MECHANISMS DRIVING PERSISTENT ATRIAL FIBRILLATION: INSIGHTS FROM ENDOCARDIAL-EPICARDIAL DISSOCIATION AND REGIONAL HIGH-DENSITY MAPPING OF THE HUMAN ATRIUM

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ABSTRACT

Atrial fibrillation (AF) is an extremely common clinical problem with increasing global prevalence. Besides its frequent association with stroke, heart failure and increased mortality, recent data have shown the significant quality of life impairment and psychological distress that results from this arrhythmia. The clinical spectrum of AF can manifest as brief episodic paroxysmal AF or as a sustained arrhythmia in persistent AF in patients with progressive atrial disease. Mechanistically, paroxysmal AF is often triggered by rapidly firing impulses that originate in the pulmonary veins, allowing catheter-mediated elimination of sources, with clinical success rates of 70–85%. However, in persistent AF, the mechanism that sustains the arrhythmia remains incompletely understood and is a topic of ongoing debate. Recent advances in cardiac mapping and computational methods have suggested localised drivers and non-pulmonary vein triggers particularly from the left atrial appendage but there is also accumulating evidence that the atrium frequently functions electrically as a 3-dimensional structure and there exists endocardial-epicardial dissociation in activation during AF.

The aims of this thesis are three-fold: Firstly, we review the evidence for the current and expanding indications for catheter ablation in AF and highlight some of the novel tools and technological advancements that have emerged in the recent years for achieving durable pulmonary vein isolation (PVI). Secondly, we investigate the role of some of the novel mechanisms that potentially sustain persistent AF. We addressed this first by systematically reviewing the evidence for a computational mapping technique thought

to identify localised sources and then performed a series of cardiac mapping studies in humans. These high-density mapping studies characterised atrial endocardial-epicardial electrical dissociation in the presence of structural heart disease and explored the mechanistic role of localised sources in the left atrium and the left atrial appendage (LAA) in persistent AF. Finally, given the emerging evidence for the mental health effects from AF, we discuss the rationale and methodology of a randomised controlled study comparing catheter ablation with medical therapy on psychological distress and neurocognitive function in patients with AF.

Chapter 1 summarizes several aspects of AF including the epidemiology, our current understanding of the classic and novel mechanisms of AF the mechanistic role of risk factors and their implications in remodelling and atrial cardiomyopathy.

Chapter 2 reviews the role of catheter ablation in AF and highlights the recent technological advancements. Catheter ablation is a safe and effective rhythm control strategy for symptomatic patients who failed medical therapy or who prefer not to take medications and there is emerging evidence for its role in mortality reduction in AF patients with heart failure. Pulmonary vein isolation is the cornerstone approach and both radiofrequency and cryoablation have similar efficacy. Mounting evidence demonstrates the importance of risk factor management for improving ablation outcomes.

In the era of high-density cardiac mapping, FIRM (focal impulse and rotor modulation) emerged as a novel computational mapping technique to identify rotors and focal sources that could potentially be targeted during catheter ablation. Despite early promising results, many studies that followed showed mixed outcomes and indeed, some others showed a pro-arrhythmic consequence. Chapter 3 presents a systematic review and meta-analysis of 11 observational studies and demonstrates the wide variability in the medium-term outcomes of FIRM guided ablation and explores the significant heterogeneity between published studies.

Chapters 4 and 5 examine the characteristics of endocardial-epicardial dissociation (EED) in patients with structural heart disease. We performed high-density simultaneous endocardial-epicardial phase mapping of the right atrium in patients undergoing cardiac surgery to study this. In Chapter 3 we report the for the first time, functional EED based on observations of synchronous activation during sinus rhythm and EED in activation timing and wavefront propagation during pacing drive and premature extra-stimulation providing compelling evidence for the functional nature of the atrial substrate. Chapter 4 presents data of phase mapping prolonged persistent AF recordings. The results provide novel evidence for endocardial-epicardial wave front mismatch in AF along with marked EED with temporal heterogeneity.

In Chapter 6 we sought to characterise the preferential 3-dimensional nature of sinoatrial conduction in humans using simultaneous endocardial-epicardial mapping of the sinus node region. In intact hearts of patients with structural heart disease, data confirmed the

presence of multiple differential endocardial and epicardial sino-atrial exits and hence the redundant structure of the pacemaker complex. This is consistent with data from optical mapping of ex-vivo human hearts and demonstrates that clinical sinus node dysfunction only occurs in the setting of advanced atrial structural remodelling.

Recently, data from cohort studies and a randomised controlled trial have shown that LAA isolation improves ablation outcomes in patients undergoing redo ablation for persistent AF. However, there have been concerning reports that such empirical ablation is associated with a heightened risk of LAA thrombus, even in patients who are anticoagulated. Furthermore, data from mapping studies have also shown mixed results on the potential role of LAA as a driver in persistent AF. In Chapter 7 we examine the role of localised sources in the left atrium particularly in the LAA by performing regional high-density mapping of persistent AF. In addition to finding infrequent drivers in the left atrium, this project also showed paucity of triggers from the LAA providing further evidence of its passive role rather than an active driver in persistent AF.

Besides physical symptoms that patients with AF experience, recent data has shown the enormity of mental health effects that AF can have that is often underappreciated by clinicians. More importantly, preliminary data from observational studies show the benefits of catheter ablation to improve mental health. Chapters 8 and 9 present the methodology and rationale of a multicentre, randomised controlled trial that assesses the impact of catheter ablation on psychological distress and neurocognitive function in patients with AF. The study has completed recruitment and successfully enrolled 100

participants across the Royal Melbourne and Alfred Hospitals and completion of analysis is expected by March 2022.

Chapters 10 and 11 conclude by summarizing the key findings of the studies and their clinical implications. Further, it paves the way for future work that might progress our understanding of AF, especially in light of novel mechanisms

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 is made in the text. The work was performed by the candidate in Melbourne in the Cardiology Departments of The Royal Melbourne Hospital, Parkville and The Alfred Hospital, Prahran and the Department of Medicine, The University of Melbourne, Parkville 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 tables, figures, appendices and bibliography.

Ramanathan Parameswaran

PREFACE

This work was performed in collaboration with the following departments and institutions:

1. Department of Cardiology, The Royal Melbourne Hospital
2. Department of Cardiothoracic Surgery, The Royal Melbourne Hospital
3. Department of Medicine, The University of Melbourne
4. Department of Clinical Psychology, The University of Melbourne
5. Department of Cardiology, The Alfred Hospital

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. 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.

Chapters 3-5 involved a collaborative effort with the Department of Cardiothoracic Surgery at The Royal Melbourne Hospital for participant recruitment and data collection. However, my contribution was >80%. Chapters 7 and 8 required assistance from the Department of Clinical Psychology, The University of Melbourne for protocol design and the Department of Cardiology at the Alfred Hospital for participant recruitment. My contribution was > 80%.

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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'.

PEER-REVIEWED PUBLICATIONS

CHAPTER 1

- Parameswaran R et al. **Atrial Arrhythmias in Patients With an ASD: Where to From Here?** JACC Clin Electrophysiol. 2020 May;6(5):549-551. doi: 10.1016/j.jacep.2020.01.012. PMID: 32439039.

- Parameswaran R et al. **Coherent mapping: A step toward physiological mapping of complex arrhythmias?** J Cardiovasc Electrophysiol. 2020 Jun;31(6):1448-1451. doi: 10.1111/jce.14455. Epub 2020 Apr 6. PMID: 32227544.

- Parameswaran R et al. **APPLE score in atrial fibrillation: a simple solution to predict a complex process?** Europace. 2019 Jan 1;21(1):1-2. doi: 10.1093/europace/euy157. PMID: 29992328.

- Parameswaran R. **Left Atrium and Cardiovascular Risk: Does Functionality Matter More Than Size?** J Am Heart Assoc. 2018 Mar 30;7(7):e008930. doi: 10.1161/JAHA.118.008930. PMID: 29602765.

