in either group. Average length of hospital stay was 7.3 ± 1.5 hours in the EL-CV group and 8.0 ± 4.4 hours in the ED-CV group (p = 0.59).

All patients were followed up for 12 months. At follow-up, patients managed with the ED-CV strategy had less AF-related symptoms than the EL-CV group. Modified EHRA symptom scores assessed at the 12-month time point are shown in Figure 2. Modified EHRA symptom score was reported as at least mild (≥ 2a) in 44% of the ED-CV group vs 72% in the EL-CV group (p=0.005) and at least moderate (≥ 2b) in 12% of ED-CV vs 42% of EL-CV (p=0.001).

At 12-months, 42/75 (56%) in the EL-CV cohort and 25/75 (33%) in the ED-CV cohort developed recurrent AF (p = 0.005). Time to AF recurrence is shown in Figure 3A and was longer in the ED-CV group (295±15 vs 245±15 days; logrank p=0.001). Referral for catheter ablation was undertaken in 32/75 (45%) of EL-CV patients vs 21/75 (28%) of ED-CV patients (p=0.06) during the 12 month follow-up period. Time to AF ablation referral was significantly different between the two groups (314±13 ED-CV vs 276±15 days EL-CV; logrank p=0.01), as shown in Figure 3B.

Changes in LA area on serial echocardiography (baseline and follow-up) are shown in Figure 4. Baseline LA size was similar between the two groups (EL-CV 28±11 cm^2 vs ED-CV 27±4 cm^2; p=0.67). LA size significantly increased from baseline by 12% in the EL-CV group (p=0.046) while there was a non-significant reduction in LA size by 4% in the ED-CV group (p=0.31). The EL-CV group had larger LA area at follow-up (31±8 vs 26±6 cm^2; p=0.007).

Multiple linear regression analysis was performed to determine multivariate clinical predictors of AF-free survival at 12 months post CV. Elective cardioversion (standardized β-coefficient = 0.23; p=0.019) and female gender (standardized β-coefficient = -0.20; p=0.047) significantly predicted earlier AF recurrence. Age (p=0.84), diabetes (p=0.89), hypertension (p=0.98), body mass index (p=0.13), class I/III antiarrhythmic use (p=0.53), dyslipidemia (p=0.45) and valvular heart disease (p=0.74) were not statistically significant.

Discussion

This study compared a strategy of Emergency versus Elective CV for intermittent symptomatic PeAF in a cohort of 150 patients managed at two tertiary referral centres. Early cardioversion patients presented immediately to an ED for CV while elective patients waited for referral to and an appointment with a managing cardiologist.

There are several key findings:

First, the strategy of ED cardioversion was associated with a significantly lower risk of AF recurrence at one year. This translated into a lower likelihood of referral for invasive and costly AF ablation.

Second, ED cardioversion was associated with a much shorter period of time spent in AF (1 day vs 3 months). As a result, patients with recurrent persistent AF more frequently found this an acceptable management strategy with significantly less overall impact on quality of life.

Finally, there was less progression of remodelling with ED compared with Elective cardioversion thus providing a rationale for the observation that sinus rhythm begets sinus rhythm in this patient population.

Improvement in Quality of Life

The impact of AF on quality of life and mood has been observed to be greater in persistent compared to paroxysmal AF patients[472], and addressing these factors is central in AF management. The reduction in AF burden from 3 months to 1 day in the current study represents a dramatic change and no doubt is a key factor in QoL improvement. However, reduction in AF burden may not be the only factor responsible for the observed reduction in AF symptom severity in the ED-CV cohort[473,474]. The impact of an unpredictable and recurrent condition associated with perceived loss of control has significant psychological impacts on patients[4,475]. Patient education, development of an AF 'action plan' and empowerment were likely responsible for some of the reduction in morbidity observed in the ED-CV group, as other studies have demonstrated[476,477].

AF begets AF. Does Sinus rhythm beget sinus rhythm?

The concept that AF begets AF was first demonstrated in a classic study by Wijfells et al who showed significant shortening of the atrial effective refractory period and thereby easier AF inducibility after 2 – 4 weeks of AF, all of which completely resolved within 1 week of sinus rhythm[20]. However, when AF was allowed to continue for 4-months, structural remodelling persisted even 4 months after resumption of sinus rhythm[478]. These pre-clinical studies of AF mediated atrial remodelling were subsequently supported by clinical studies with similar findings[479,480]. Metabolic and electrophysiological 'adaptations' occur within hours to days following AF onset, the process by which electrical and structural remodelling ensues and become 'irreversible' begins to occur over many weeks to months[469].

On the basis of these observations, a number of prior clinical studies investigated whether the reverse would be true and that repeated early resumption of sinus rhythm would lead to sinus stabilisation (ie. sinus rhythm begets sinus rhythm). These studies yielded divergent results. Fynn et al found no improvement in maintenance of sinus rhythm with a policy of early repeated cardioversion within the first month in persistent

AF patients[481]. In a study of 15 patients with long-standing drug-resistant persistent AF using patient-activated atrial defibrillators, only 2 (13%) had a decreasing frequency of AF recurrences[482]. In contrast, Bertaglia et al, using a similar protocol of repeated cardioversion within the first month observed a greater proportion of patients in SR at 1 year in those who had repeat CV[483]. We hypothesise that one reason for this variability relates to the activity of triggering foci. In the current study we excluded patients who had demonstrated a tendency to early (within 1 month) AF recurrence post cardioversion. In doing so we excluded patients with particularly active triggers. Maintenance of sinus rhythm in persistent AF patients is dependent upon the critical interaction between triggers and substrate[484]. In patients with early recurrent AF, active triggering foci will prevent the possibility of reverse substrate remodelling. However, in patients with less active triggers, our study demonstrates that a policy of early return to SR (EL-CV median duration 3 months vs ED-CV of 1 day) not only improves the patients overall quality of life, but may prevent progression of remodelling. Thus this strategy is only applicable to that phenotype of persistent AF which has a "meaningful period" of sinus rhythm after successful cardioversion.

The advent of smartphone technology enabling characterisation of AF onset is likely to aid implementation of a more aggressive CV strategy by emergency department physicians[485]. Close collaboration between cardiology and ED departments, appropriate patient selection, education of patients and physicians and resource allocation remain vital to successful implementation of ED-CV for intermittent PeAF.

Current guidelines state that it is reasonable to perform repeated CV in PeAF if a clinically meaningful period exists between procedures[144]. The current study demonstrates the benefits of performing this in a timely fashion. Utilizing the Emergency Department as part of an AF action plan focussing on documentation of symptom onset, anticoagulation plan, patient education and empowerment led to a markedly shorter AF duration. This resulted in improvement in overall quality of life, prevented the progression of LA remodelling and delayed both onset of the next AF episode and referral for ablation.

Potential financial implications

While earlier studies in the 'pre-ablation' era did not demonstrate financial savings with respect to earlier CV[486], the reduction in subsequent referral rates for AF ablation by 34% (in addition to lower recurrence rates) observed in our study may be associated with cost savings to the health system. In a study of AF-related healthcare costs in five European countries, catheter ablation was over 30 times more expensive than cardioversion[487]. Moreover, a management strategy of cardioverting patients then discharging them directly from ED has been associated with significant hospital cost savings compared with inpatient admission ($5,460 vs $23,202)[488].

This study highlights the benefits of restoring sinus rhythm within an appropriate timeframe. Rather than creating an excessive burden on emergency department resources, innovative models of care are required. These may include rapid-access AF clinics that incorporate patient education, AF (and anticoagulation) action plans and timely elective cardioversion.

Limitations

Like other non-randomized studies, the benefits observed in the ED-CV group may be related to confounding and selection bias whereby clinicians were more likely to employ this strategy in 'healthier' patients, or in those with more severe symptoms. One may postulate that the longer time from first AF diagnosis in the ED-CV group suggests these patients may have had closer follow up and been more compliant with medical therapy. While patients in both groups appeared to be similar with respect gender, age and comorbidities, there was a trend towards EL-CV patients being older and more overweight, with the study underpowered to detect small differences in these variables which may have subsequently impacted recurrence rates. The authors should discuss how this issue could have influenced the selection of included patients. The clinical applicability of this study's findings to patients with asymptomatic AF is unclear as these patients were excluded from this study. Recent studies suggest that these patients have a higher risk of stroke and all-cause mortality[128]. The emergence of new technologies incorporated into smartphones and smartwatches may enable earlier detection and treatment of AF in these patients.

Despite our attempts to exclude true paroxysmal AF patients based on prior history (from both this analysis and the ED-CV treatment strategy), we are unable to definitively exclude that some of the patients electrically cardioverted in ED would not have spontaneously reverted without CV. Of those excluded from the study shown in the Supplementary Appendix, two were excluded due to spontaneous reversion in the Emergency department while 3/7 patients managed with rate control in the ED and discharged were found to be in sinus rhythm at follow-up.

Conclusion

In symptomatic patients with intermittent episodes of persistent AF, a strategy of early presentation for cardioversion to the emergency department appears to be an acceptable long-term management strategy for patients with clinically meaningful periods between episodes. Early ED cardioversion resulted in a lower rate of AF recurrence at 1 year. Furthermore, this strategy is associated with improved quality of life and slowing of disease progression. Delays in sinus rhythm restoration may accelerate adverse atrial remodelling, leading to earlier arrhythmia recurrence and accelerating referral for AF ablation.

Table 1: Baseline Characteristics

Parameter	Elective CV (n=75)	Emergency CV (n=75)	p-value
Age (years)	63±12	59±14	0.11
Gender (% male)	72%	72%	1.0
Weight (kg)	90±29	86±20	0.43
Body mass index (BMI)	31±6	28±7	0.12
Hypertension (%)	37%	41%	0.56
Dyslipidemia (%)	24%	23%	0.85
Diabetes mellitus (%)	15%	12%	0.54
Valvular heart disease (%)	14%	15%	0.92
CHA_2DS_2-VASc Score	1.7±1.2	1.6±1.5	0.76
Time from first AF diagnosis (y)	2.3±4.0	5.1±3.6	0.03
Number of previous CVs	0.7±0.9	1.9±1.3	0.001
Antiarrhythmic therapy	61%	65%	0.57
Amiodarone	28%	22%	0.43
Sotalol	24%	36%	0.12
Flecainide	8%	6%	0.73
Baseline echocardiographic data			
Left atrial area (cm^2)	27±11	28±4	0.82
LVEF (%)	53±12	50±17	0.29
Mean E/E'	10±6	10±4	0.94

Abbreviations: AF – atrial fibrillation, CV – electrical cardioversion, LVEF – left ventricular ejection fraction.