CHAPTER 2

- Parameswaran R et al. **Catheter Ablation for Atrial Fibrillation: Current Indications and Evolving Technologies**. Nat Rev Cardiol. 2020 Oct 13. doi: 10.1038/s41569-020-00451-x. Online ahead of print.

CHAPTER 3

- Parameswaran R et al. **Clinical Impact of Rotor Ablation in Atrial Fibrillation: A Systematic Review**. Europace. 2018 Jul 1;20(7):1099-1106. doi: 10.1093/europace/eux370. PMID: 29340595.

CHAPTER 4

- Parameswaran R et al. **Functional Atrial Endocardial-Epicardial Dissociation in Patients with Structural Heart Disease Undergoing Cardiac Surgery.** JACC Clin Electrophysiol. 2020 Jan;6(1):34-44. doi: 10.1016/j.jacep.2019.08.016. Epub 2019 Oct 30. PMID: 31971904.

- Parameswaran R et al. **Enhanced Functional Atrial Endocardial-Epicardial Electrical Dissociation and Signal Complexities in Patients with Structural Heart**

Disease Undergoing Cardiac Surgery. J Arrhythmia. Atrial Fibrillation., 35: 76-327. doi:10.1002/joa3.12267 (2019)

CHAPTER 5

- Parameswaran R et al. Endocardial-Epicardial Phase Mapping of Prolonged Persistent Atrial Fibrillation Recordings: High Prevalence of Dissociated Activation Patterns. Circ Arrhythm Electrophysiol. 2020 Jul 7. doi: 10.1161/CIRCEP.120.008512. Epub ahead of print. PMID: 32634027.

- Parameswaran R et al. Endocardial-Epicardial Phase Mapping of Persistent Atrial Fibrillation: Enhanced Dissociation, Marked Conduction Heterogeneities and Driver Characteristics. J Arrhythmia. Atrial Fibrillation., 35: 76-327. doi:10.1002/joa3.12267 (2019)

CHAPTER 6

- Parameswaran R et al. Simultaneous Epicardial-Endocardial Mapping of the Sinus Node in Humans with Structural Heart Disease: Impact of Overdrive Suppression on Sino-atrial Exits. Heart Rhythm. 2020 Jul 2:S1547-5271(20)30633-0. doi: 10.1016/j.hrthm.2020.06.034. Epub ahead of print. PMID: 32622994.

- Parameswaran R et al. **Author's reply to: Investigating sino-atrial node activation during sinus rhythm using phase mapping.** Heart Rhythm. 2020 Oct 10:S1547-5271(20)30949-8. doi: 10.1016/j.hrthm.2020.10.006. Online ahead of print.

- Parameswaran R et al. **Sino-atrial Conduction in Humans with Structural Heart Disease: Impact of Overdrive Suppression on Arrhythmogenesis from and Endocardial-Epicardial Perspective.** Heart Rhythm. 2019: Volume 17, Issue 5, S477 - S570. doi: 10.1016/j.hrthm.2020.04.010

CHAPTER 7

- Parameswaran et al. **Paucity of Driver Domains in Persistent Atrial Fibrillation: Insights from Regional High Density Double PentaRay Mapping of the Left Atrium.** (To be submitted)

CHAPTER 8

- Parameswaran et al. **Randomised Evaluation of the Impact of Catheter Ablation on Psychological Distress in Atrial Fibrillation: Rationale and Design of the**

REMEDIAL-PD study'. American Heart Journal (Under review as of December 2020)

CHAPTER 9

- Parameswaran et al. Randomised Evaluation of the Impact of Catheter Ablation on Neurocognitive Function in Atrial Fibrillation: Rationale and Design of the REMEDIAL-CF study'. International Journal of Cardiology (To be submitted)

AWARDS

- **'Best Oral Presentation' –** Melbourne Health Research Week, June 2019 (Chapter 4)
- **'Young Investigator Award'** 12th Asia-Pacific Heart Rhythm Society Annual Scientific Sessions, Bangkok, Thailand. Oct 24-27, 2019 (Chapter 5)

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On a more personal note, I am hugely indebted to my parents *Mr Parameswaran Subramanian* and *Mrs Geetha Parameswaran* and brother *Dr Subramanian Parameswaran* for the constant support and guidance. To my wife *Priyavalli*, I thank you for all the sacrifices you have made - moving away from your family, migrating to a new country, giving up your job to accompany me during training and for all the encouragement and positive vibes during difficult times- this PhD would not have been possible without you in my life.

ABBREVIATIONS

AAD	anti-arrhythmic drugs
AF	atrial fibrillation
ANOVA	analysis of variance
BDI	Beck depression inventory
BMI	body mass index
BSA	body surface area
CA	catheter ablation
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CES-D	centre for epidemiological studies-depression
CFAE	complex fractionated atrial electrograms
CL	cycle length
CPAP	continuous positive airway pressure
cSNRT	corrected sinus node recovery time
CV	conduction velocity
DCCV	direct current cardioversion
DF	dominant frequency
EAT	epicardial adipose tissue
ECG	electrocardiograph
EED	endocardial-epicardial dissociation

EGM	electrogram
ERP	effective refractory period
FEED	functional endocardial-epicardial dissociation
FIRM	focal impulse and rotor modulation
HADS	hospital anxiety and depression scale
HFrEF	heart failure with reduced ejection fraction
Hz	Hertz
IQR	inter-quartile range
LA	left atrial
LAA	left atrial appendage
LPeAF	long-standing persistent atrial fibrillation
LVEF	left ventricular ejection fraction
MCS	mental component summary
ms	milliseconds
MWF	multiple wave front
OSA	obstructive sleep apnea
PAF	paroxysmal atrial fibrillation
PCS	physical component summary
PeAF	persistent atrial fibrillation
PES	premature extra-stimulation
PSS	perceived stress scale
PV	pulmonary veins

PVI	pulmonary vein isolation
QoL	quality of life
RA	right atrium
RCT	randomised controlled trials
RFA	radiofrequency ablation
RR	relative risk
S	seconds
SACP	sino-atrial conduction pathways
SAN	sinus node
SD	standard deviation
SHD	structural heart disease
SR	sinus rhythm
SVC	superior vena cava
SWF	single wave front
VHD	valvular heart disease
WF	wave front

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CHAPTER – 1

LITERATURE REVIEW

INTRODUCTION

Atrial fibrillation (AF) is an exceedingly common arrhythmia encountered in clinical practice affecting more than 33 million patients globally[1]. In addition to increased risk of stroke[2], heart failure[3] and mortality[4], patients with AF have substantially impaired quality of life (QOL)[5,6]. AF-related hospitalizations also impose a significant economic burden to the health care system. A recent study showed that between 2001-2015, AF hospitalizations increased by over 200% in Australia and was considerably more than other cardiovascular conditions like heart failure and myocardial infarction[7].

There are multiple risk factors for development of AF and although age is the most powerful non-modifiable risk factor[8,9], several cardiometabolic factors like hypertension[10], obesity[11,12], obstructive sleep apnea (OSA)[13] and alcohol consumption[14,15] are modifiable. These modifiable risk factors are increasingly prevalent and are not only important contributors to the growing burden of AF world-wide but also impact AF progression and treatment outcomes.

The last two decades have seen several important developments including newer insights into the pathogenesis, improved detection, novel therapies and most importantly the interaction between modifiable risk factors and the development of AF and outcomes of AF management. A large part of this thesis will investigate some of the novel mechanisms that have been hypothesized to sustain AF with focus on the roles of atrial endocardial-epicardial dissociation and localized sources and non-pulmonary vein triggers.

NATURAL HISTORY OF AF

AF is a progressive disease. In patients initially presenting with paroxysmal AF (PAF, AF that terminates spontaneously or with intervention within 7 days of onset), longitudinal studies have shown that the risk of clinical progression to persistent AF (PeAF, AF that is sustained beyond 7 days) to be 15% at 1 year[16] and 24.7% by 5 years[17]. Predictors of progression included age, hypertension, prior transient ischemic attack (TIA) or stroke, and chronic obstructive pulmonary disease. In another study of 564 patients with PAF waiting for AF ablation, 11% progressed to PeAF during a 10-month follow-up period. In this study, heart failure (HF) and a left atrial (LA) diameter >45 mm were predictive of progression. Hence it is possible that the clinical progression of AF could be driven by the development of associated comorbidities as opposed to the arrhythmia itself. Many of these factors are implicated in changes in the electrical, structural and functional properties of the atria that collectively are referred to as atrial myocardial remodeling which provide the substrate for sustaining AF.

CLINICAL IMPACT OF AF

AF is responsible for substantial morbidity and mortality in the general population and this is often related to thrombo-embolism or suboptimal rhythm control.

Stroke

Epidemiologic and clinical studies have generally indicated that AF constitutes a major independent risk factor for stroke, with a 3–6 fold increased risk after adjusting for other risk factors[18-20] and is similar in both paroxysmal and non-paroxysmal forms of AF[21]. AF-related strokes are also more severe than those not related to AF[22]. However, this risk is not uniform and depends on the presence of additional risk factors[23]. There is good evidence for increased risk in patients with previous stroke or systemic embolism, age at least 65 years, recent decompensated heart failure[24] moderate-to-severe left ventricular dysfunction on cardiac imaging, diabetes mellitus, hypertension, or vascular disease (ie peripheral artery disease or previous myocardial infarction)[25]. Female sex is probably a stroke risk modifier, with accentuation of risk in those older than 65 years or with at least one additional stroke risk factor[26,27].

Mortality

AF has been shown to be associated with premature death[28-30]. In a 21-year community-based study of patients with newly diagnosed AF[28], mortality risk was shown to be high within the first 4 months of diagnosis followed by an attenuated but nonetheless increased mortality risk thereafter. Tachycardia at AF diagnosis, lower BMI, history of chronic renal impairment and malignant disease were all strongly associated with early

death and cardiovascular comorbidities were important predictors for late death. Data also support that left ventricular hypertrophy, history of MI and diabetes increases the risk of sudden cardiac death in patients with AF[4].

Heart Failure

Among patients with recurrent AF, there is a 2-fold increased risk of heart failure[31]. Bothe entities frequently co-exist and share a similar pathophysiological process. In the Framingham Heart Study, over 38 years of follow-up, heart failure was the strongest predictor of incident AF, conferring a six- to eight-fold increase in the incidence of AF, with an attributable risk of 10–12%[9]. Age, the presence of NHYA class greater than II and a non- ischaemic aetiology of heart failure were strong predictors for co-existence of AF[32]. Importantly, the co-existence of both conditions confers increased mortality and morbidity[33].

Cognitive dysfunction

AF is also linked to cognitive decline and dementia in patients with and without a manifest stroke[34-36] further contributing to increased morbidity and mortality[37,38]. Several potential mechanisms have been illustrated by neuroimaging for this and can include silent cerebral infarcts, cerebral microbleeds and a potential pro-inflammatory state that is associated with AF[39]. Catheter ablation (CA), increasingly used to maintain sinus rhythm in patients with AF, has also been shown to be associated with the formation of new silent cerebral lesions[40-42]. Although subtle cognitive decline has been observed in patients undergoing catheter ablation up to 3 months post-op[43], long term follow up has shown

that the rates of stroke and dementia in patients undergoing ablation were lower than those not undergoing ablation and similar to those in individuals without AF[44].

Psychological Distress

Patients with AF have a high prevalence of depression and anxiety[45,46]. Indeed, a recent report showed that nearly 20% of AF patients reported suicidal ideation[46]. It is also understood that psychological factors also influence AF symptomatology. Depression, anxiety, and somatization are associated with worse general health status and AF attributed symptom severity and more frequent visits to seek medical attention for AF[47].

Quality of Life

AF causes a wide variety of symptoms, including fatigue and reduced exercise tolerance which collectively impairs QOL[5]. Indeed, patients with AF report poorer quality of life (QoL) than those with other cardiac conditions (such as coronary artery disease and congestive heart failure) and healthy individuals[5], particularly younger patients (aged <65 years) with PAF[48]. It is also notable that asymptomatic status is associated with similar (or worse) prognosis compared with symptomatic status[49].

PATHOPHYSIOLOGY OF AF

The mechanisms underlying AF vary with the type of AF and involves a complex interplay between triggers that initiate the arrhythmia and the underlying substrate that sustains

it. Based on the duration and spontaneous termination, AF is broadly classified into the following three types:

- Paroxysmal AF: AF that terminates spontaneously or with intervention within 7 days of onset
- Persistent AF: Continuous AF that sustains beyond 7 days but less than 12 months' duration
- Long-standing persistent AF: Continuous AF of greater than 12 months' duration

In general, patients with PAF are likely to have a predominance of factors that trigger AF, whereas patients with non-paroxysmal forms are more likely to have a predominance of perpetuating factors. Although such gross generalization has clinical usefulness, often there is considerable overlap of these mechanisms.

PULMONARY VEIN TRIGGERS

The role of focal atrial triggers in the genesis of AF was postulated more than a century ago[50] but the first theories suggested that these triggers are distributed throughout the atria. Multiple theories emerged in the ensuing years but it was not until the pioneering work by Haissaguerre et al[51] that ectopic activities originating from PV's were shown to trigger AF. In their series, 94% of patients had spontaneous initiation of AF from ectopics originating within the PVs'. Furthermore, discrete ablation targeting the site of origin of the ectopic activities abolished the arrhythmia and prevented its recurrence in 62% of the cases after a follow-up of 8 months. In another study that followed, Chen et al

observed 88.8% of ectopics initiating AF originated from the PV's[52]. Contrary to historical postulates these studies became vital from mechanistic and therapeutic stand-points.

PV Anatomy

There are several anatomical characteristics of the LA-PV myocardial sleeve that have been implicated in the mechanism of AF.

Extension of LA myocardium into the PV's has been long recognised and the length of these sleeves can vary between 13 and 25mm[53]. The superior veins, which have longer muscular sleeves, have been shown to be more arrhythmogenic than the inferior veins[51]. Data from intravascular ultrasound studies have reported that patients with AF have thicker PV myocardial tissue, with areas of regional thickening correlating with high-frequency potentials and PV ectopy[54]. Lin et al. reported that AF patients have more dilated superior PV's[55]. Corroborating evidence came from Takase et al who performed MRI studies in AF patients[56]. Yamane et al. demonstrated that in AF patients, arrhythmogenic PVs have a larger diameter than non- arrhythmogenic PVs[57].

Electrophysiological Characteristics of PV Myocardial Sleeve

The electrophysiological characteristics of PV myocytes have been reported to be distinct to those of atrial tissue. Compared to LA, the action potential of PVs is lower in amplitude and upstroke velocity and have a shorter duration[58]. Hocini et al demonstrated that the action potential duration at the distal PV is shorter than that at the ostium[59]. Data also suggested that the electrophysiological characteristics of PV myocytes change in

response to chronic rapid pacing. Chen et al. reported that in isolated canine myocytes, rapid atrial pacing results in a shortening of the action potential with a higher incidence of both early and late afterdepolarisations[60]. They also observed a higher incidence of spontaneous arrhythmias in PVs from chronically paced dogs[61].

PV Arrhythmogenesis

The basic mechanisms underlying PV arrhythmogenesis are yet to be fully characterized. Re-entry, automaticity or potentially a combination of mechanisms have been reported to underlie PV arrhythmogenicity.

Re-entry

In canine LA preparations, Arora et al. demonstrated marked conduction slowing in the proximal PV relative to the distal vein. Atrial extra-stimuli resulted in functional unidirectional conduction block and re-entry within the proximal PV[62]. Chou et al. demonstrated that re-entry circuits induced by pacing clustered at the junction between the LA and the PV[63]. These regions of clustering of re-entry circuits corresponded with areas of abrupt change in myofiber orientation.