Figure 1: CONSORT Flow Diagram of Included Patients

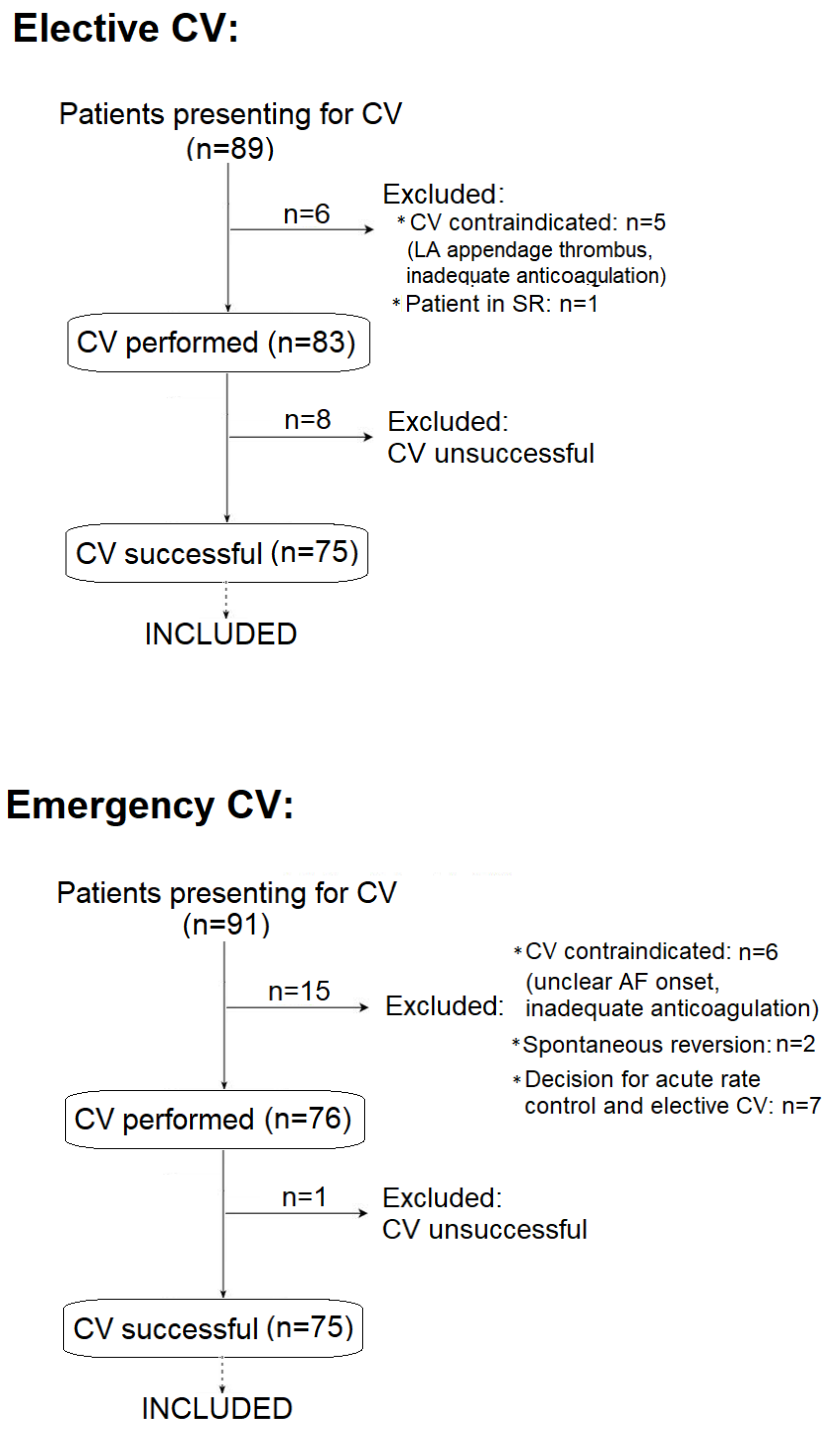


Figure 2: Comparison of AF symptom severity at 12-months between both groups

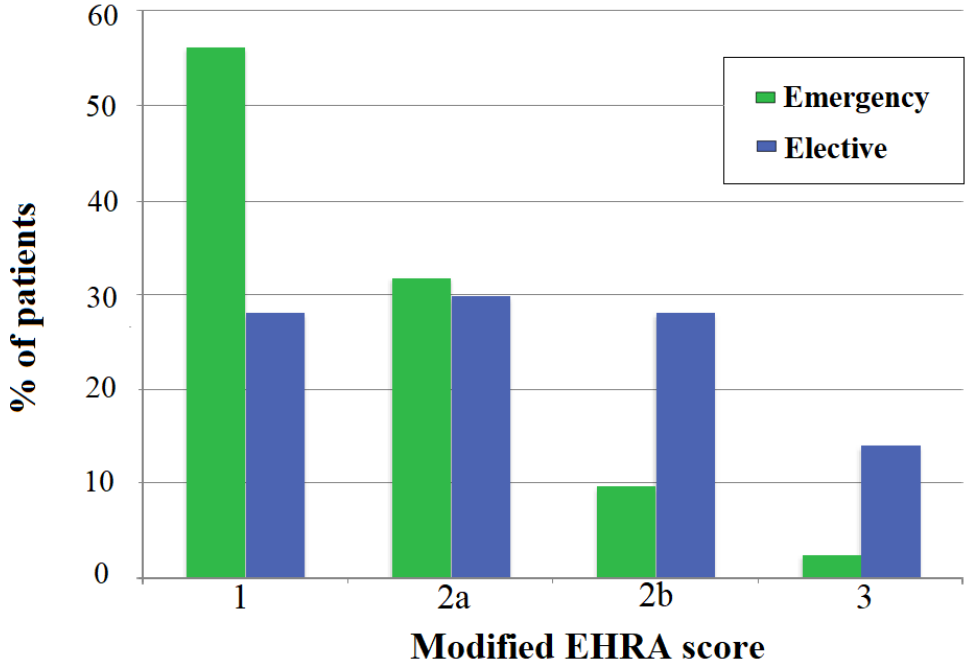


Figure 3: A. Comparison of time to first AF recurrence between both groups; B. Comparison of time to referral for AF ablation between both groups

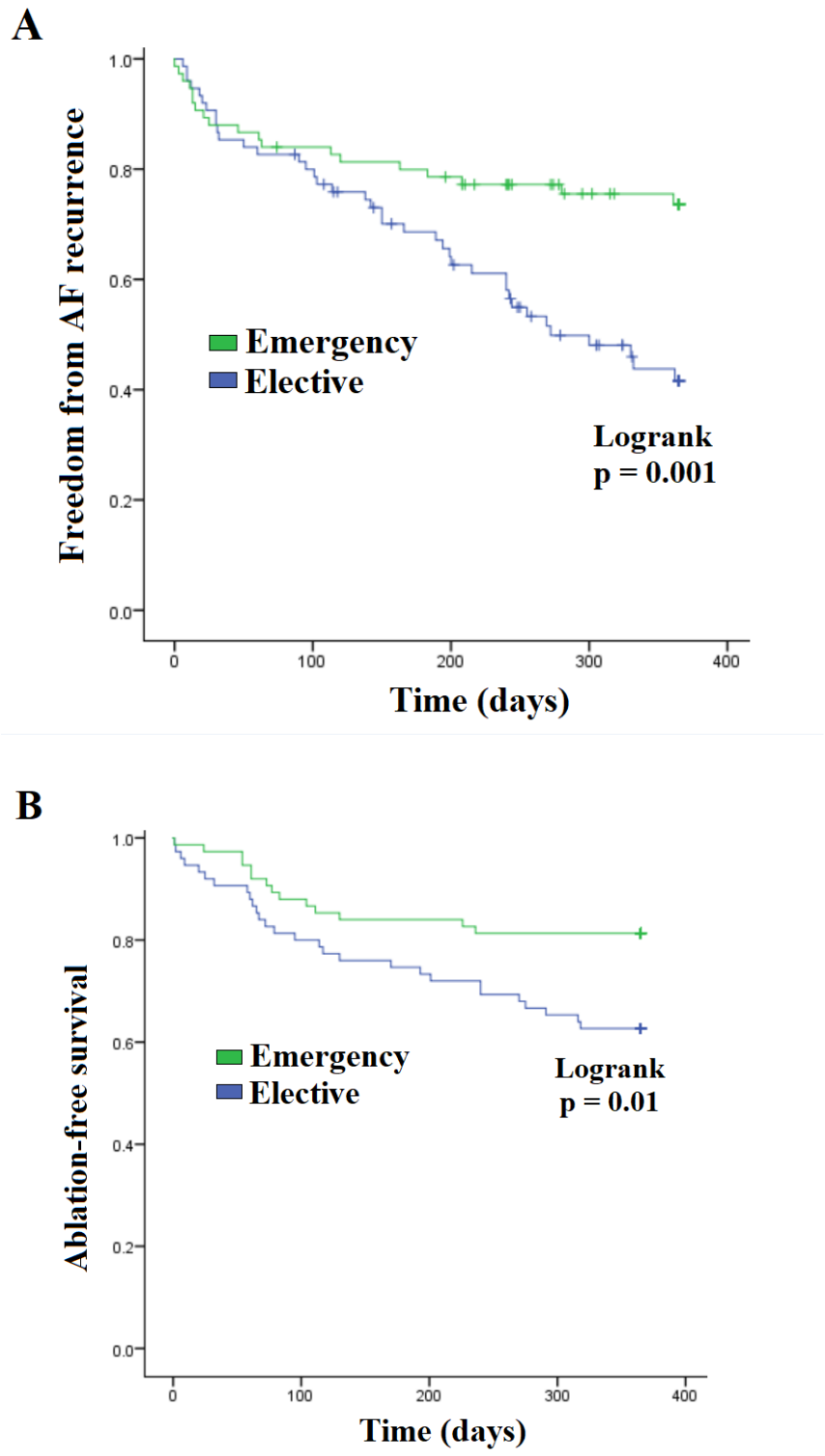
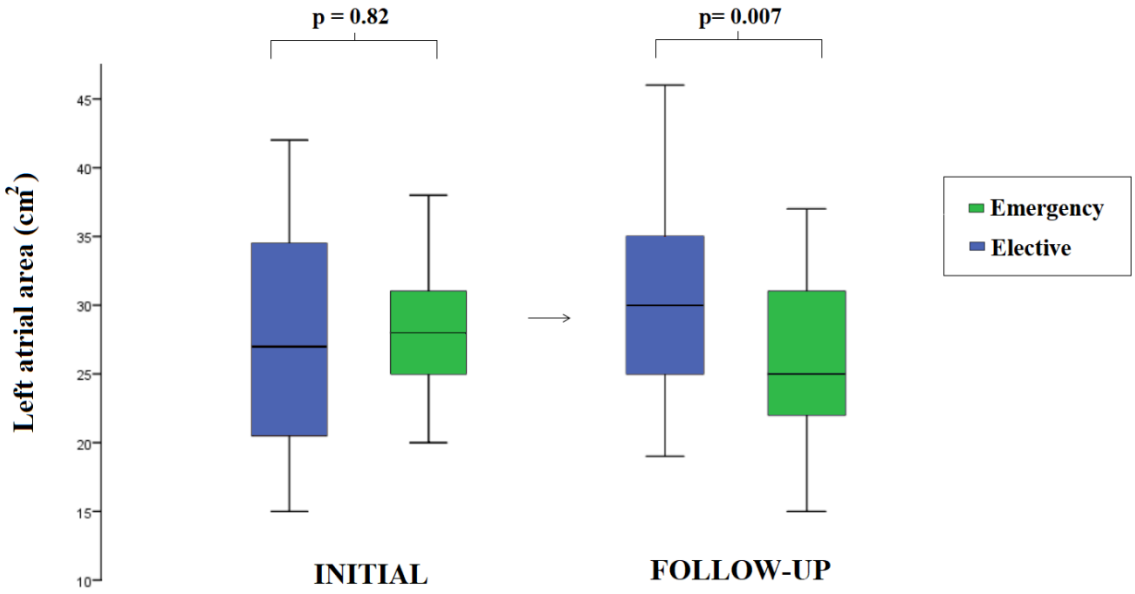


Figure 4: Comparison between both groups with respect to atrial size at baseline and follow-up



Chapter 8: Revisiting pulmonary vein isolation alone for persistent atrial fibrillation – A systematic review and meta-analysis

Introduction

While pulmonary vein isolation (PVI) is a well-established treatment for paroxysmal atrial fibrillation (AF), early studies of PVI only in patients with persistent AF (PeAF) reported suboptimal success rates. This led to the development of novel strategies to target atrial substrate, including linear lesion (LL) creation, ablation of complex fractionated atrial electrograms (CFAEs) and non-PV triggers and more recently rotor ablation. However, data from STAR AF-II indicated that addition of linear lesions or CFAE ablation did not improve outcomes over PVI alone[339]. Similarly, evidence for rotor ablation efficacy is observational and has not been widely reproduced. In this context, and with the advent of more advanced technologies (including contact force sensing catheters and the second-generation cryoballoon) a number of recent studies have revisited the approach of PVI only for management of persistent AF. The focus of this systematic review is to examine these recently reported success rates for 'PVI only' in PeAF utilising the latest technology iterations and to identify predictors of success.

Methods

Search strategy and data extraction

We performed a comprehensive literature search of Medline, EMBASE, Web of Science, PubMed and the Cochrane controlled Trials Register in August 2016. The search was restricted to studies involving humans that were published in English. In addition, the reference lists of all relevant trials and reviews were hand searched. Key search terms were 'persistent atrial fibrillation', 'catheter ablation', 'pulmonary vein isolation', and 'second generation cryoballoon'. With respect to trials involving the same group of patients, only the most recently published trial was used. Study selection, validity assessment, and data extraction were performed by three independent reviewers (AV, NH, JM) in an unblinded standardized manner. Another investigator (JK) was consulted whenever a disagreement arose about the eligibility of a trial. The study was performed in accordance with the MOOSE Guidelines for Meta-Analyses

and Systematic Reviews of Observational Studies, and the MOOSE checklist is included in Appendix A.

Study eligibility and outcomes

Studies were eligible for inclusion if they included patients with PeAF (including long-standing PeAF > 12 months – LsPeAF) undergoing 'PVI only' using either radiofrequency energy (RF) with three-dimensional mapping or the second-generation cryoballoon (CB-2G). Contact force-sensing catheters were not mandated. Studies were excluded if isolation was not an endpoint of ablation, maximum follow-up was shorter than 12 months, outcome measures for paroxysmal and persistent AF were not reported separately, and if studies had fewer than 20 patients or were only published as conference abstracts. Randomized controlled trials, prospective non-randomized studies and retrospective case- control studies were all included. Analyses of 'PVI only' efficacy were limited to studies published after 2010. The primary outcome was arrhythmia-free survival at 12-months after initial procedure. Arrhythmia events included a composite of atrial fibrillation, atrial flutter or atrial tachycardia. The definitions of post-PVI blanking period and use of antiarrhythmic drugs were left to individual study design. If on-antiarrhythmic and off-antiarrhythmic success rates were reported, off-antiarrhythmic data were included. Predictors of recurrence were examined from studies utilizing a PVI only approach, and a meta-analysis was performed if four or more studies examined the parameter. We also examined the incidence of complications.

Statistical analysis

Arrhythmia-free survival data presented as Kaplan–Meier analyses or actuarial recurrence rates were used, with a graphic digitization software (DigitizeIt) used for Kaplan–Meier data. Predictors of arrhythmia recurrence were examined using univariate hazard ratios (HR). Study estimates and confidence intervals (CI) were then pooled using the random effects model based on logit transformed proportions. Statistical analysis was then performed using Comprehensive Meta-Analysis software, Version 3 (Biostat). Heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ defined as significant heterogeneity. Potential publication bias was assessed graphically using funnel plots. In all analyses, a P-value < 0.05 was considered significant.

Results

From the 2,218 citations first screened, 84 full-text articles were reviewed and 14 met inclusion criteria for analysis of the primary outcome (Figure 1). Baseline patient characteristics and single-procedure 12-month arrhythmia-free survival of the included studies are presented in Table 1 and Table 2 respectively. Of the 956 patients with PeAF undergoing PVI only included in the analysis, 419 (45.2%) underwent PVI alone with RF, while 509 (54.8%) underwent cryoballoon PVI. Seven studies were prospective by design, of which three were randomized controlled trials. All studies included a 3-month blanking period, as is conventional in studies of PVI outcome. Intensity of follow-up differed between studies, with the majority of studies (9/14) undergoing ≥ 24-hour Holter monitoring on at least 3 occasions during the first year of follow-up (Table 2).

The majority of included patients (80.5%) were off antiarrhythmics at 12-months (all patients off antiarrhythmics in 6/14 studies, majority off antiarrhythmics in 4/14 studies), as shown in Table 2. Only a minority of included patients had long-standing persistent AF (LSPeAF), defined as continuous AF > 1 year, as shown in Table 1. In fact, this was an exclusion criteria in 6/14 studies. Very few patients had significant systolic dysfunction (ejection fraction < 35%) or severe left atrial dilatation (≥ 5.2 cm in men or ≥ 4.7 cm in women). Mean age, LVEF and LA diameter were 61.3 years, 57.2%, and 4.5 cm respectively (Table 1). The vast majority (13/14) of studies were published in 2015 – 2016 (including ahead of print).

The pooled single-procedure success rate (freedom from all arrhythmias) at 12-months was 66.7% (95% CI 60.8% – 72.2%), as shown in Figure 2. There was significant heterogeneity between studies (I^2 = 70.3%), hence a random effects model was justified. Funnel plot analysis (Appendix B) did not demonstrate any significant publication bias, confirmed by Egger's test (p = 0.89, two-tailed). With respect to predictors of outcome, univariate hazard ratios reported by ≥ 4 studies were available for four parameters, and a meta-analysis was performed (Figure 3). Blanking period recurrence (HR 4.68; 95% CI 1.70 – 12.9), but not left atrial size, hypertension or age, was the only significant predictor of arrhythmia recurrence identified. It should be noted that study patients across these 14 studies were relatively homogeneous. They were relatively young (median age of 62 years), had normal LV function and generally

mild left atrial enlargement only (Table 1). There was a low prevalence of structural heart disease.