Studies in human subjects have also provided evidence to support PV re-entry. Atienza et al supported the re-entrant mechanism by demonstrating acceleration of drivers and increased dominant frequency (DF) in both persistent and paroxysmal AF patients and in the subset of PAF patients the highest DF was recorded at the LA-PV junction[64]. Data from high-density mapping of the LA-PV junction with basket catheters showed that the distal

PV had a shorter effective refractory period (ERP) than the LA-PV junction. This study also showed that the conduction delay from the LA-PV junction to the distal PV was longer than the delay from the distal PV to the LA-PV junction from anisotropic conduction[65]. Jais et al reported that patients with AF display significant electrophysiological alterations when compared to those in sinus rhythm[66]. Specifically, they demonstrated that in patients with AF, the ERPs were significantly shorter. They also demonstrated decremental conduction in the PVs. These changes are predicted to promote PV re-entry, which may drive AF[67]. More recently, Lee et al performed high-density epicardial mapping using a customized plaque (128 electrodes/6.75cm^2) in 18 patients undergoing cardiac surgery and no history of AF to characterize conduction at the right superior PV-LA junction. They were able to demonstrate functional conduction delay and circuitous activation patterns which creates a substrate for re-entry at the PV-LA junction[68].

Automaticity/Triggered Activity

Chen et al investigated the action potential characteristics and ionic currents in canine PV myocytes. They demonstrated that in response to rapid atrial pacing, the myocytes with pacemaker activity displayed faster beating rates in addition to a high incidence of early and delayed after depolarizations. Measurement of ionic currents demonstrated that these PVs have smaller slow inward and transient outward and larger transient inward and pacemaker currents[60]. An attenuated inward rectifier current is predicted to enhance ectopic pacemaker activity.

The sodium current has also been implicated as an important mediator of enhanced automaticity in PV myocytes. Malecot et al demonstrated that PVs have a higher basal permeability to sodium compared with left atrial myocytes. Pharmacological blockade of the I_{Na} current resulted in a decrease in the incidence of catecholaminergic automatic activity by reducing the slope of slow depolarization[69].

Increased catecholaminergic activity is an important mediator of enhanced automaticity in PV myocytes. Dolsne et al previously demonstrated that PV myocytes demonstrate differential responses in terms of response to catecholaminergic stimulation. Specifically, they reported that PV's demonstrate enhanced automaticity in response to catecholaminergic stimulation while LA cells do not. The effect was suppressed by administration of beta blockers[70].

Triggered activity has also been demonstrated as a possible mechanism in PV arrhythmogenesis. Honjo et al demonstrated that in rabbit PV preparation, administration of ryanodine promotes depolarization of the resting membrane potential and generation of spontaneous pacing activity[71]. Patterson et al demonstrated that autonomic nerve stimulation of PV's results in shortening of the PV action potential with associated early afterdepolarizations. They also demonstrated that enhanced calcium transients are important for generation of triggered activity[72]. Chou et al demonstrated that in canine PV preparations, rapid pacing induces focal discharge, which is mediated by spontaneous voltage-independent calcium release[73]. The same group also reported that in a canine model or heart failure, administration of acetylcholine increases the

incidence of triggered activity in the PVs. Early and delayed after depolarizations in the PV's have also been shown to increase with thyroid hormone, temperature and beta-adrenergic agonists[74-77].

MECHANISMS RESPONSILE FOR SUSTAINING AF

For many years, the "multiple wave reentry" hypothesis was the most widely held theory on the maintenance of AF and was a key development in our understanding of the mechanism of AF. On the basis of a computer model of AF, Moe et al hypothesized that AF is sustained by multiple randomly wandering wavelets in both atria that collide with each other and extinguish themselves or create new, daughter wavelets that continually re-excite the atria and perpetuate the arrhythmia[78] and experimental data suggested that four to six simultaneous re-entrant wavelets were needed to sustain arrhythmia. Further evidence supporting multiple wavelets in AF was demonstrated in a separate model, which evaluated the effect of various antiarrhythmic drugs on canine myocardium. This model demonstrated that termination of AF was associated with a reduction in the number of simultaneous atrial re-entrant wavelets[79,80]. Cox et al subsequently mapped multiple re-entrant atrial wavefronts during human AF, and this formed the basis for the surgical maze procedure in which multiple, small, electrically-isolated atrial compartments were created to prevent sustained re-entry[81].

With technological advancements and improvement in cardiac mapping abilities including computational methods novel experimentally based ideas about the mechanisms underlying AF maintenance have emerged in recent years.

Localised Source Hypothesis

Allessie et al first described the 'leading circle model', wherein circus movement of a unidirectional wavefront results in constant centripetal activation of the center of the circuit which renders it continuously refractory. This refractory area then forms a functional barrier which can sustain reentry in a way similar to a fixed anatomic barrier such as a scar. In the leading circle model, unidirectional block in tissue allows an impulse to initiate circus movement in one direction, with the impulse simultaneously spreading radially outwards to activate the adjacent myocardium and radially inwards towards the centroid of the circuit. Reentry compatible with the leading circle model was elegantly demonstrated in experiments on rabbit myocardium[82]. A key feature of the leading circle concept is that the functional reentry is governed by activity in a limited region for which the wavelength occupies virtually the entire pathway of reentry.

Computer simulations and experiments suggest that functional reentry is better explained by rotors or spiral waves[83-85]. In rotors or spiral waves, instead of being circular, the wavefront has a curved or spiral form, and the wavefront and wave tail meet at a focal point called a phase singularity (PS). Unlike the leading circle model, however, the wavefront velocity in a rotor is not constant, depending instead on wavefront curvature due to current source–sink mismatch associated with the propagation of nonplanar wavefronts. The wavefront in close proximity to the PS is the region of highest curvature, and therefore is also the area of slowest wavefront conduction velocity. Indeed, at the PS, the wavefront curvature is so high and conduction velocity is so slow, that the propagating wavefront is unable to invade a core of tissue in the center of the rotor. This

tissue core is therefore effectively unexcitable, thus forming an area of functional block similar to the center of a leading circle reentrant circuit. Unlike the leading circle model, tissue at the core of a rotor is not truly refractory. Because conduction velocity at the PS is so slow, tissue in the core is simply extremely difficult to penetrate and excite[84,86]. The concept of rotor can also be applicable to anatomical reentry in the atria; a pectinate muscle or the orifice of a PV can stabilize a reentrant rotor[87,88].

Evidence for Drivers in AF

Much of the knowledge on rotors and their role in AF is based on experimental studies on isolated cardiac tissue that allowed for an increased spatial resolution and a more reliable detection of local action potentials than electrical recordings.

On sheep and canine epicardial tissue Davidenko et al used potentiometric dye in combination with charge-coupled device imaging technology to demonstrate spiral waves[89]. They observed that the spirals were anchored to small arteries or bands of connective tissue and gave rise to stationary rotations. In some cases, the core drifted away from its site of origin and dissipated at a tissue border.

In an isolated sheep heart model, Mandapati et al[90] found a highly significant correlation between the rotation period of rotors and the dominant frequency (DF) at the same sites. The same study found that these re-entrant sources were more frequently located in the posterior free wall of the LA and were associated with a left-to-right reduction in activation frequencies. Further studies found that concomitant with LA to RA gradients

of DF[91], propagation of waves was predominantly from the LA to the RA[92] from the fast to the slow atrium. The driving role of LA rotors in this AF model was further confirmed by Mansour et al who showed that ablation of interatrial conduction paths decreased the DF of the RA whereas it did not modify the DF of the LA, which was typically higher[92]. Lazar et al extended the concept of DF mapping to humans and demonstrated LA to RA DF gradients in patients with PAF, with the highest DFs at the LA-PV junction. This gradient, however, was not present among patients with PeAF, again suggesting a different mechanism for sustaining AF of longer duration[93]. The correlation between sites of high DF and rotor-like activity was not assessed in this study. In a later study by the same group, atrial DF gradients were assessed before and after pulmonary vein isolation (PVI). Although all patients did not have a pre-procedure DF gradient, LA to RA DF gradients in patients with PAF were abolished with successful ablation. The presence of a pre-ablation LA to RA DF gradient was correlated with improved freedom from recurrence of AF after conventional PVI, and patients with recurrence of AF after PVI also had recurrence of LA to RA DF gradients at the time of repeat ablation[94].