Reported complication rates were very low and there were no procedure-related deaths. There were no cases of atrio-esophageal fistula, transient ischemic attack / stroke, pulmonary vein stenosis, or myocardial infarction. There were 5 cases of cardiac tamponade (0.6%) and 19 access-related complications (1.6%) encompassing femoral arterio-venous fistula, pseudoaneurysm and retroperitoneal hemorrhage. Five CB2 patients developed persistent phrenic nerve palsy (0.9%), which did not occur in any of the RF patients.

Discussion

Based on results from recent studies using latest technology, we observed a 66.7% single procedure 12-month arrhythmia-free survival using PVI only in a PeAF population with a low prevalence of structural heart disease. This result is comparable to data reported in an earlier meta-analysis (2011) of PVI in paroxysmal AF which observed a 12-month success rate of 66.6%[338]. However, for PVI alone in persistent AF, the same meta-analysis observed a 12-month success rate of just 51.9%. Improved success rates since this meta-analysis are likely multifactorial, related to patient population, use of wide antral ablation which incorporates some substrate and technology evolution. The current study which includes almost exclusively studies published within the last 12 months demonstrates that PVI alone is now a legitimate strategy for persistent AF patients with minimal structural heart disease.

PVI only vs PVI plus adjunctive ablation strategies for PeAF

Until recently, the dominant paradigm in approach to ablation of persistent AF was that atrial substrate modification was necessary (in addition to PVI) to achieve acceptable success rates. Patients with persistent AF were recognized to have more advanced atrial remodelling than those with paroxysmal AF[489]. Importantly a number of meta-analyses[490,491] demonstrated the superiority in ablation outcomes when substrate ablation (CFAE or linear) was added to PVI in PeAF patients. However, the studies included in these meta-analyses were generally quite small single centre series. The recent and much larger CHASE-AF[492] and STAR AF-II[339] randomized trials were

pivotal in demonstrating that adjunctive RF ablation strategies (lines, CFAEs) did not result in a higher freedom from arrhythmia than a PVI only strategy utilising RF, but were associated with higher fluoroscopy and procedure times. Follow-up meta-analyses which included these 2 studies now demonstrated no benefit in arrhythmia-free survival with left atrial linear ablation or CFAE ablation in the PeAF population[493]. Strengthening the rationale to abandon these ineffective approaches are the considerable data demonstrating the pro-arrhythmic potential of these lesion sets. Recent studies examining the role of focal impulse and rotor modulation (FIRM)-guided ablation have also yielded conflicting results; Success rates (arrhythmia-free survival on/off anti-arrhythmics) as high as 70.4% at 29 months follow-up[41] and as low as 21% at 16 months[494] have been reported and considerable debate exists. This again underscores that at present no strategy is proven to improve outcomes for PeAF ablation beyond PVI.

Impact of ablation strategy and technology

Reasons why PVI alone may have yielded lower success rates in these prior studies is that they utilized earlier technology iterations than currently exist and that ablation procedures were more frequently ostial[495] and segmental[496] rather than wide antral. The past decade has seen rapid evolution in ablation technology and strategy. When using point by point RF, both mapping and ablation technologies have evolved to create more reliable lesions with less likelihood of discontinuities. Furthermore, wide area PV antral isolation is more routinely performed and often incorporates a significant part of the posterior LA. Recent studies suggest that contact force-sensing catheters, are associated with more effective lesion formation, with a recent meta-analysis of 11 studies demonstrating lower recurrence rates (OR 0.62; 95% CI 0.45-0.86) with this technology[497]. These were utilized in five of the eight RF studies included in our systematic review. However, only one of these studies[498] utilized this technology for all included patients. One may speculate that routine use of these catheters may result in even higher success rates in the future.

Concurrently, development of the second generation cryoballoon (CB2) with a larger and more homogenous freezing zone, has similarly resulted in more durable isolation and a wider area of LA myocardium incorporated[499]. It is probable that these changes have at least in part been responsible for the improved outcomes reported in these recent

studies of PVI alone for persistent AF. While no randomized studies exist comparing RF with CB2 in PeAF, the FIRE AND ICE trial demonstrated similar success rates in the paroxysmal AF population[336].

Patient selection and predictors of success for PVI in PeAF

While the medium-term outcomes for PVI only in PeAF are encouraging based on the studies included, it is critical to analyse the patient populations included. This was a relatively homogeneous population with a median age of 62, a low prevalence of structural heart disease and few patients with long-lasting persistent AF. Patients by and large had normal LV function, mild left atrial enlargement and a low prevalence of coronary artery disease or diabetes. In this context, it is perhaps not surprising that none of these factors seemed predictive of outcome; patients were selected from a relatively narrow band. One may speculate that the inclusion of more patients with heart failure, severe atrial enlargement and long-lasting persistent AF for example might have resulted in the identification of these factors as predictive of outcome.

The only factor predictive of late AF recurrence in the studies in the current meta-analysis was early recurrence. The first 3 months post ablation has traditionally been considered a blanking period during which recurrences were due to a transient atrial inflammatory response[500] and not necessarily predictive of late recurrence. However, another recent meta-analysis also observed that early recurrence within 30 days was strongly predictive of late recurrence (OR 4.3) with similar predictive power as for LA diameter > 5.0 cm (OR 5.1) and valvular AF (OR 5.2)[501].

Clinical implications

The current systematic review demonstrates that PVI alone is now a legitimate strategy for persistent AF patients with minimal structural heart disease. While there are no long-term follow-up data for the studies included, an initial strategy for AF recurrence of simple pulmonary vein re-isolation appears reasonable; in STAR AF-II, re-isolation of the veins improved AF-free survival from 59% to 72% at 18 months[339].

These results argue in favour of early intervention in a persistent AF cohort before further remodelling supervenes and before AF becomes long-lasting. Risk factor management in this population might further improve outcomes. However, more

research is required to determine the optimal ablation strategy for persistent AF patients with more advanced atrial remodelling and structural heart disease and in those patients with long-lasting persistent AF.

Limitations

This systematic review has several limitations. There was considerable variability in study quality, ranging from randomized controlled trials to retrospective observational studies. Only three studies encompassing 136 patients were randomized controlled trials. There was significant heterogeneity between studies, with variable follow-up and ascertainment of arrhythmia recurrence. Moreover, use of antiarrhythmics varied between studies. The inclusion of only published studies may have resulted in a publication bias towards more favourable ablation outcomes from more experienced centres.

Conclusion

In patients with persistent AF and minimal structural heart disease, PVI alone yields a 1-year single-procedure arrhythmia free survival of 66.7% and is a legitimate strategy. These medium term outcomes in lower risk patients are now comparable to results in the paroxysmal AF population, with very low complication rates. Ongoing technological advances, earlier referral in the disease process and addition of risk factor modification may further improve outcomes.

Table 1 – PVI only for PeAF: patient characteristics of included studies

Study	*PeAF population*	Life-time AF (mths)	Age (yrs)	LVEF (%)	LA size [383]	HTN	BMI	DM	CAD
Lemes 2016 [502]	Median AF duration 48 months; 63% in AF at PVI	48	63±10		4.6±0.5	67%		12%	18%
Tscholl 2016 [503]	LSPeAF excluded	40±46	65±10	66±8	4.4±0.6	70%	29 ± 4	18%	22%
Straube 2016 [504]	LSPeAF excluded	29	64±10	54±8	4.6±0.7	71%	27.3±5		13%
Guhl 2016 [505]	67% in AF at PVI		59±8	53±7	4.5±0.6	54%		13%	
Wynn 2016 [506]	Median duration continuous PeAF 5.5±4.2 mths. LSPeAF excluded.		62±10	61±11	4.3±0.6	52%	29±9	9%	8%
Jadidi 2016 [507]	79% in AF at PVI		59±10		4.6±0.5	58%			3%
Pavlovic 2016 [508]	LSPeAF excluded		60±7	55±5	4.3±0.5	68%		8%	12%
Khurram 2016 [509]	AF duration 6.0 ±7.4 yrs	72±89	59±10	56±7	-	51%	31±6	9%	16%
Koektuerk 2015 [510]	Median duration continuous PeAF 5.5±3.7 mths (6% LSPeAF)		63±10			61%		8%	15%
Ciconte 2015 [498]	LSPeAF excluded	30±31	62 ±10	57±4	4.7±0.6	60%	28±4	11%	7%
Vogler 2015 [492]	AF termination during PVI excluded, longest AF 324±436 days	52±48	63±10	60±7	4.5±0.7	83%	27±5		27%
Verma 2015 [339]	78% had constant AF > 6-months	52±76	58±10	55±11	4.4±0.6	48%	59% had BMI<29	9%	3%
Khan 2011 [511]	Mean duration of PeAF episode 6 months; LSPeAF excluded	61±66	59±10	55±8	4.1±0.7	51%		7%	

*included patients on antiarrhythmics after 3 months

Abbreviations: PVI: pulmonary vein isolation, PeAF: persistent AF, LSPeAF: long-standing persistent AF, LVEF: left ventricular ejection fraction, HTN: hypertension, BMI: body mass index, DM: diabetes mellitus, CAD: coronary artery disease, RF: radiofrequency ablation, CB2: second-generation cryoballoon.

Table 2 – Pulmonary vein isolation only for persistent atrial fibrillation: single-procedure arrhythmia-free survival

Study	*RF or CB2*	*Study design*	*LSPeAF included*	*AF ascertainment (other than routine follow-up)*	*Antiarrhythmics after 3-months*	*Follow-up (months)*	*Single Procedure Arrhythmia-Free Survival**
Lemes 2016 [502]	CB2	Retrospective	✓	3,6,12 month 24hr-Holter	On (33%) Off (67%)	13.9±5.9	34/49 (69%) at 12 months
Tscholl 2016 [503]	CB2	Retrospective	×	N/A	On (10%) Off (90%)	22±11	28/50 (56%) at 22±11 months
Straube 2016 [504]	CB2	Prospective observational	×	3,6,12,18 month 24hr-Holter	On (17%) Off (83%)	14 (IQR 12-19)	129/157 (82%) at 12 months
Guhl 2016 [505]	CB2¶	Retrospective	✓	Event monitor at 6-months	On (17%) Off (83%)	20.2	40/69 (59%) at 12 months
Irfan 2016 [512]	CB2	Retrospective	✓	3, 6, 12 month 24-hr Holter	Off	12.2±3.8	38/62 (61%) at 12 months
Wynn 2016 [506]	RF	Randomized trial	×	3,6,12 month 24hr-Holter	Off	12	28/39 (72%) at 12 months
Jadidi 2016 [507]	RF	Retrospective	✓	6,12 month 24-hr Holter	Off	13 (IQR 11-15)	31/66 (47%) at median 13 months
Pavlovic 2016 [508]	RF	Retrospective	×	3, 6, 12 month 7-day Holter	Off	12	17/25 (68%) at 12 months
Khurram 2016 [509]	RF	Prospective	✓	Event monitor if symptomatic	On/Off	10.2±5.7	42/71 (59%) at 10.2±5.7 months
Koektuerk 2015 [510]	CB2	Prospective observational	✓	7-Day Holter at 3 & 6-months	On (6%) Off (94%)	10.6±6.3	67/100 (67%) at 10.6±6.3 months
Ciconte 2015 [498]	RF/CB2	Retrospective	×	3,6,12 month 24hr-Holter	Off	12	RF: 27/50 (56%) CB2: 28/50 (60%)
Vogler 2015 [492]	RF	Randomized trial	✓	3,6,9,12 month 24-72hr-Holter	On	12	27/36 (75%) at 12 months
Verma 2015 [339]	RF	Randomized trial	✓	Transtelephonic monitor, 3,6,9,12,18 month 24hr-Holter	On (21%) Off (79%)	18	30/61 (49%) at 18 months
Khan 2011 [511]	RF	Prospective observational	×	Transtelephonic monitor, 3,6,12,18 month 48hr-Holter	Off	12	50/71 (70%) at 12 months

*After a 3-month blanking-period

¶Majority of patients (12% had 1st generation CB)

Abbreviations: RF: Radiofrequency energy, CB2: Second-generation Cryoballoon , LSPeAF: Long-standing persistent AF, IQR: Interquartile range