Studies that have explored a strategy of real-time DF mapping and ablation at the site of maximal DF have resulted in improved freedom from AF recurrence[95]. It is important to realise, however, that although animal studies have correlated sites of maximal DF with rotor-like activity, it remains unclear if all sites of maximal DF represent areas of rotor-like re-entry or other types of localised re-entry, especially in humans. Further studies with high-resolution mapping systems will be needed to further define the local

activation in areas of high DF, and to determine if these sites are truly caused by functional re-entry due to rotors.

Mapping 'Drivers' in AF

Spectral analysis/Dominant Frequency Mapping:

Spectral analysis is used to map the distribution of AF frequencies and localize the areas with the highest activation frequencies. Earlier efforts in locating rotors in human AF relied on the mechanistic relationship between high DF sites and rotors driving AF[91,96]. Sanders et al demonstrated a hierarchical pattern of activation rates that was consistent with previous observations in isolated sheep hearts, with HDF sites typically located in the PV area in PAF, although the HDF sites were more widespread in PeAF patients[97]. Atienza et al showed that abolishing DF gradients by ablation results in freedom of AF[95]. However, frequency domain analysis is limited by methodological issues, particularly due to fractionation from wide CL variance as seen in AF[98]. Indeed, clinical outcomes of DF based ablation have not been consistent and a recent prospective randomized clinical trial of 232 patients with paroxysmal and persistent AF reported no improvement in ablation outcomes with a DF-based approach compared with PVI alone[99].

Complex Fractionated Atrial Electrograms (CFAE's):

CFAEs are electrograms with highly fractionated potentials or with a very short cycle length (<120 ms) and are typically low-voltage multiple potential signals between 0.06 and 0.25 mV[100,101]. Several mechanisms have been proposed for CFAE. Cosio et al initially

observed split potentials after premature stimuli that were thought to arise from slowed conduction in patients with or without AF[102]. Konings et al showed that CFAE observed during intraoperative mapping of human AF are found mostly in areas of slow conduction and at pivot points where the wavelets turn around at the end of the arcs of functional blocks[103]. Evidence from optical mapping has suggested that rapid deflections producing continuous fractionation may represent areas within a few millimetres of focal drivers where wave fronts collide and fail to propagate in a 1:1 fashion[104,105]. One of the other potential mechanisms underlying the formation of CFAE is the hyperactive state of the intrinsic cardiac autonomic nervous system. Katritsis et al showed that the distribution of the CFAE appeared to coincide with the presumed locations of the major atrial ganglionic plexi in nearly 70% of patients[106].

Earlier reports of targeting CFAE for catheter ablation in AF by Nademanee et al showed promising results[100] but CFAE elimination often needed extensive ablation and long term results have been less favorable[107]. In the more recent CHASE-AF[108] and STAR AF II[109] trials there was no additional benefit in targeting CFAE in addition to PVI than PVI alone among patients with PeAF.

Phase Mapping:

Phase mapping is a complementary approach to activation mapping that enables visualization of the spatiotemporally distributed patterns of propagation during cardiac fibrillation by determining the local phase of the activation/recovery cycle at each time

point[110]. It makes it possible to detect the phase singularities (i.e., the rotor pivots) that organize re-entry and fibrillation.

Phase analysis of activation during fibrillation was first described by Gray et al using optical mapping of voltage sensitive fluorescent dyes[111]. These investigators were able to demonstrate the presence of organized rotors during ventricular fibrillation in rabbit hearts. Subsequent work by Chen et al used a similar method of phase analysis and optical mapping in sheep atria[112]. These authors observed the presence of high frequency organized wavefronts. Further refinements of this technique to create a more mathematically robust approach was developed by Bray and Wikswo who utilized the Hilbert transform to calculate phase values[113]. More recently, phase analysis based on the Hilbert transform has been used in human studies to calculate instantaneous phase during AF[114].

Focal Impulse and Rotor Modulation (FIRM):

Using a proprietary software (FIRM) Narayan et al showed that among 92 consecutive patients localised sources could be identified in 97% cases with sustained AF, each exhibiting 2.1 ±1.0 sources. In this CONFIRM trial, AF termination or consistent slowing was achieved in 86% of FIRM guided cases versus 20% of FIRM-blinded cases. Single procedure freedom from AF at 1 year was more with FIRM-guided than FIRM-blinded ablation (82.4% vs. 44.9%; $p < 0.001$). Subsequent observational studies showed mixed results and in Chapter 3 we present a meta-analysis showing the wide variability in reported outcomes and discuss the limitations of this proprietary algorithm[115]. The

ineffectiveness of FIRM guided ablation was more recently confirmed in the randomised REAFFIRM trial as well[116]. This technology has fallen out of favour due to non-reproducible results and potential inaccuracies.

Multielectrode Plaque Epicardial Electrical Mapping:

In patients undergoing cardiac surgery, epicardial mapping with customised multi-electrode plaques have shown evidence for localised sources in PeAF. Several groups observed focal patterns on epicardial mapping in acutely induced[117] and persistent AF distributed across both atria[118-122]. De Groot et al characterised these focal patterns as epicardial breakthroughs occurring over the entire atrial wall emerging from multiple sites rather than a cellular focal mechanism[123]. Lee et al performed regional high density epicardial mapping (posterior LA wall, LA and RA appendage and RSPV-LA junction) in PeAF patients using high-density epicardial plaques (128 electrodes/6.75 cm^2) and demonstrated highly dynamic and heterogeneous patterns of atrial activation consisting predominantly of multiple unstable wavefronts (56.2 + 32%) and disorganized activity (24.2 + 30.3%) but no regions with sustained focal activity highlighting the dynamic and complex activation patterns in these patients[124].

CARTOFINDER:

CARTOFINDER was developed as a novel technique to identify localised sources based on local activation time of atrial signals during AF. Unlike computational spatiotemporal phase mapping algorithms that required offline analysis, CARTOFINDER presented the unique advantage of automated annotation to identify localised sources based on

wavelet analysis of high quality unipolar electrograms obtained from a bipolar electrogram window. Following the initial validation study by Daoud et al[125] several studies on CARTOFINDER panoramic atrial mapping[126-129] and regional mapping of LA[130-132] have shown evidence for reliable identification of localised sources which have been targeted during catheter ablation with good clinical outcomes in PeAF. In Chapter 7 we present our CARTOFINDER data on regional high-density mapping of LA and LAA in PeAF.

Non-Contact Charge Density Imaging and Mapping:

One of the limitations of conventional voltage guided mapping systems is the need for serial collection of contact points over time which are unable to display the continuous chaotic activation that is characteristic of PeAF. To overcome this limitation, a novel, full-chamber, noncontact imaging and mapping system that uses ultrasound to reconstruct atrial chamber anatomy and an inverse algorithm to derive charge density was developed (AcQMap; Acutus Medical, Inc, Carlsbad, CA). Unlike a previous version of non-contact mapping technology (EnSite Array, Abbott Laboratories, St. Paul, MN)[133,134] which was limited with inaccuracies due to inclusion of far-field QRS complexes on unipolar atrial EGM's[135], this proprietary technology used charge density and was shown to have the ability to globally discern both focal and rotational patterns, as well as other more complex patterns characterized by localized changes in conduction velocity, direction, and wave front pivoting[136,137]. Reconstructed atrial EGM measurements in SR or AF, from charge density maps were also comparable to contact mapping when the anatomical site of interest is ≤40 mm from the mapping catheter[138]. In the prospective non-randomised UNCOVER AF trial this mapping system safely guided ablation of non-PV targets in PeAF

patients with 73% single procedure and 93% second procedure freedom from AF at 12 months.

Stochastic Trajectory Analysis of Ranked Signals (STAR) mapping:

One of the newest additions to the armamentarium of driver mapping in AF is STAR mapping. The principle of STAR mapping is to use data on multiple individual wavefront trajectories to identify atrial regions that most often precede activation of neighbouring areas with the aim of identifying intermittent drivers[139]. The STAR mapping method has been validated in vivo using optical mapping of calcium transit in spontaneous fibrillating HL1 cells and in human studies mapping atrial tachycardias[140]. Preliminary data on ablation guided by STAR mapping have been shown to produce favourable clinical outcomes[139] but this needs further confirmation in large scale RCT's.