Figure 1: Flow diagram of included studies for primary outcome

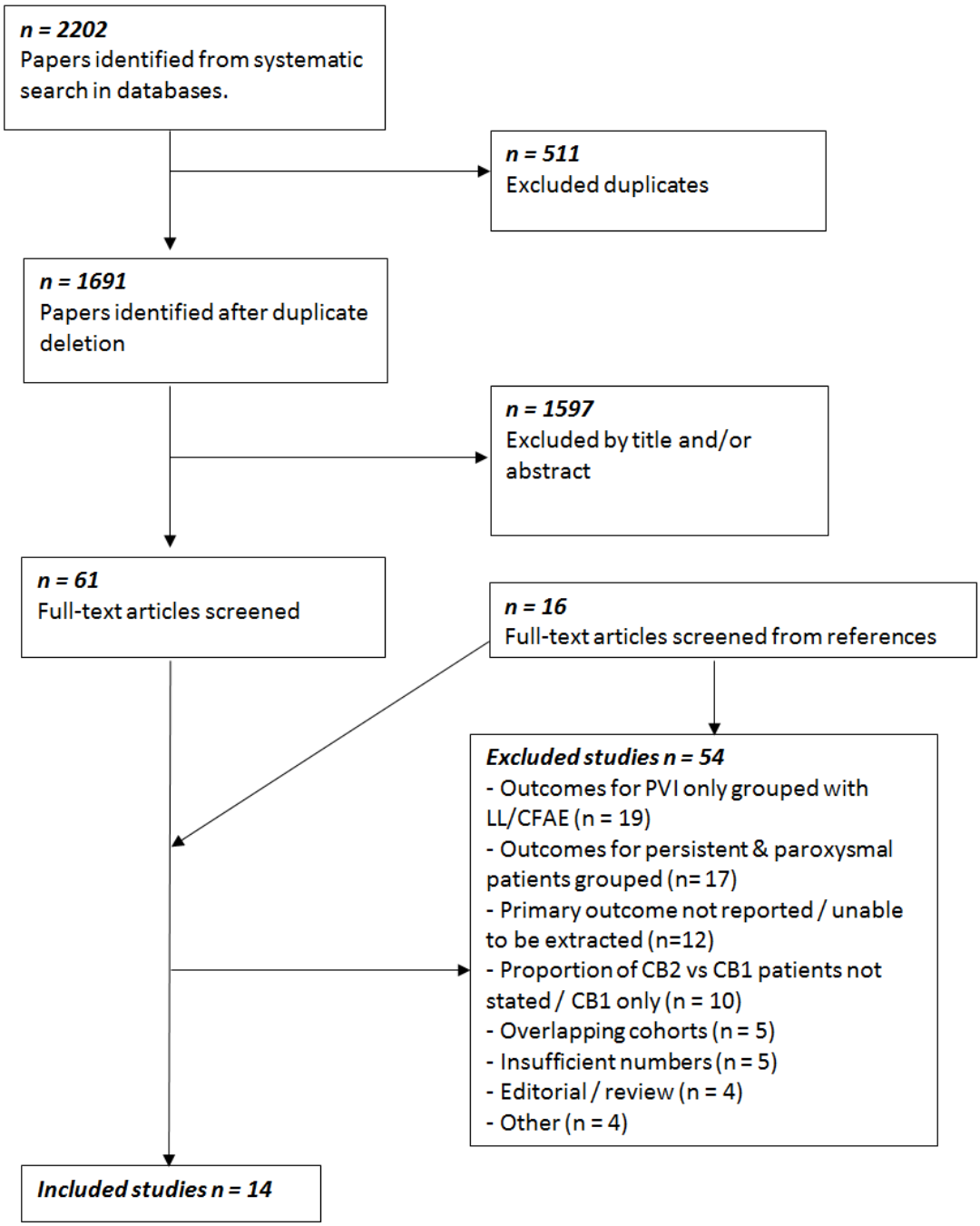


Figure 2: Single procedure arrhythmia-free survival at 12 months in PeAF

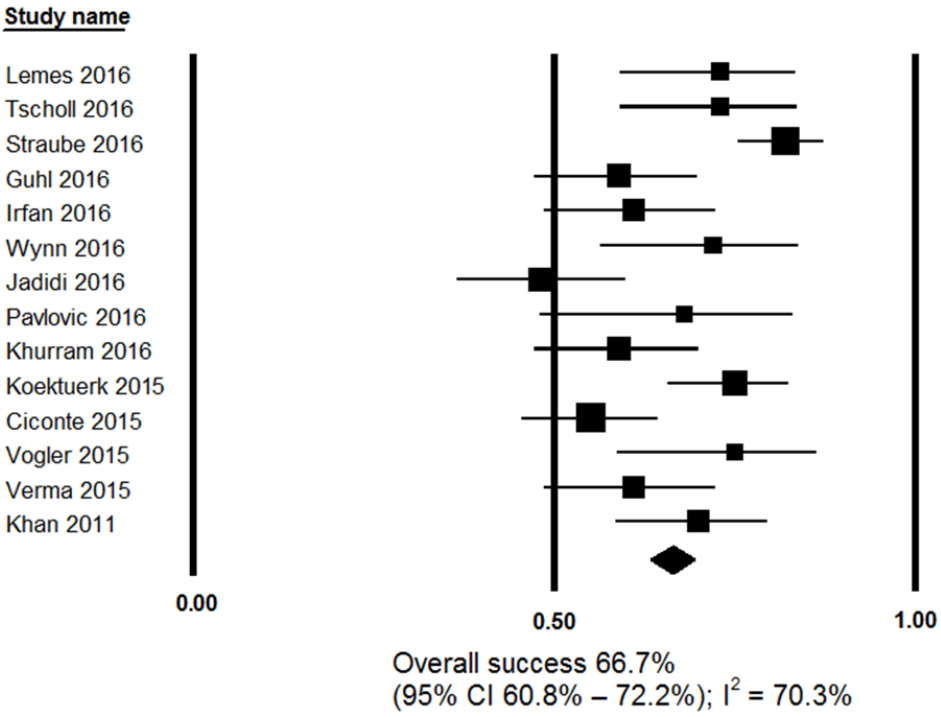
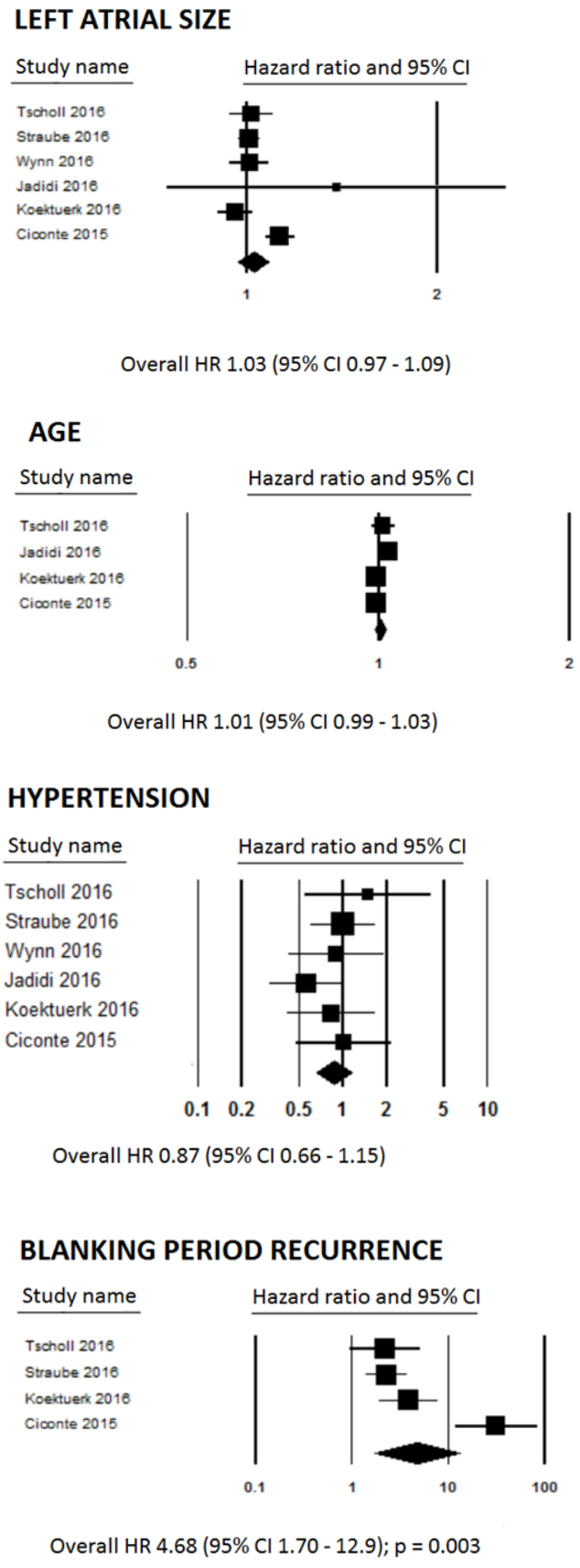


Figure 3: Predictors of recurrence for PVI only approach in PeAF



Appendix A: MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	Page 3
2	Hypothesis statement	Page 3
3	Description of study outcome(s)	Pages 3 – 4
4	Type of exposure or intervention used	Pages 3 – 4
5	Type of study designs used	Page 4
6	Study population	Pages 3 – 4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Page 4
8	Search strategy, including time period included in the synthesis and key words	Pages 3 – 4
9	Effort to include all available studies, including contact with authors	Pages 3 – 4
10	Databases and registries searched	Page 3
11	Search software used, name and version, including special features used (eg, explosion)	Page 3
12	Use of hand searching (eg, reference lists of obtained articles)	Page 4
13	List of citations located and those excluded, including justification	Page 18
14	Method of addressing articles published in languages other than English	Page 3
15	Method of handling abstracts and unpublished studies	Page 4
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Page 4
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Page 4

19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Page 4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Page 4
22	Assessment of heterogeneity	Page 5
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 5
24	Provision of appropriate tables and graphics	Pages 15 – 20
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Page 19
26	Table giving descriptive information for each study included	Pages 15 – 16
27	Results of sensitivity testing (eg, subgroup analysis)	-
28	Indication of statistical uncertainty of findings	Page 11
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Page 22
30	Justification for exclusion (eg, exclusion of non-English language citations)	-
31	Assessment of quality of included studies	Page 11
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Page 11
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Pages 7 – 11

34	Guidelines for future research	-
35	Disclosure of funding source	Page 1

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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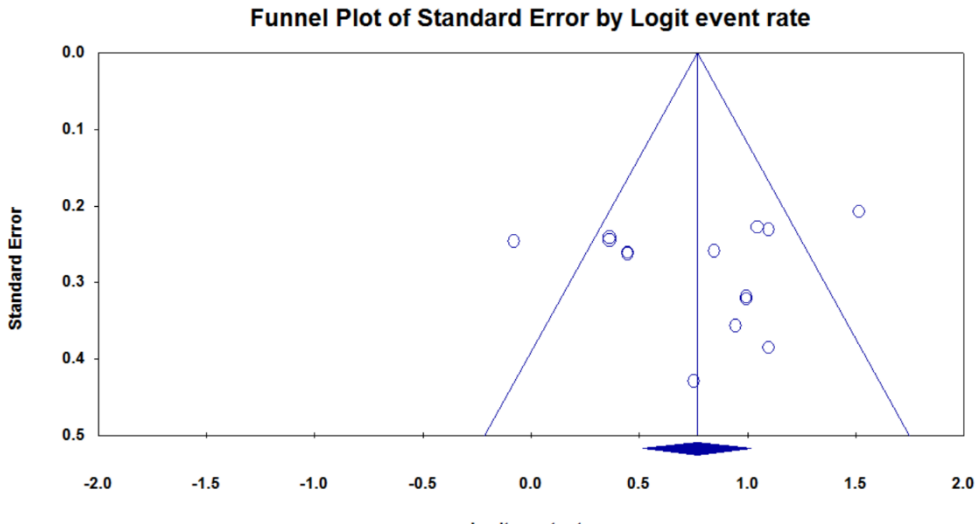
Appendix B: Funnel plot of 1-year arrhythmia free survival



Chapter 9: Reduction in radiation dose for atrial fibrillation ablation over time – A 12 year single centre experience of 2,344 patients

Introduction

Atrial fibrillation (AF) ablation by pulmonary vein isolation (PVI) and adjunctive strategies has evolved over the last decade to become a cornerstone of AF management. As the population ages and AF incidence continues to grow, electrophysiologists are likely to spend increasing periods of time in the catheterization laboratory. Electrophysiologists are currently exposed to approximately 4.3 mSv per year of scattered radiation, the equivalent of ~25 CT chest scans during a career and a 1 in 100 increase in cancer risk[513]. Patients too are exposed to ever-rising radiation doses. A lengthy ablation procedure may potentially increase the lifetime risk of fatal malignancy by 0.05–0.1% and the risk of genetic defects by one per million births[514]. We sought to analyze trends in radiation exposure at our centre for AF ablation over the last 12 years, aiming to identify factors associated with lower radiation doses for operator and patient.

Methods

Study population and endpoints

This was a single-centre retrospective cohort study of prospectively collected data of consecutive pulmonary vein isolation cases performed for atrial fibrillation at the Royal Melbourne Hospital between January 2004 and December 2015. All cases utilized three-dimensional electroanatomical mapping systems. Our centre is a quaternary electrophysiology referral centre with experienced electrophysiologists and EP fellows at different stages of training. The primary indication for pulmonary vein isolation was symptomatic paroxysmal or persistent atrial fibrillation refractory to medical therapy. Our

dedicated electrophysiology laboratories are equipped with the Philips Allura Xper (FD10 from 2004-7, FD20 from 2008-15) fluoroscopy system (Philips Medical Systems, Eindhoven, The Netherlands) which uses automatic brightness control to select tube current and kilovoltage, and includes selectable copper beam filtration. There were no additional hardware upgrades, and software upgrades were performed annually during the follow-up period. Cases were also performed in a laboratory containing Siemens AXIOM Artis dFC Magnetic Navigation (2007-15) which underwent 4 major software upgrades. Between 2004-6, this lab used a GE Healthcare Advantx LUA system.

Pulse fluoroscopy rates were pre-programmed at 3.75 frames per second and did not differ between electrophysiologists. X-ray beam collimation was actively encouraged to the minimum required field of view. The fluoroscopy system provided a cumulative dose for absorbed dose (Air Kerma in mGy) and Dose Area Product (in $Gy.cm^2$). The effective dose was derived by multiplying the Dose Area Product in $Gy.cm^2$ by a conversion factor[515] of 0.2. Primary endpoints were fluoroscopy time (min), absorbed dose (Air Kerma in mGy) and effective dose (mSv). Fluoroscopy time for insertion of diagnostic catheters and completion of double transseptal puncture ('transseptal fluoroscopy time') as well as during ablation in the left atrium ('LA dwell time') were also prospectively recorded.

PVI protocol

Standard practice at our centre was to perform PVI under general anaesthetic with transesophageal echocardiography guidance for transseptal access and exclusion of left atrial thrombus. All catheters were inserted via the right femoral vein, with the internal jugular vein used for difficult coronary sinus cannulation. Intracardiac catheters prior to

transseptal included a decapolar coronary sinus catheter (with proximal bipole at the coronary sinus ostium) and a quadripolar His-bundle/right ventricular catheter. Double transseptal puncture was performed using a BRK™ needle via 8F and 8.5F long SL1 sheaths (St. Jude Medical, St. Paul, MN). An ablation catheter and steerable circular multipolar pulmonary vein (PV) mapping catheter were then introduced into the left atrium (LA) using fluoroscopy. A non-fluoroscopic 3D electroanatomical mapping system was then used to create a left atrial and PV geometry.

All patients underwent point-by-point circumferential ablation of the left and right sided pulmonary veins using radiofrequency energy delivered through an irrigated catheter during CS-pacing. Power was maintained at 30W on the anterior surface and 25W posteriorly with up to 20 seconds of RF (posterior) or up to 30 seconds of RF (anterior) delivered at each point. The mapping catheter was used to confirm elimination of all PV potentials and enduring bidirectional block as the procedural endpoint. If PV reconnection occurred after a waiting period of 30 minutes, additional RF lesions were applied. From 2010, intravenous adenosine (two doses, up to 18mg) was used to assess dormant conduction at the discretion of the operator, and additional RF applied. An identical protocol was followed for redo cases, with re-isolation of the pulmonary veins performed in all patients in the event of reconnection.

Additional lesions were performed at the discretion of the operator for persistent AF or redo cases. These included lines at the left atrial roof, between the lateral mitral annulus and left inferior pulmonary vein, left atrial posterior wall isolation (roof and floor lines) and ablation of complex or fractionated electrograms (CFAEs). A cavotricuspid isthmus

line was performed in patients with previous typical right atrial flutter with the same ablation catheter, with bidirectional block being the procedural endpoint.