Non-Invasive Mapping of Drivers:

Electrocardiographic mapping (ECGi) is a non-invasive technology that allows to map the activation of AF from chest recordings in a beat-to-beat manner[141,142] and has been shown to map localised sources[142-145]. The technique involves using a 252-electrode vest on the patient's torso for recording cardiac electrograms and high-resolution 3-D images of the biatrial geometry from a non-contrast CT scan. Unipolar AF electrograms between cycles of long R-R intervals (≥1000 ms) are reconstructed during each cycle using mathematical algorithms and projected on the biatrial shell. Activation maps are computed using the traditional unipolar electrogram intrinsic deflection-based (-

dV/dTmax) method. Maps of AF are then generated using algorithms combining phase mapping and filtering to eliminate artifacts in signal morphology.

Data from clinical studies have shown encouraging results. Cuculich et al first used ECGi to map AF and identified multiple wavelets (defined as contiguous area of epicardial activation lasting ≥5 ms) as the most common pattern (92% of the patients). Rotor activity was present in 15% of the cases, only in patients with non-paroxysmal AF[142]. Haissaguerre et al observed predominantly unstable re-entrant activations (80.5%) and co-localised focal activations (19.5%) and targeting these driveres with catheter ablation resulted in acute AF termination in 75% of whom 85% remained AF free at 12 months[146]. Localised sources are also reportedly predominant in the PV antral and adjacent regions but with longer AF duration, multiple drivers were identified at extra-PV sites[147,148].

It is important to consider the limitations of non-invasive mapping before widespread clinical adoption. Firstly, there is a potential for signal attenuation and while crossing the thorax and the recorded signals by each electrode on the torso may represent the average of multiple signals. Secondly ECGi does not explore intra-mural and endocardial activities. Subsequently, it is unable to discern the mechanisms of focal activities that may be micro-reentry, epicardial breakthrough of endocardial activity, focal activity[142]. Finally, it is unable to accurately analyze the septal activity where wavefronts from the left and right atria can be projected.

Endocardial-Epicardial Dissociation

Endo-epicardial dissociation in the atrium was first described in an ex-vivo model by Schuessler et al[149]. They performed simultaneous endo-epicardial mapping in isolated canine RA and found that the dispersion of time differences was smallest during normal sinus rhythm and continuous pacing and largest after premature stimulation which in effect stresses atrial connectivity. Differences in the activation sequence correlated with the underlying anatomic architecture. The largest differences in activation times between the epicardium and endocardium were associated with those regions of the atrium where pectinate muscles ran below the epicardial surface. The pectinate muscles in those areas were often discontinuous with the epicardial surface and facilitated the discordant epicardial-endocardial activation. However, the discordant activation was also found in regions where the atrial wall thickness was < 0.5 mm and correlated with transmural differences in fiber orientation. In this model, a tachyarrhythmia induced in the presence of acetylcholine, which demonstrated a focal activation pattern, was shown to have a reentrant loop that used free-running muscle bundles connecting the epicardial and endocardial surfaces, resulting in a three-dimensional pathway. Data from animal studies have also demonstrated that dyssynchrony is more pronounced in the thicker parts compared to the thinner regions of the atria[150,151].

Everett et al compared endocardial and epicardial activation in three different canine models of AF (heart failure, mitral regurgitation and rapid atrial pacing) using non-contact endocardial mapping and direct contact mapping epicardially. The models with strongly increased fibrosis (mitral regurgitation and heart failure) had smaller activation

differences between the endo- and the epicardial surface and more repetitive activation patterns compared to the rapid atrial pacing model. AF was persistent in the rapid atrial pacing group only and multiple wavelets and large endo-epicardial activation differences were predominantly seen in this group[152]. Recently, Maesen et al studied propagation patterns in goats with either acute or persistent (5 months) AF. They mapped the epicardial surface of the atrium and correlated propagation patterns with fibre orientation on MRI of the excised atrial segment. They observed that after months of AF, differences in endo-epicardial bundle direction increased. In non-remodelled atria, epicardially recorded fibrillation waves propagated most rapidly along the direction of endocardial bundles, with little influence of epicardial fiber orientation. In structurally remodelled atria, epicardially recorded fibrillation waves conducted fastest along epicardial fibres. The authors hypothesised this was due to endo-epicardial dissociation of electrical activity and 3D conduction during AF[153].

In humans endocardial-epicardial dissociation was postulated as a novel hypothesis by Allessie and co-workers based on observations from epicardial maps of long-lasting persistent AF in patients undergoing epicardial mapping at the time of cardiac surgery[123,154]. In these high-density mapping studies, the investigators did not observe any evidence of rotors or foci. However, they observed longitudinal dissociation of muscle bundles within the atrium presumably as a result of extensive atrial remodelling and development of fibrosis. This facilitated the presence of many activation wavefronts defined by the presence of these individualized muscle bundles. The authors evocatively described this as a result of “cracks” opening up in the remodelled atrial wall. Importantly

they also observed the presence of focal atrial activations which they hypothesized were due to the presence of endocardial epicardial breakthrough. Such an electrophysiological phenomenon would only be possible in the presence of dissociation between epicardial and endocardial atrial muscle bundles. Allessie et al hypothesized that this results in a ping-ponging effect of atrial activation from endo to epi and vice versa and that this together with the longitudinal dissociation described above sustains the atrial arrhythmia. Although it was doubtful if such a phenomena could exist in human atria wherein many regions are only several millimetres thick, De Groot et al elegantly showed direct evidence of endo-epi dissociation that creates an opportunity for transmural conduction of fibrillation waves, creating new breakthrough waves in the opposite layer and sustain AF via a 3-dimensional process[155].

To further characterise endo-epicardial dissociation in humans with PeAF and describe the simultaneous wave-front patterns and to analyse potential 3D driver characteristics we undertook simultaneous endocardial-epicardial mapping of prolonged (2 minutes) AF recordings in patients with structural heart disease undergoing cardiac surgery. The results of this novel study are presented in Chapter 5.

REMODELLING IN AF

Atrial remodelling plays an important role in the pathogenesis of AF and includes structural, electrical and autonomic remodelling that promote atrial arrhythmias.

Structural Remodelling

The hallmark of structural remodelling is atrial dilatation and is frequently accompanied by increased interstitial fibrosis with cardiac structural alterations[156]. In patients with AF, atrial fibrosis is a common finding but whether this fibrosis is a result of or a cause to AF remains unclear. Besides, several risk factors for AF like valvular heart disease, age, systemic hypertension, diabetes mellitus, heart failure and obesity can also promote atrial fibrosis[157-165]. Biomarkers (atrial natriuretic peptide (ANP), BNP, vascular cell adhesion protein 1 (VCAM-1) and L-selectin) and scoring systems incorporating some of these risk factors have been also been studied in the recent years to predict structural remodelling[166,167].

In vitro studies on cell cultures showed an increase in TGFß-1, a driver of fibrosis, in atrial myocytes stimulated by rapid pacing[168]. Work from animal models has also suggested that there were regional variations in tissue fibrosis with the atria more susceptible than the ventricles[169]. Fibrosis is less when ventricular rate is controlled and regular ventricular rate after His bundle ablation than in the setting of intact AV conduction[170,171].

The association between atrial fibrosis and AF have also been demonstrated in human studies. In LA tissue samples from patients with AF undergoing cardiac surgery, concentrations of collagen I and collagen III were significantly greater than controls in sinus rhythm both of which are form the cellular components of fibrotic process[172]. In a study analysing RA biopsies, patients with AF were noted to have histological abnormalities consistent with fibrosis when compared to Wolff-Parkinson-White

syndrome controls[173]. Similarly, in a study of explanted hearts from patients with dilated cardiomyopathy and end-stage heart failure undergoing cardiac transplantation, immunofluorescence staining of the LA showed increased volume of type 1 collagen in AF cohort than controls[174].