Evolution of technology during the follow-up period

Two electroanatomical mapping systems were primarily used to create left atrial geometry and aid catheter navigation during the follow-up period: CARTO (Biosense Webster) and NavX (St. Jude Medical, St. Paul, MN, USA). Choice of mapping system and ablation catheters was at the operator's discretion. There were 8 software and 2 hardware upgrades between 2004 – 2015, with CARTO-3 and NavX EnSite Velocity being the dominant systems used towards the end of the follow-up period. Fusion with a pre-procedural CT (NavX fusion and Cartomerge) was first performed in 5/2007, and became standard practice from 1/2009 onwards. Cine pulmonary vein angiography was performed prior to this for all non-CT cases. Progressive improvements over time included visualization of both mapping and ablation catheters (including shaft location) and anatomical reconstruction of the left atrium and pulmonary veins.

There was considerable evolution of irrigated catheter technology during the 12-year period, including flexibile bidirectional tips (D,F,J curve) conforming to tissue, advanced cooling mechanisms, and more recently those with force-sensing spring mechanisms. The most commonly used catheters included Cool Flex™ and Flexability™ catheters (St Jude) and Navistar Thermocool™ and Thermocool SmartTouch™ (Biosense Webster). The Thermocool SmartTouch™ catheter (Biosense Webster) was introduced at our centre in 2011 and was the predominant contact force-sensing catheter used for the remainder of the follow-up period. Target contact force (CF) was ≥10 g and <40 g for lesion application.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 23 (IBM Corp, Armonk, NY). Summary statistics for continuous data are presented as mean ± standard deviation or median, as appropriate. Categorical variables were compared using a chi-square or Fisher exact test. Normally-distributed variables were compared using a Student t-test, with ANOVA used to compare three or more means. Univariate and multivariate analyses were performed using logistic regression analysis.

A p value < 0.05 was considered statistically significant. This study complies with the Declaration of Helsinki and was approved by the Melbourne Health Human Research Ethics Committee.

Results

A total of 2,344 patients underwent ablation for AF between 2004 – 2015, of which 1,914 were de novo PVI (81.7%) and 430 redo PVI (18.3%). Baseline characteristics are summarized in Table 1, with the majority of patients male (72.8%) and overweight (mean body mass index 28.3±4.7). The proportion of persistent AF patients undergoing PVI increased from 11.1% of cases between 2004-6 to 25.1% of cases between 2013–5. Ablation strategy is summarized in Table 2. PVI only was the most common strategy used (75.8%), followed by PVI + lines (13.2%), PVI + cavotricuspid isthmus ablation (10.6%) and PVI + posterior wall isolation (7.1%).

Fluoroscopy time, absorbed dose and effective dose all significantly and progressively decreased over the 12-year period for PVI as summarized in Table 3. These improvements were gradual, and coincided with higher case volume (and operator experience), greater

emphasis on radiation-reduction strategies and technological advancements such as CT-merge, as well as contact force-sensing catheters (Figure 1). A strong inverse linear relationship between annual case volume and mean fluoroscopy time was seen (r = -0.953). There was a weak correlation between fluoroscopy time and effective radiation dose (r = 0.350) likely representing differential utilization of collimation and fluoroscopy quality settings between operators.

To assess the impact of a 'learning curve' for fellows, we compared average fluoroscopy times between the fellows' first ten and last ten PVI cases at our centre between 2004–15. Average fluoroscopy times were shorter at the conclusion of a 2-year fellowship in 18/20 (90%) of fellows (mean 95±38 cases per fellow) by an average of 6.5 minutes (33.3±15.7 mins vs 26.8±13.9 mins; p = 0.0002).

Both fluoroscopy time for insertion of diagnostic catheters / transeptal puncture and ablation in the left atrium also progressively decreased over time (Figure 2). From 2010, combined fluoroscopy during catheter insertion and transeptal was longer than fluoroscopy during left atrial ablation. By 2015, only 26.6% of the total fluoroscopy time was used during ablation the left atrium (mean LA dwell time 3.2 min), compared to 57.8% in 2006 (mean LA dwell time 33.6 min). Figure 2 also demonstrates mean fluoroscopy times for slow pathway ablation (n = 1465) of typical AV nodal reentrant tachycardia (AVNRT) between 2006 – 2015. Comparison of best-fit linear regression lines showed that fluoroscopy times for AVNRT ablation did not decrease to the same degree as for AF ablation (slope -0.81 and $R^2 = 0.80$ vs slope -3.28 and $R^2 = 0.96$; $p < 0.001$). Nevertheless, between 2006 and 2015, fluoroscopy times for AVNRT ablation decreased by 46.4% (20.9±13.2 min vs 11.2±7.3 min; $P < 0.001$).

When comparing contemporary 3D mapping systems for AF ablation, fluoroscopy time using the CARTO® 3 3D-mapping system (16.9±8.4 min; n=660) was significantly shorter ($p<0.001$) than for NavX™ EnSite™ Velocity (27.1±9.1 mins; n=300). Contact force-sensing catheters were used for 357/508 'PVI only' cases and 108/121 'PVI + LA substrate modification' cases between 2014-5 (Table 4). Fluoroscopy times were significantly shorter with this catheter, regardless of ablation strategy (PVI only 11±5 vs 21±8 mins; $p<0.001$ and PVI + LA substrate modification 12±4 vs 18±6 mins; $p<0.001$). Both contact force catheters (OR 0.66; 95% CI 0.49-0.89) and fusion with pre-procedural CT (OR 0.09; 95% CI 0.04-0.20) were significant multivariate predictors of shorter fluoroscopy times. Paroxysmal AF (OR 1.05; 95%CI 0.70-1.55), sinus rhythm pre-PVI (OR 0.77; 95% 0.54-1.09) and additional substrate modification (OR 1.35; 95% CI 0.90-2.00) were not significant predictors.

Over 5.5±3.7 years of follow-up, 360/1914 (18.8%) developed recurrent arrhythmias necessitating repeat ablation. Multivariate predictors of recurrent arrhythmias necessitating repeat ablation were sought using logistic regression analysis. Fluoroscopy time at initial PVI was the only statistically significant multivariate predictor of recurrence (OR 1.018; 95% CI 1.002 – 1.035; $p = 0.025$), although the absolute difference was small. In this analysis, patient age ($p=0.21$), ablation time ($p=0.53$), additional substrate modification ($p=0.915$), type of AF ($p=0.29$), rhythm at PVI ($p=0.20$), use of adenosine ($p=0.053$) and contact force catheters ($p= 0.09$) were not significant multivariate predictors of recurrence.

Discussion

Atrial fibrillation has been described as an emerging epidemic[516], and AF ablation has become an increasingly utilized treatment strategy. In the initial decade of AF ablation, reported mean fluoroscopy times in excess of 50 minutes were the norm[372,517]. The current study demonstrates that these times have demonstrated a progressive, gradual and significant decline to the point where PVI can now be performed with fluoroscopy times below 10 minutes using lower radiation doses than coronary angiograms (which utilize higher radiation cine loops)[518]. But how low can we go? Lee et al recently reported that a median fluoroscopy time of 3.5 minutes is achievable in the CF era with appropriate training[519]. This was exclusively the time required to position diagnostic catheters and perform the transeptal puncture[520,521].

Several studies have reported excellent outcomes with fluoroless ablation using a combination of intracardiac echocardiography, intracardiac electrograms and electroanatomic mapping to guide catheter placement, navigation and transeptal puncture, without affecting procedure duration, efficacy or complication rate[522-524]. Bulava et al reported that physicians and nurses were able to completely forego lead aprons and radiation protection equipment frequently associated with spinal problems and chronic back pain[524]. Knecht et al demonstrated that mapping and ablation without fluoroscopy (after transseptal) is safe and feasible in 97% of patients using mapping technology alone, without the need for contact force catheters, intracardiac or transesophageal echocardiography[525]. We too report progressive annual reductions in fluoroscopy times during ablation from 33.6 mins in 2006 to 3.2 mins by 2015.

Recent studies have focussed on the impact of contact force sensing catheters on radiation exposure[526-528]. Although the reduction in fluoroscopy time over 12 years was

multifactorial, we observed a 46% lower fluoroscopy time and 58% lower effective radiation dose when contact force catheters were used compared with when they were not used. This is consistent with a recent meta-analysis of 11 studies demonstrating that CF significantly reduced fluoroscopy time (28 vs 36 mins, standardized mean difference -0.94 [95% CI -1.66; -0.21], p=0.01)[497]. The current study demonstrates that reduction in radiation exposure long preceded the introduction of contact force catheters. There is no inflection point at the time of contact force introduction (Figure 1), arguing that reductions in radiation exposure are multifactorial.

There have been multiple other technology upgrades over the period of this report. These include in the ability to merge with a CT scan[529], rapid anatomical reconstruction of the left atrium and pulmonary veins, introduction of respiratory gating, improvements in catheter design, advanced catheter location enabling catheter shaft visualization, and the use of deflectable sheaths[520]. In parallel, we observed increasing procedural case numbers and operator experience. Interestingly, our multivariate analysis suggested that technological factors had a stronger association with shorter fluoroscopy times than patient factors or ablation strategy. Additional substrate modification was not predictive of longer fluoroscopy time as it was only performed in a small proportion of the overall cohort, was generally quite limited, and in recent years was performed predominantly with 3D-navigation. Greater clinician emphasis on minimizing radiation over the last decade has also been a significant factor. This is evidenced by concurrent reductions in radiation exposure for AVNRT ablation, which is routinely performed at our institution without 3D-mapping or contact force catheters.

Despite dramatic reductions in fluoroscopy times over the past decade of AF ablation, the ALARA doctrine ('As Low As Reasonably Achievable') remains critical to reduce both patient and physician risk. For procedural cardiologists, recent reports highlight a disproportionate incidence of left sided brain and neck tumors[530] and cataracts[531]. For patients, total exposure to ionizing radiation has nearly doubled over the past two decades, owing to increased exposure from interventional fluoroscopy procedures and CT scans which are now ubiquitous in medical practice[532]. Thus routine collimation to the minimum required visual field[533], use of very low frame rates and appropriate shielding including use of the radiation cabin[534] all remain important.

Limitations

This study has several limitations. This is a heterogeneous population with respect to AF type and ablation strategy. Redo rates underestimate true recurrence rates, particularly for those with shorter follow-up duration. The retrospective observational design makes the study subject to confounding. In particular, numerous concurrent rapidly evolving technological advances during the follow-up period made it difficult to draw definitive conclusions about which individual factor(s) were most critical in reducing radiation exposure. Lower radiation doses from CF-sensing catheters at a single center may be related to features of the mapping system used, including evolution of CT integration software, or operator technique. Moreover, the retrospective nature did not enable us to obtain organ doses of radiation for both operator and patient to assess risk of malignancy over time.

Conclusion

Radiation exposure has progressively and dramatically decreased over the last decade for PVI, and is related to operator experience, annual case volume, technology evolution and more recently contact force-sensing catheters. This is likely to have significant implications for both patient and operator long term risk.

Table 1: Patient Characteristics

Parameter	*Total (n = 2,344)*
Age (years)	58.6±11.5
Gender	
Male	1,706 (72.8%)
Female	638 (27.2%)
Body mass index	28.3±4.7
Type of AF	
Paroxysmal	1,842 (78.6%)
Persistent	502 (21.4%)
Long-standing Persistent	16 (0.7%)
History of other arrhythmias	
Atrial flutter	234 (10.0%)
SVT	25 (1.1%)
Atrial tachycardia	21 (0.9%)
Prior ablation	617 (26.0%)
Prior PVI	429 (18.3%)
Pre-procedural rhythm	
Sinus rhythm	1,685 (71.8%)
Atrial fibrillation	590 (25.2%)
Other	69 (3.0%)

Abbreviations: AF: Atrial fibrillation, PVI: Pulmonary vein isolation, SVT: supraventricular tachycardia

Table 2: Procedural Characteristics

Parameter	*Total (n = 2,344)*
AF ablation number	
Initial PVI	1,914 (81.7%)
Redo PVI	430 (18.3%)
AF ablation strategy	
PVI only	1,777 (75.8%)
Additional ablation	567 (24.2%)
Additional AF ablation	
Lines	310 (13.2%)
Posterior wall isolation	167 (7.1%)
CFAE	90 (3.8%)
Additional non-AF ablation	
Atrial flutter	248 (10.6%)
SVT	22 (0.9%)

Abbreviations: AF: Atrial fibrillation, PVI: Pulmonary vein isolation, CFAE: complex fractionated atrial electrograms, SVT: supraventricular tachycardia

Table 3: Radiation exposure over a 12-year period for pulmonary vein isolation (PVI) only

Parameter / Years	*2004-2006*	*2007-2009*	*2010-2012*	*2013-2015*	*p-value (ANOVA)*
Fluoroscopy time (min)					
Initial PVI	60.6±27.2	46.3±14.0	30.6±10.6	17.3±8.7	<0.001
Redo PVI	44.8±25.7	41.8±11.3	28.5±10.7	16.1±7.9	<0.01
Absorbed dose (mGy)					
Initial PVI	-	1365±1369	464±339	304±758	<0.01
Redo PVI	-	1234±670	499±420	265±225	<0.01
Effective dose (mSv)					
Initial PVI	-	11.3±12.5	9.0±10.4	5.5±6.7	<0.01
Redo PVI	-	11.9±12.8	9.6±13.1	5.7±7.1	<0.01

*All values expressed as mean±standard deviation.

Table 4: Impact of contact force-sensing catheters for AF ablation (2014-5)

Parameter	*CF-sensing catheter*	*No CF-sensing catheter*	*p-value*
PVI only	*n=357*	*n=151*	
Fluoroscopy time (min)	11.4±5.0	21.3±8.0	<0.001
Absorbed dose (mGy)	200±524	470±1326	0.004
Effective dose (mSv)	3.1±3.0	7.5±6.9	<0.001
Substrate modification*	*n = 108*	*n = 13*	
Fluoroscopy time (min)	11.6±4.4	18.0±5.8	<0.001
Absorbed dose (mGy)	196±154	295±179	0.04
Effective dose (mSv)	4.4±8.3	6.5±5.1	0.40

*in addition to PVI

Abbreviations: PVI - pulmonary vein isolation, CF – contact force.

Figure 1: Mean Fluoroscopy Time and Number of Cases per year

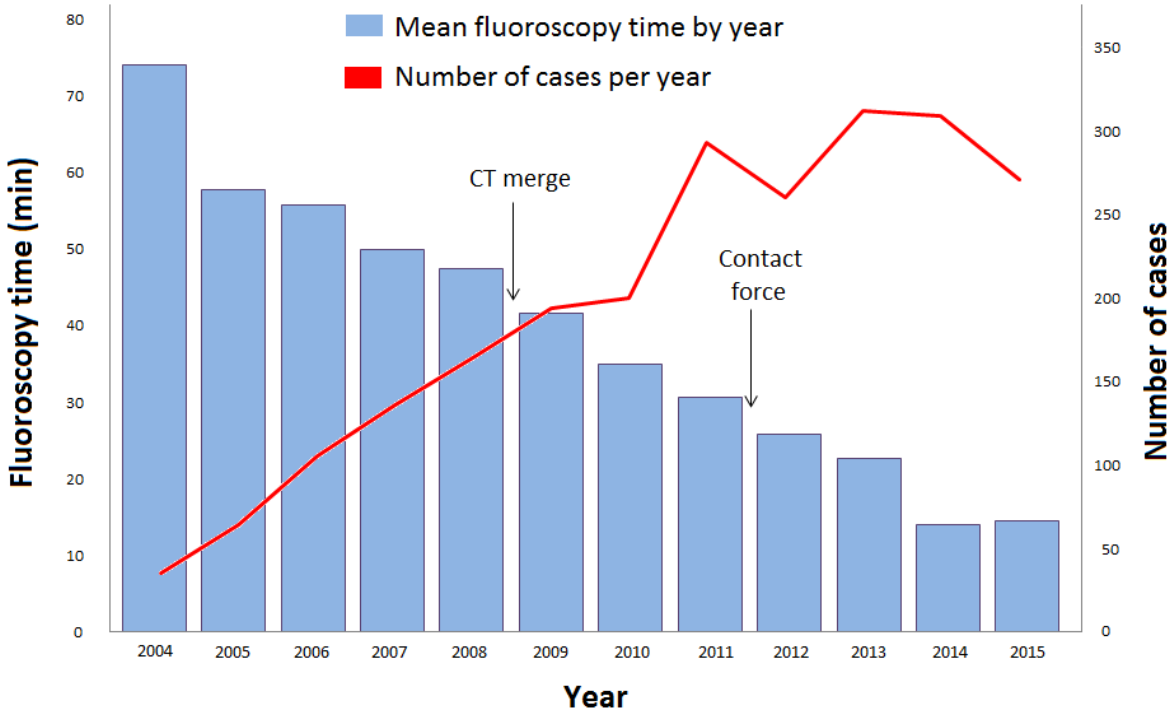
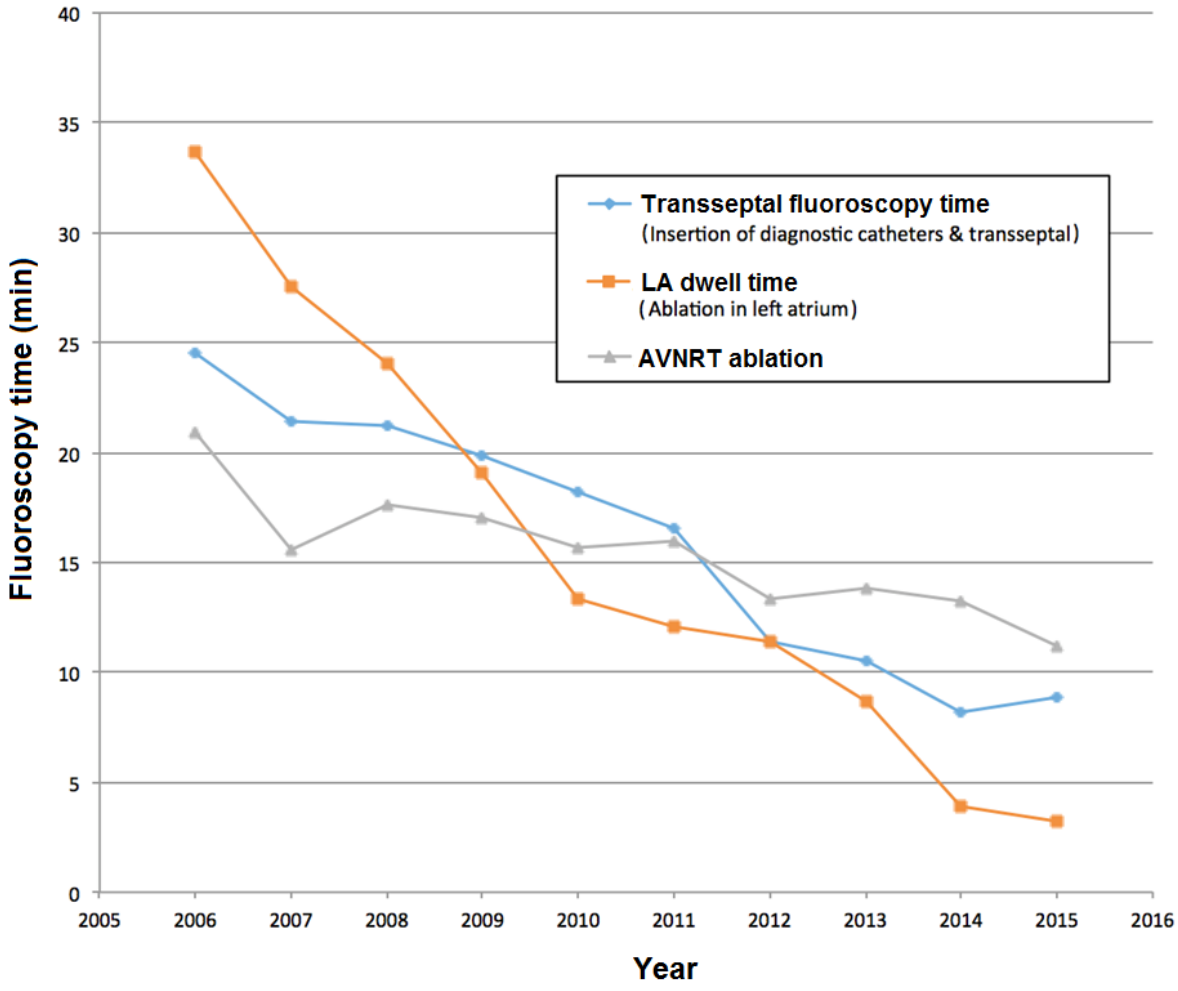


Figure 2: Fluoroscopy time during insertion of diagnostic catheters & transseptal puncture vs during ablation in the left atrium



Chapter 10: Low rates of major complications for radiofrequency ablation of atrial fibrillation maintained over 14 years – a single centre experience of 2,750 consecutive cases

Introduction

Over the past decade, performance of catheter ablation procedures for atrial fibrillation has increased exponentially[535]. However, in the context of a procedure performed primarily for quality of life, minimization of complications remains critical. Both early and contemporary studies continue to report widely varying major complication rates; as low as 0.8%[536] in some series and as high as 9.1% in others[537]. Various reasons have been invoked to explain this variance including operator and hospital experience[538], reporting bias in voluntary registries[539], type of technology used, extent of the ablation procedure and patient population. We reviewed complication rates for AF ablation using radiofrequency energy (RF) at a high-volume tertiary referral centre over a 14-year period.

Methods

Study population

This is a single-centre study of prospectively collected data of 2,750 consecutive atrial fibrillation (AF) ablation procedures performed at the Royal Melbourne Hospital / Melbourne Private Hospital between January 2004 and May 2017. The primary indication for ablation was symptomatic paroxysmal or persistent AF refractory to medical therapy. All ablations were performed by 1 of 4 experienced interventional electrophysiologists with an electrophysiology fellow assisting.

AF ablation protocol

All AF ablations were performed using radiofrequency energy, general anaesthetic and either CARTO® (Biosense Webster, Diamond Bar, CA, USA) or NavX™ (St Jude Medical, St Paul, MA, USA) three-dimensional electroanatomical mapping systems. After induction of general anaesthesia, a transoesophageal echocardiogram (TOE) probe was routinely inserted by the attending anaesthetist or echocardiologist. Baseline

TOE was performed to exclude left atrial (LA) thrombus and left in-situ to guide transeptal puncture, and then removed.

All catheters were inserted via the right femoral vein (two 8 French sheaths, one 7 French & one 6 French sheath), with ultrasound performed for difficult access in all cases, and routinely for cases from 2016 onwards. The internal jugular vein was used for difficult coronary sinus cannulation. Urinary catheters were inserted at the discretion of the anaesthetist. Intracardiac catheters prior to transeptal included a decapolar coronary sinus (CS) catheter and a quadripolar His-bundle/right ventricular catheter. Double transeptal puncture was performed using a BRK^{TM} needle via 8F and 8.5F long SL1 sheaths (St. Jude Medical). Puncture site was guided by fluoroscopy in left anterior oblique and right anterior oblique projections with the His and CS catheters used as anatomical landmarks, as well as TOE which defined the point of maximal septal tenting prior to crossing. Ablation and steerable circular multipolar pulmonary vein (PV) mapping catheters were then introduced into the left atrium (LA) using fluoroscopy. The mapping system then created LA and PV geometry. Surface registration with a pre-procedural CT became standard practice from 2009.

All patients underwent point-by-point wide antral circumferential ablation of the left and right sided PVs using RF delivered through an irrigated catheter during CS-pacing (flow rate 17 mL/min). Power was maintained at 30W on the anterior surface and 25W posteriorly with up to 20 seconds of RF (posteriorly) or up to 30 seconds of RF (anteriorly) delivered at each point. The mapping catheter was used to confirm elimination of all PV potentials and enduring bidirectional block was the procedural endpoint. If PV reconnection developed after a waiting period of 30 minutes, additional RF lesions were applied. From 2010, intravenous adenosine (two doses, up to 18mg) was used to assess dormant conduction at the discretion of the operator, and additional RF applied. Catheters and sheaths were then removed and a FemoStop^{TM} vascular clamp applied to the femoral puncture site for 2–4 hours until haemostasis was achieved. A transthoracic echocardiogram at the completion of the procedure was performed in most cases to assess for pericardial effusion.

The anatomic location of the oesophagus was marked in all cases with the TOE probe which was removed following transeptal puncture prior to ablation. Oesophageal temperature monitoring was not routinely performed.

Lesion sets

Additional lesions were performed at the discretion of the operator for persistent AF patients. These included lines at the LA roof, between the lateral mitral annulus and left inferior pulmonary vein, LA posterior wall isolation (roof and floor lines) and ablation of complex or fractionated electrograms (CFAEs). A cavotricuspid isthmus line was performed in patients with previous typical right atrial flutter or if sustained atrial flutter developed during the case. Bidirectional block was the target endpoint for all linear lesions.

Ablation catheters

There was considerable evolution of irrigated catheter technology during the study period, including flexible bidirectional tips (D,F,J curve) conforming to tissue, advanced cooling mechanisms, and contact force-sensing (CF) spring mechanisms. The most commonly used catheters included Cool Flex™ and Flexability™ catheters (St Jude) and Navistar Thermocool™ and Thermocool SmartTouch™ (Biosense Webster). The Thermocool SmartTouch™ catheter (Biosense Webster) was introduced at our centre in 2011 and was the predominant CF catheter used for the remainder of the follow-up period. Target CF was ≥10 g and <40 g for lesion application. There were 8 software and 2 hardware upgrades during the follow-up period.

Periprocedural Anticoagulation

Anticoagulation practise evolved over the study period. In the early years, warfarin was ceased 3–5 days prior to the procedure with bridging low molecular weight heparin (LMWH) commenced at 1 mg/kg bid when international normalized ratio (INR) fell below 2.0. The last dose of LMWH was given the night before the procedure. Post-procedure, enoxaparin was commenced at 6–10 hours and continued at therapeutic dose until INR>2.0. From 2009–2010, the majority of procedures were performed on therapeutic warfarin[540]. Since availability of novel oral anticoagulants (NOACs), patients on NOACs ceased these 24–48 hours prior to procedure depending on the renal function and CHA_2DS_2-VASc score. Post procedure NOAC was recommenced at 6–18

hours. During the procedure, patients received a bolus of 100 IU/kg of intravenous heparin prior to transeptal, and further boluses given to maintain Activated Clotting Time (ACT) 300–350 secs (target of 350) during the ablation. Heparinization was not routinely reversed at procedure completion.

Follow-up and AF Database

All patients were prospectively entered into an AF database in which demographics, procedural data, and follow-up were recorded. Procedural complications were entered by an AF clinical nurse specialist at completion of the ablation procedure, at discharge, and after the first follow-up visit. Outpatient follow-up, including clinical screening for late pulmonary vein stenosis was performed routinely at 3, 6, and 12 months and at least every 6 months thereafter. Major and minor complications were defined according to the 2012 Heart Rhythm Society Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[9]. For the purposes of this report, the entire database of 2,750 patients was independently reviewed as was each individual complication.

Statistical analysis

Summary statistics for continuous data are presented as mean ± standard deviation and categorical variables as percentages. Statistical analyses were performed using SPSS Statistics version 23 (IBM Corp, Armonk, NY). A p-value < 0.05 was considered statistically significant. This study complies with the Declaration of Helsinki and was approved by the Melbourne Health Human Research Ethics Committee.

Results

In total, 2,750 consecutive AF ablation procedures were performed at our institution between January 2004 – May 2017. Patient and procedural characteristics are summarized in Table 1 and 2 respectively. Of 2,255 initial and 495 redo procedures, ablation strategies were: PVI only 2,097 (76.3%), PVI + LA lines 368 (13.4%), PVI + posterior wall 191 (6.9%), PVI + cavotricuspid isthmus 277 (10.1%). Acute procedural success (complete isolation of all four pulmonary veins) was achieved in 98.7% of cases. Left atrial thrombus was seen on TEE in 4 cases, and the procedure aborted prior to transseptal puncture.

There were 23 major (0.84%) and 20 minor (0.73%) complications, as summarized in Table 3. Rates of cardiac tamponade (5 cases – 0.18%) and phrenic nerve palsy (1 case – 0.04%) were very low. Major vascular complications necessitating surgery or blood transfusion occurred in 5 patients (0.18%). There were no deaths, atrio-esophageal fistulae or symptomatic PV stenosis. There were 5 TEE probe-related complications (0.18%). There was one case of thromboembolism (left middle cerebral artery stroke).