Both endocardial-epicardial dissociation and altered conduction can result from atrial fibrosis and have been implicated in AF arrhythmogenesis. Fibrosis can increase separation of the myocytes within sub-endocardial atrial bundles and between the endocardial and epicardial layers leading to endo-epicardial dissociation[175,176]. It forms barriers to the propagation of the activation wavefronts and isolates atrial myocytes. These obstacles affect the wavefront shape and can induce spiral waves through vortex shedding or by causing localized conduction block in narrow isthmuses[177,178]. The interaction between the wavefront and the boundaries of the fibrotic area are determinant for the wavefront curvature by influencing the propagation velocities and the ERP's[179]. This stabilizes rotor activity[180,181] and anchors them to the scar boundaries[181,182]. Fibrotic pattern also affects the velocity of the activation wavefront. Kawara et al analysed the wavefront activation in explanted human hearts and identified different conduction curves according to the fibrotic patterns. The zones of dense, patchy fibrosis with long fibrotic strands were associated with prominent activation delay while dense, diffuse fibrosis with short fibrotic strands only marginally affected conduction curves. The conduction curve was also dependent on fibre orientation[183].

Structural atrial remodelling also includes atrial fatty infiltration, inflammatory infiltration, necrosis and amyloid deposition. Adipose tissue has a paracrine effect through the release of adipokines with pro-fibrotic properties. It also forms barriers to wavefront conduction and favour re-entrant circuit[184]. In a more recent study, Nalliah et al[185] elegantly showed that epicardial adipose tissue (EAT) correlated with slowed conduction, greater electrogram fractionation, increased fibrosis, and lateralization of cardiomyocyte connexin-40. In addition, atrial conduction heterogeneity was increased with more extensive myocardial epicardial adipose tissue infiltration. In the same study, co-culture experiments showed that cardiac adipose tissue-secreted factors slowed conduction velocity and contained proteins with capacity to disrupt inter-myocyte electromechanical integrity.

Finally, in addition to remodelling of the atria, the sinus node can undergo remodelling in AF, resulting in SND and bradyarrhythmias caused by reduced sinus node automaticity or prolonged sinoatrial conduction. This phenomenon likely contributes to the episodes of bradycardia seen in the tachycardia-bradycardia syndrome and may reduce sinus rhythm stability and increase the stability of AF[186]. It is important to note that elements of the sinus bradycardia appear to be functionally reversible if appropriate AF management[187-189].

Electrical Remodelling

Electrical remodelling results from the high rate of electrical activation and primarily includes shortening of the action potential duration and atrial ERP, reduction in the

amplitude of the action potential plateau and abnormal restitution which prevents the atrial ERP to lengthen appropriately at slow rates.

Both animal models and human studies have shown that the effect of AF on atrial ERP. Wijffels et al showed that artificial maintenance of AF leads to a marked shortening of atrial ERP, a reversion of its physiological rate adaptation, and an increase in rate, inducibility and stability of AF. All these changes were completely reversible within 1 week of sinus rhythm/control of tachycardia[190-193]. Several ion channel modifications have been implicated in altering atrial ERP. Studies in animal models and in patients with chronic AF have shown decreased L-type Ca^{2+} current ($I_{Ca,L}$; reduced depolarisation power); increased inward rectifier K^+ current (I_{K1}; enhanced repolarisation power); and constitutively-active acetylcholine-independent K^+ current ($I_{K,ACh,c}$ enhanced repolarisation power) that underlie such electrical changes[194-200].

Besides shortening of atrial ERP, lower bipolar voltages, decreased intra-atrial conduction velocity, sinus node dysfunction and increased atrial refractoriness have also been demonstrated in AF patients and shown to collectively sustain the electrical remodelling process and arrhythmia[201].

Autonomic and Neural Remodelling

Several ganglionated plexi (GP) are interspersed in the epicardial fat pads outside the heart and along the great vessels in the thorax[202]. These form an integral part of the intrinsic cardiac autonomic nervous system and predominantly contain parasympathetic neurons and some sympathetic neurons. The nerve densities are much more pronounced

within 5 mm of the PV–LA junction and are higher in the epicardial surface than in the endocardium[203,204].

The role of GP in contributing to AF has been widely recognised in animal and human studies. In an animal model of PAF, injection of parasympathomimetics into the fat pad adjacent to the PV-LA junction resulted in spontaneous or easily induced sustained AF, suggesting that a hyperactive ANS can play an important role in patients with focal AF arising from the PV[205,206]. Stimulation of GP by pacing at the base of the PV can also provide a substrate of AF initiation from PV firing[207,208]. Several studies have also identified a link between GP and CFAE's and AF triggers[106,207,209].

Patients with PeAF have been shown to have an increase in the density of cardiac autonomic innervation. In 24 patients (12 in SR and 12 in AF) undergoing bypass surgery, Gould et al quantified the degree of sympathetic innervation by measuring the amount of staining for tyrosine hydroxylase and tissue norepinephrine and showed heightened atrial sympathetic innervation in patients with PeAF when compared to controls in sinus rhyhm, suggesting autonomic remodelling may be part of atrial substrate for AF[210]. Neural remodelling is also implicated in AF arrhythmogenesis in other cardiac conditions like post myocardial infarction[211] and cardiomyopathy[212].

Despite strong mechanistic links to AF, it remains uncertain whether ablation targeting autonomic nervous system/GP impacts the outcomes of AF ablation as with currently available technology, accurately localising these sites of GP are challenging.

Atrial Imaging to Detect Remodelling

Atrial imaging plays an important role in assessing the degree of structural and functional remodelling. Besides echocardiogram, CT and cardiac magnetic resonance (CMR) have emerged as important prognostic imaging modalities in patients with AF.

Echocardiography

With atrial dilatation being the hallmark of structural remodelling, echocardiography is the initial imaging modality of choice for screening and serially following patients with diseases involving the LA morphology and function[213].

Two-dimensional echocardiographic LA volumes are typically smaller than those reported from computed tomography or cardiac magnetic resonance imaging (CMR)[214,215]. The advent of 3-D ECHO has improved the accuracy of ECHO volume measurements which correlate well with cardiac CT[216,217] and magnetic resonance imaging[218,219]. Recent advances in 2D and 3D echocardiography including in Tissue Doppler imaging, and speckle tracking for strain analysis[220] have also allowed evaluation of atrial function during AF. The LA function index (LAFI) uses volumetric measurement of the LA and is a composite rhythm-independent measure of LA function. It is a ratio that incorporates analogues of cardiac output, atrial reservoir function and LA size and is calculated as LAFI = LAEF × LVOT VTI/LAESVI. (LAEF = LA emptying fraction; LVOT VTI = velocity time integral across the left ventricular outflow tract; LAESVI is the largest LA volume measure in ventricular systole indexed to body surface area)[221].

The association between echocardiographic parameters of atrial remodeling and AF has also been extensively documented. In a case control cohort, structural and functional LA remodeling assessed by echocardiogram were independently and strongly associated with paroxysmal AF[222]. In patients with AF, LA enlargement and dysfunction was also predictive of adverse events including MACCE[223] and stroke risk[224]. Assessment of LA size and function has also been useful to predict the success of restoring sinus rhythm in patients with AF after either direct-current cardioversion[225] or catheter ablation[226]. Electrophysiologic mapping studies have demonstrated that these echocardiographic markers of remodeling are associated both with electrical conduction slowing and with regional atrial fibrosis; both also strongly linked to progression of AF[227].

Cardiac Computed Tomography

Cardiac CT may be used for accurate assessment of atrial volumes. Volumetric data from cardiac computed tomography (CCT) are comparable to data generated by CMR and 3D echocardiographic imaging and is superior to 2D echocardiography[218]. The LA volume prior to catheter ablation and the presence of asymmetry of chamber geometry predicts the likelihood of maintaining sinus rhythm post-procedure[228]. As the LA enlarges, the shape of the LA roof initially becomes flat and then becomes coved, and this progression may correlate with development of non-PV substrate in patients undergoing AF ablation[229].