Further details regarding major non-vascular complications are provided in Table 5. There were no instances of left atrial perforation since the introduction of contact force. Of note, only 4 patients had mild late persistent symptoms with no patients having major permanent disability as a result of any complication. Of the 43 (1.56%) patients who suffered either a major or minor complication, 17 (37.8%) were female and mean age was 58.2±8.9 years. Women accounted for 8/17 (47.1%) of vascular complications, despite comprising only 27.6% of the total study population.

Logistic regression analysis was performed to identify multivariate predictors of complications. Female gender (OR 2.14; 95% CI 1.07 – 4.26; p = 0.03) was the only significant predictor identified. AF type either paroxysmal or persistent (OR 0.66; 95% CI 0.25 – 1.73), contact force catheter (OR 1.37; 95% CI 0.69 – 2.72), prolonged ablation time (OR 1.00; 95% CI 0.45 – 2.22), additional substrate modification (OR 0.68; 95% CI 0.16–2.87) and age > 70 (OR 1.01; 95% CI 0.31 – 3.38) were not significant predictors of complications. None of the 253 (9.2%) patients over 70 years of age undergoing AF ablation (mean age 72.3±2.3 years; age range 70–86) suffered a major complication; although 3 had minor complications (AV fistula, femoral pseudoaneurysm, air embolism causing transient ischemia).

Discussion

Contemporary studies continue to report widely varying major complication rates, ranging from 0.8 – 9.1%, with a pooled average acute complication rate of 2.6% in a recent meta-analysis[541]. Various reasons have been invoked to explain this variance including operator and hospital experience[538], reporting bias in voluntary registries[539], patient population including age and sex, type of technology used and extent of the ablation procedure.

The current study demonstrates that it is possible to achieve and maintain a very low rate of major complications (~1%) during radiofrequency AF ablation in a population with a low prevalence of comorbidities. Multiple factors throughout this period may have contributed to these outcomes.

Patient factors

While our cohort had a low prevalence of advanced structural heart disease, the patient profile is not dissimilar to other contemporary studies focusing on complications and risk prediction (Table 3). Mean age is approximately 60 years; 60-80% are male, 25-50% of the patients have persistent AF and the CHA_2DS_2-VASc score is generally low. Prior studies have generally demonstrated an increased risk of major complications in patients with more advanced structural heart disease, more comorbidities and higher CHA_2DS_2-VASc scores[542]. A recent US registry of 106,105 patients highlighted the impact of medical comorbidities, with higher-risk patients experiencing complication rates of 29.5–45.7% and 4.6–6.1% inpatient mortality[543]. One key comorbidity that has been associated with increased risk is the BMI[544]. In the current study, mean BMI was 28 and the absence of morbidly obese patients in the cohort may also have contributed to a low event rate.

As in previous studies[257,545,546], complication rates in the current study were higher in women. Postulated mechanisms include thinner left atrial wall and smaller atrial volume predisposing to tamponade[547], as well as closer proximity and/or overlap of the femoral artery and circumflex branches to the femoral vein leading to a higher risk of inadvertent arterial puncture[548]. In our study, 4 of the 5 TEE related complications occurred in women possibly due to their smaller size and emphasising the need for great care with the TEE probe. Four of these 5 events occurred in the first 1000 cases and a change in protocol (softer TEE probe, esophageal imaging only, minimization of lateral probe flexion and removal of the probe immediately after transeptal crossing) has markedly reduced this complication. While routine use of intracardiac echocardiography (ICE) would eliminate the possibility of this complication, it may increase the risk of vascular complications. For example, Aldhoon et al reported a 2.3% incidence of vascular injury for ICE-guided AF ablation[549].

Studies reporting complication rates in the elderly have provided conflicting results with some suggesting an increase[550] and others finding no difference[551]. This may in part reflect the definition of increased age (different studies have used cut-points from as low as 65 years[552] up to age of 80 years[553]) and in part the selected nature of the older population. In the current study, patients over the age of 70 did not have an increased risk of adverse events indicating that ablation can be safely performed in this cohort. However, in this as in other studies, patients over 70 represented a small % of the overall cohort; an inversion of what is expected in an unselected AF population and indicative that patients in older age groups referred for ablation are generally highly selected[554].

Operator factors

At our institution, AF ablation volume has increased over the past decade and for 6 years has stabilised at approximately 300 procedures per year (Figure 1). A number of studies have indicated the importance of procedure volume to maintain low complication rates although the ideal number is not well characterised. A U.S registry of 93,801 AF ablations found that both >50 annual cases per operator (OR 0.38; 95% CI 0.21 – 0.69) and >100 annual cases per hospital (OR 0.64; 95% CI 0.51 – 0.81) were highly predictive of lower complication rates[555]. In that study, only 19% of AF ablations were performed by operators performing > 25 per year and 32% of hospitals had volumes > 50 procedures. A pooled multivariate analysis from 29 European centres also observed that operator experience (OR 0.5; 95% CI 0.4 – 0.7) was an independent predictor of increased complications. In addition to the impact of an experienced operator is that of an experienced centre[556]. Highly-trained support staff including anaesthetists, EP laboratory technicians and nursing staff familiar with AF ablation both in the laboratory and on the ward are all likely important in contributing to a low complication rate.

In high volume tertiary institutions responsible for training the next generation of heart rhythm experts, it is possible that higher complication rates may occur due to inexperienced fellows performing some or all of the catheter manipulation. Baman et al observed a higher complication rate for procedures performed in July and August (OR=2.1) compared with other months of the year coincident with the commencement period for new fellows[557]. It is a requirement in our institution that when a fellow is

manipulating catheters, the attending electrophysiologist must be at the bedside for the duration of the procedure. This close supervision may potentially contribute to lower overall complication rates. Sobering data from Winkle et al found that a learning curve of ~6 years was required to minimize ablation complications[538]. The advent of ablation simulators may prove to be important with respect to complication rates.

Procedural factors

The low tamponade rate in the current study (Table 4) may relate to multiple procedural factors such as routine use of general anaesthesia limiting unexpected patient movements, echocardiographic guidance of transeptal puncture, conservative power settings and ablation duration particularly on the posterior wall and limited adjunctive ablation[558]. These measures were undertaken throughout the entire study period, as illustrated in Figure 1. As in prior reports[559], this study reinforces the notion that aggressive therapeutic anticoagulation does not increase the risk of tamponade.

Approach to anti-coagulation in this study reflects the change in guideline practice over this extended time period as outlined in the Methods. Overwhelming evidence has demonstrated the reduction in embolic risk with adherence to aggressive anticoagulation policy. Ultrasound-guided femoral venous access is now becoming routine and this may decrease the vascular complication rate particularly in an anticoagulated population[560].

Recent studies have suggested that newer technologies may be associated with lower risk of complications. In an observational study with an overall 11.3% complication rate, Akca et al observed a lower incidence of tamponade and a lower overall complication rate when contact force catheters were used[561]. While the current study was underpowered to detect any differences, contact force catheters may nevertheless provide an important efficacy and safety tool when training fellows.

We also found no symptomatic cases of PV stenosis which may predominantly reflect a wide antral approach to ablation. Between 2003–6, an international survey found that rates of PV stenosis requiring intervention had already dropped 3-fold to just 0.29%, and are now so rare (Table 4) that less than a quarter of leading arrhythmia experts routinely screen for this rare complication[562]. Our study also confirmed that phrenic

nerve palsy is an extremely rare complication when using RF, seen in only 1 patient (0.04%). In a recent multi-centre randomized trial of 762 patients comparing RF and cryoballoon, there were no cases of phrenic nerve palsy in the RF group, as compared with 2.7% in the cryoballoon balloon group[336].

Limitations

This is a single-centre analysis but nevertheless demonstrates that very low major complication rates for AF ablation can be maintained over time when a single department maintains a consistent procedural approach. Because of the low overall incidence of each complication, the power to detect complication predictors is reduced.

Conclusion

Radiofrequency ablation of atrial fibrillation by pulmonary vein isolation can be achieved in a high volume centre with a very low major complication rate over a sustained period of time.

Table 1: Patient characteristics

Parameter	Total (n = 2,750)
Age (years)	59.0±12.5
Gender	
Male	1,990 (72.4%)
Female	760 (27.6%)
Body mass index	28.3±4.7
Type of AF	
Paroxysmal	2,148 (78.1%)
Persistent	582 (21.2%)
Long-standing Persistent	20 (0.7%)
Comorbidities	
Hypertension	30.8%
Diabetes Mellitus	5.3%
Stroke / TIA	4.0%
Mean CHA_2DS_2-VASc score	1.2±1.3
Mean LVEF (%)	58.5±5.3
LVEF < 50%	8.4%
LVEF ≤ 35%	1.3%
History of other arrhythmias	
Atrial flutter	252 (9.2%)
SVT	27 (1.0%)
Atrial tachycardia	23 (0.8%)
Prior ablation	709 (25.8%)
Prior PVI	495 (18.0%)
Pre-procedural rhythm	
Sinus rhythm	1,959 (71.2%)
Atrial fibrillation	712 (25.8%)
Other	79 (2.9%)

Abbreviations: AF: Atrial fibrillation, PVI: Pulmonary vein isolation, SVT: supraventricular tachycardia, TIA: transient ischemic attack, LVEF: Left Ventricular Ejection Fraction

Table 2: Procedural Characteristics

Parameter	*Total (n = 2,750)*
AF ablation number	
Initial PVI	2,255 (82.0%)
Redo PVI	495 (18.0%)
AF ablation strategy	
PVI only	2,097 (76.3%)
Additional ablation	653 (23.7%)
Additional AF ablation	
Lines	368 (13.4%)
Posterior wall isolation	191 (6.9%)
CFAE	94 (3.4%)
Additional non-AF ablation	
Atrial flutter	277 (10.1%)
SVT	22 (0.8%)
Acute procedural success*	2713 (98.7%)
LA thrombus – case aborted	4 (0.15%)
Trans-septal abandoned	6 (0.22%)
Stopped due to complication	4 (0.15%)
Incomplete isolation of all 4 pulmonary veins	
Pre-2010	19 (0.73%)
Post-2010	4 (0.15%)
Median Fluoroscopy time (min)	24.6 (14–39)
Median Ablation time (min)	41.6 (30–53)

*Successful isolation of all four pulmonary veins (entry & exit block)

Abbreviations: AF: Atrial fibrillation, PVI: Pulmonary vein isolation, CFAE: complex fractionated atrial electrograms, SVT: supraventricular tachycardia, Left Atrium

Table 3: Major and minor complications from atrial fibrillation ablation.

Complications (*n = 2,750)*	Total (%)
Major	**23 (0.84%)**
Death	0
Cardiac tamponade	5 (0.18%)
TIA / Stroke	1 (0.04%)
Acute myocardial infarction	0
Phrenic nerve palsy	1 (0.04%)
Gastroparesis (vagal nerve injury)	2 (0.07%)
Atrio-oesophageal fistula	0
Symptomatic pulmonary vein stenosis	0
Aspiration pneumonia	1 (0.04%)
Prolonged pericarditis (>1 month)	1 (0.04%)
Urethral stricture	1 (0.04%)
Atonic bladder	1 (0.04%)
Oesophageal / gastric (TOE probe)	
Oesophageal haematoma	3 (0.11%)
Gastric tear	1 (0.04%)
Oesophageal perforation	1 (0.04%)
Major vascular complications (surgery / transfusion)	
Retroperitoneal haematoma	2 (0.07%)
Sheath sheared in femoral vein	1 (0.04%)
Thigh haematoma	1 (0.04%)
Femoral pseudoaneurysm	1 (0.04%)
Minor	**20 (0.73%)**
Minor vascular complications	
Femoral pseudoaneurysm (compression / thrombin injection)	9 (0.35%)
Femoral arterio-venous fistula (compression / observation)	3 (0.12%)
Asymptomatic pericardial effusion	3 (0.12%)
Transient myocardial ischaemia	3 (0.12%)
Urinary tract infection	1 (0.04%)
Pharyngeal trauma	1 (0.04%)

Abbreviations: AF: Atrial fibrillation, PVI: Pulmonary vein isolation, CFAE: complex fractionated atrial electrograms, SVT: supraventricular tachycardia, Left Atrium; TOE: transoesophageal echocardiography, TIA: Transient Ischaemic Attack.

Table 4: Contemporary studies examining complication rates for AF ablation using radiofrequency energy

Study	*n / Years*	*Age, % Male*	*PeAF*	*CHA_2DS_2-VASc*	*Major complications / Tamponade*	*CVA / TIA*	*Sympt PV stenosis*	*GA vs Sedation*	*Imaging for transseptal*	*Anti-coagulation*	*Power settings*
Current study	2,750 / 2004 – 2017	59 yrs, 72% M	21%	1.2±1.3	0.84% / 0.18%	0.04 %	0%	GA	TOE + Fluoroscopy	ACT 300-350	30W ant, 25W post.
Chun 2017[563]	2,125 / 2010 – 2015	67yrs, 62%M	57%	30% ≤1	4.4% / 1.5%	0.2%	0%	Sedation	Fluoroscopy	ACT target 300	40W ant, 30W post
Yang 2017[542]	1,475 / 2003 – 2015	60yrs, 82%M	31%	76% 0-2	3.9% / 1.1%	0.9%	0.07%	Sedation	Fluoroscopy (majority)	Aggressive; UFH reversed at end of case	30-40W ant, 25-30W post
Arbelo 2017[471]	3,630 / 2012 – 2015	59 yrs, 68% M	27%	76% 0-2	7.8% / 1.5%	0.5%	0.2%	Sedation (77%)	TOE 20%, ICE 13%	-	NS
Lee 2016[519]	1,515 / 2009 – 2014	61 yrs, 65% M	49%	-	- / 0.9%	-	-	Sedation	Fluoroscopy	ACT ~ 350	30W max.
Kuck 2016[336]	384 / 2012 – 2015	60 yrs, 63% M	23% prior CV	1.8±1.3	- / 1.3%	0.5%	0%	-	-	-	40W ant, 30W post (max)
Jarman 2015[526]	600/ 2010 – 2012	62yrs, 72% M	54%	-	4.0% / 1.2%	0.34 %	0.17%	Sedation	Fluoroscopy	-	35W ant, 25W post.
Bertaglia 2013[564]	2,323 / 2011	60 yrs, 73% M	26%	$CHADS_2$ = 1	4.0% / 0.5%	0.2%	0%	-	ICE 14%	ACT 350	25W post

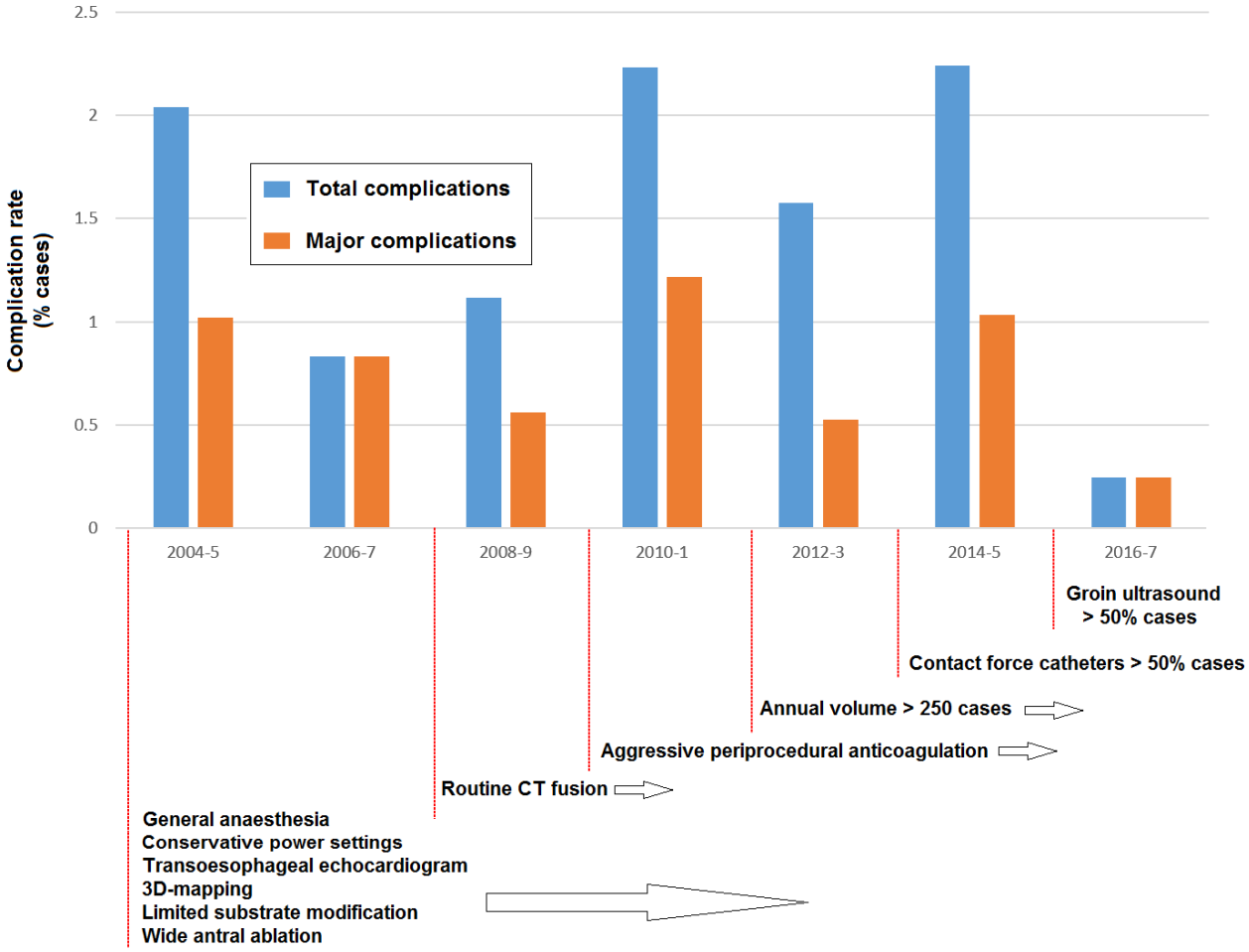
Abbreviations: PeAF: Persistent Atrial fibrillation, GA: General anaesthesia, TOE: transoesophageal echocardiography; ACT: Activated Clotting Time; ICE: Intracardiac echocardiography; RF: Radiofrequency energy; TIA: Transient Ischaemic Attack; PV: Pulmonary Vein; LA: Left Atrium; UFH: Unfractionated Heparin; CV: cardioversion; CVA: Cerebrovascular Accident (stroke).

Table 5: Details of major non-vascular complications

Complication	*Patient details*	*Ablation details*	*Year*	*Presentation*	*Management*	*LOS (d)*	*Long-term Sequelae*
Tamponade	48M, PAF	Aborted post transeptal	2005	Effusion following transeptal due to suspected perforation of LA roof from unprotected sheath.	Immediate sternotomy and pericardotomy with evacuation of blood, no clear perforation seen.	5	Nil
Tamponade	64F, PAF	No TEE, no CF	2010	Symptomatic hypotension and pleuritic chest pain 4 hours post procedure.	Emergency pericardial window (800 mL drained). Pericarditis post discharge	7	Nil
Tamponade	67M PeAF	Posterior wall RF, no CF	2011	Moderate pericardial effusion and borderline blood pressure on withdrawal of catheters.	Pericardiocentesis (sub-xiphisternal approach) with 200mL drained, protamine given.	2	Nil
Tamponade	60F, PAF	No CF	2014	Rise in impedance during geometry collection (?small roof vein) followed by hypotension	Pericardiocentesis (sub-xiphisternal approach) with 300 mL drained, protamine given.	7	Nil
Tamponade	59M, PAF, AFL	PVI + CTI, CF	2015	Steam pop during CTI. Hypotension on ward post-procedure.	Pericardiocentesis (sub-xiphisternal approach) with 250mL drained.	4	Nil
Stroke	56M, PeAF	Roof line, CV during PVI.	2010	Normal TEE & therapeutic ACT during PVI. R upper limb weakness following extubation. MRI showed L MCA infarct.	Anticoagulation continued. Resolution of weakness prior to discharge.	5	Mild R hand weakness
Vagal Injury	36M, PAF, AFL	PVI + CTI, CF	2014	Persistent burning chest pain post procedure & symptoms of gastroparesis.	Treated with domperidone, PPI & aperients.	4	Nil
Vagal injury	44M, PAF	PVI, CF	2012	Dysphagia and burning chest pain day 1 post procedure & symptoms of gastroparesis.	Medical therapy with analgesia and PPI.	3	Nil
Aspiration Pneumonia	63M, PAF	PVI	2014	Pleuritic chest pain & hypoxia day 1 post PVI with left basal consolidation on chest X-ray.	Intravenous antibiotics and chest physiotherapy	22	Nil
Pericarditis	52F, PAF	PVI	2008	Pleuritic chest pain post procedure, persisting for 1 month.	Resolution with anti-inflammatories.	3	Nil
Urethral Stricture	43M, PAF	PVI	2012	Haematuria & dysuria post catheter removal. Cystoscopy: hemi-circumferential ulcer of urethral mucosa	Endoscopic urethrotomy 2015 for urethral stricture	2	Mildly impaired urinary flow rate
Atonic Bladder	74F, PAF, AFL	PVI + RA flutter	2015	Developed loss of bladder sensation and urinary retention immediately post PVI. Normal spine/brain MRI. Cause unclear.	Sacral neuromodulation device unsuccessful. Ongoing daily self-catheterization.	5	Self catheteriz-ation
Phrenic nerve palsy	49M, PAF	PVI, no CF	2010	Mild dyspnoea on day 1 post PVI. Fluoroscopic sniff test: elevated right hemidiaphragm.	Conservative management with resolution after 6 months.	7	Nil
Oesophageal Haematoma	49F, PAF	PVI	2006	Throat pain & dysphagia for 2 days post PVI. CT: 2cm para-oesophageal hematoma. Subsequently developed hoarse voice (recurrent laryngeal nerve palsy)	Dexamethasone 8mg tds for recurrent laryngeal nerve palsy. Hoarse voice resolved over 6 months.	9	Nil
Oesophageal Haematoma	57F, PAF	PVI	2007	Ongoing dysphagia at day 3 post procedure. CT: oesophageal edema without perforation.	Conservative management acutely. Gastroscopy at 2 months: mild stricture requiring dilatation	13	Mild residual dysmotility
Oesophageal Haematoma	48M, PAF	PVI	2008	Dysphagia & odynophagia 12 hours post procedure. CT: large intramural haematoma in posterior oesophageal wall.	Anticoagulation ceased, IV pantoprazole. Symptoms resolved prior to discharge.	5	Nil
Gastric tear	59F, PAF	PVI	2011	Hematemesis and melena following procedure.	Urgent laparotomy – 3cm gastric tear oversewn.	6	Nil
Oesophageal perforation	66F, PAF, GERD	Redo-PVI	2016	Severe back pain and hematemesis 3 hours post procedure. CT: oesophageal tear & pneumomediastinum.	Urgent thoracotomy and esophageal repair. Required TPN & antibiotics for pneumonia.	42	Nil

Abbreviations: LOS: length of stay, M: male, F: female, PAF: Paroxysmal atrial fibrillation, PeAF: Persistent AF, PVI: Pulmonary vein isolation, CTI: cavotricuspid isthmus ablation, TEE: transesophageal echocardiogram, CF: contact force, CT: computerized tomography, PPI: Proton pump inhibitor, ACT: Activated Clotting Time., CV; cardiovesion

Figure 1: Multiple factors associated with maintenance of low major complication rates over a 14-year period



Chapter 11 : Conclusion and Future Directions

Rhythm control of atrial fibrillation is an increasingly pursued management strategy for patients with AF-related symptoms and/or AF-related cardiomyopathy. This strategy has undergone incredible evolution over the past decade, expanding from anti-arrhythmic drugs to a multi-faceted approach that addresses AF risk factors and embraces catheter ablation as expertise grows with this procedure.

Chapters 2 – 5 focus on an emerging risk factor for AF – excessive alcohol consumption. While binge drinking is an established AF trigger, this thesis explores the impact of 'mild to moderate' habitual consumption. While epidemiological studies suggest a higher incidence of new onset AF in regular drinkers, we explore the contribution of alcohol consumption in those with established AF.

Chapter 2 examines the electrophysiological impact of moderate consumption on the left atrium using high-density electroanatomical mapping at time of catheter ablation. The key findings were lower voltage (a surrogate for atrial fibrosis) and conduction abnormalities observed in moderate drinkers compared to non-drinkers, with no consistent differences observed in mild drinkers. Chapter 3 utilizes cardiac MRI technology to assess atrial structural properties in a large cohort of AF patients. We observe dose-related left atrial dilatation, mechanical dysfunction and impairments in reservoir function with heavy drinkers having the greatest degree of atrial myopathy. The impact of these electrical and structural changes on stroke risk, risk of post-ablation arrhythmia recurrence and overall survival require further clarification. Moreover, these studies were underpowered to determine whether there is a safe drinking level that does not have adverse consequences on left atrial 'substrate', and further research is required to clarify this.

Chapter 4 is the first-ever randomized controlled trial examining the impact of medium term abstinence on AF outcomes in moderate drinkers with a history of AF (Alcohol-AF trial). This study underscores the importance of risk factor management with abstinence associated with lower AF recurrence rates at 6-months follow-up. Other associated benefits include mild weight loss and systolic blood pressure reduction. While these improvements were seen in a motivated, selected cohort of patients, further research is required to determine how these

lifestyle changes can be implemented in the broader AF population and maintained for an extended period. While multi-disciplinary AF clinics have been promoted as a tool to enable efficacious delivery of lifestyle interventions, their implementation in an increasingly under-resourced health system amidst the backdrop of a Western lifestyle where alcohol is ubiquitous remain major challenges.

Moreover, there are considerable epidemiological data suggesting that milder levels of alcohol consumption may be beneficial with respect to cardiovascular disease, heart failure and overall mortality in the non-AF population. In Chapter 5, we explore a potential putative mechanism for this observation using cardiac MRI T1 mapping in a large cohort of stable outpatients. We observe lower markers of ventricular fibrosis in habitual mild drinkers compared to lifelong non-drinkers, a novel finding using this modality. Further research is required to histologically validate these findings and clarify the clinical significance of these observations.

Electrical cardioversion (CV) is an increasingly utilized treatment strategy for rhythm control in persistent AF and Chapters 6 – 7 focus on strategies to improve success rates and outcomes in these patients. The co-existence of AF and obesity is associated with lower CV success rates, and in Chapter 6 presents the results of the Cardioversion-BMI randomised controlled trial exclusively looking at optimum technique(s) for CV in obesity. We find that use of hand-held paddles, manual pressure augmentation and higher energy use may improve success rates. Improved strategies for long-term maintenance of sinus rhythm following CV remain an ongoing challenge in this cohort and is an area of ongoing research interest.

Chapter 7 explores the importance of early restoration of sinus rhythm in persistent AF. We assess a strategy that utilises early presentation to the emergency department for CV and compare this with an 'elective' strategy. Key findings include possible prevention of adverse left atrial remodelling with earlier CV with an observed lower rate of subsequent AF recurrence, improvements in symptoms scores and lower likelihood for referral for ablation. Further research is required to verify these findings in a prospective randomized trial and explore a potential framework for delivering early CV in different health care settings.

Chapters 8 – 10 assess factors that may improve safety and efficacy of catheter ablation – another important and evolving facet of AF rhythm control. Chapter 8 presents the findings of a meta-analysis of studies utilizing pulmonary vein isolation alone in persistent AF. We find

that satisfactory procedural success rates are achievable with this strategy (comparable to the paroxysmal AF population), even if further substrate modification is not performed. Further research will focus on improving long-term success rates further, either through further targeted ablation strategies or adjunctive risk factor management.

In Chapter 9, we find that radiation exposure has markedly reduced over time with ablation. Some centres currently have reported fluoroless ablation with greater utilization of electroanatomical mapping and intracardiac echocardiography, and further research will focus on achieving further reductions in this area. In Chapter 10, we analyse the potential factors that have contributed to relatively low complication rates maintained over time at a high volume centre. Ensuring complications are minimized as patient complexity and age increase and achieving similar safety at low-volume centres remain priorities for further research as AF ablation becomes increasingly mainstream.

We have witnessed a significant evolution in techniques and technologies designed to achieve and maintain sinus rhythm. However in spite of this, there is no 'cure' for AF. This PhD adds to the growing body of work in this field, and highlights that a multi-faceted approach incorporating lifestyle management, as well as improved cardioversion and ablation strategies are pivotal to rhythm control of AF. Nevertheless, AF incidence is expected to rise as smartphone and smartwatch technologies improve AF detection, coupled with an ageing population and Western lifestyle. While novel risk factor management strategies, antiarrhythmic agents and ablation technologies will form the foundations for future research, AF prevention may also provide a fertile ground for further research.

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