Besides volumetric and thickness assessments, CT is considered a gold standard for quantifying epicardial adipose tissue[230]. Several studies have demonstrated that the EAT

quantity as assessed by CT correlates with important clinical end points such as disease progression and post ablation recurrence[231,232]. EAT has also been associated with CFAE burden[233], high DF sites[234] and electrical remodelling[185]. Preliminary data on tissue characterisation using contrast enhanced multidetector CT is also encouraging[235] but this is still in its early stages that may develop with the advent of higher generation CT scanners.

Cardiac Magnetic Resonance Imaging

Both late-gadolinium-enhanced (LGE) (detection of replacement fibrosis) and post-contrast T1 mapping (detection of interstitial fibrosis) have been correlated with bipolar voltage measured during invasive mapping[236]. However, its widespread adoption is limited by cost and the need for specialised post-imaging processing to achieve adequate image resolution of the thin-walled atria. Using a systematic scoring system for the extent of delayed enhancement, a recently-published multicentre study has related the extent of LGE CMR detected fibrosis to the outcome of AF ablation[237]. The risk of recurrent AF increased from 15% for stage I fibrosis (<10% of the atrial wall) to 69% for stage IV fibrosis (≥30% of the atrial wall). The authors suggested that CMR quantification of fibrosis may play a role in the appropriate selection of patients most likely to benefit from AF ablation.

Haissaguerre et al[238] showed that the borders of the fibrotic areas determined by CMR hosted the majority of the re-entrant activities and indeed, 80% of the re-entrant activities were located in areas with a fibrotic density >70%. In another recent study, Cochet et al[239] used high resolution LGE-CMR to characterize atrial fibrosis in patients

with AF undergoing ECGi guided catheter ablation. They observed that fibrosis was significantly associated with the number of re-entrant regions, to the LA volume and to the AF duration. Interestingly, re-entrant activities were predominantly clustered at the LGE borders. Moreover, areas with high re-entrant activity had a significantly higher local LGE density.

Finally, fibrosis identified by CMR is an independent factor of AF recurrence after CA. In a post-analysis of the DECAAF study, Akoum et al[240] analyzed LGE CMR 3-months after the ablation in 177 cases. Baseline fibrosis and residual fibrosis were significantly correlated to the need for repeat catheter ablation. Similar observations have also been made in multiple other studies[241-243].

GENETIC PREDISPOSITION TO ATRIAL FIBRILLATION

Genetics now has an established role in the pathogenesis of AF.

Over the last decade, multiple studies have observed familial aggregation of individuals with lone AF[244]. Based on a study on monozygotic twins, the heritability of AF has been estimated as high as 62%, indicating a strong genetic component[245]. In aggregate, these studies have consistently observed an increased risk of AF particularly when a first-degree family member is affected and among individuals with early onset forms of arrhythmia[246]. In more recent work, Weng et al[247] used genetic data to estimate that the heritability of AF based on common genetic variants in individuals of European ancestry is about 22%.

Using genome-wide association studies the chromosome 4q25 locus remains the most significant genome independently associated with AF risk. Carrying a single variant at this 4q25 locus near the gene PITX2 conferred over a 60% increased risk of disease in the general population and an even greater risk in younger individuals[248]. Proposed effects of PITX*2c* deficiency (predominant isoform in the heart) include defective development of the PV myocardial sleeve or failure of suppression of sinus node-related genes in the LA with subsequent changes in electrical and structural properties that predispose to AF[249-252].

Several haplotypes on chromosome 4q25 have been associated with the risk, the strongest has been found for the haplotype tagged by the rs2200733 single nucleotide variant (SNV). Data on the effect of SNV's at the 4q25 locus on PVI outcomes are variable with some suggesting worse outcomes[253-256] and increased risk of recurrence[254,255] while others showing no such link[257]. However, these studies had limited follow up (12 months) and without continuous monitoring. More recently, on long term follow up (median – 27 months) and with more intense rhythm monitoring (>50% with continuous monitoring), Wong et al showed that rs2200733 SNV carriers had relatively increased LA electrical remodelling (increased CV heterogeneity, regional LA slowing or conduction block particularly in the posterior and lateral walls) and lower arrhythmia-free survival post ablation[258].

It is also important to note that missense mutations in the PLEC gene[259] that encodes the cytoskeletal protein plectin and myosin gene MYH6[260] (previously associated with sick sinus syndrome) have also been significantly associated with AF. Emerging data also demonstrate the link between loss of function mutations in the gene TTN and AF. There is evidence to show an increased frequency of TTN mutations (2-7%) in individuals with early onset AF[261,262]. Beyond patients with early onset AF, Choi et al used exome sequencing data in 1400 AF cases and >40000 controls from the UK Biobank to assess TTN mutation in general population with AF. They observed a similar strong association between loss of function variation in TTN and AF. Furthermore, in this study the penetrance of AF among TTN mutation carriers was markedly higher among individuals with an increased AF polygenic risk[263].

SCN5A mutations are also linked to AF[264,265]. The phenotypic manifestation is often mixed and can include other cardiac abnormalities and arrhythmic disorders such as dilated cardiomyopathy, Brugada syndrome, sick sinus syndrome and long QT variants. AF-causing variants have been reported in both the α-subunit (encoded by the SCN5A gene) and associated β-subunits (encoded by the genes SCN1B-SCN4B). Uncovering the underlying mechanisms of these mutations has multiple challenges such as the mixed phenotypes reported, how both loss and gain of function mutations could cause these different phenotypes and the lack of an animal model with pure AF phenotype. More recently, mutations in the SCN10A gene were also shown to be related to AF[266].

The field of genetics and AF is evolving rapidly, and several experiments are in progress investigating tools that allow the detection of structural variation such as inversions, translocations, and large insertions and deletions, functional cellular knockout assays, single cell RNA sequencing and machine learning. These refinements in the genetic basis of AF will ultimately facilitate the identification of new therapeutic targets and enable more precise risk stratification for this common arrhythmia.

CHAPTER – 2

CATHETER ABLATION FOR ATRIAL FIBRILLATION:

CURRENT INDICATIONS AND EVOLVING TECHNOLOGIES

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice with a worldwide prevalence of >33 million[1]. AF is frequently associated with stroke[2], heart failure[3] and increased mortality[4]. Numerous risk factors are implicated in the development of AF, many of which are modifiable, including hypertension[10], obesity[11,12], obstructive sleep apnoea[13] (OSA), and alcohol consumption[14,15]. The primary goals of treatment patients with AF involve improving symptoms, controlling the rate or rhythm and reducing risk of stroke.

Catheter ablation has emerged as an important treatment strategy for symptom improvement and rate or rhythm control[267,268] and is the most common ablation procedure performed in electrophysiology. Data from randomized, controlled trials (RCTs) also support efficacy of catheter ablation in patients with comorbid AF and heart failure[269,270]. Pulmonary vein isolation (PVI) has been the predominant catheter ablation technique since the original study describing its role in initiation of paroxysmal AF (PAF)[51]. The procedure has evolved substantially over the last two decades with multiple energy

sources and a variety of ablation tools being available to make it both safe and effective. Several ongoing trials are currently evaluating newer tools and different ablation strategies to improve patient outcomes. Lifestyle modification and risk factor management is also increasingly recognized as an important approach to further improve ablation outcomes in patients with AF.

In this Review, we discuss the current and evolving indications for catheter ablation in patients with AF, describe the latest advances in technology that aim to improve safety and efficacy of catheter ablation procedures and review the data that support the importance of lifestyle modifications for improving post-ablation outcomes.

ESTABLISHED INDICATIONS

Catheter ablation for AF is a well-established treatment option for patients with symptomatic AF. Although catheter ablation is a safe procedure with a low periprocedural complication rate[271], several variables need to be considered when identifying patients with potential lower success rates or a higher complication rates, such as the presence of concomitant heart disease, obesity and sleep apnoea, as well as left atrial size, patient age and frailty, and the type of AF.

Current guidelines recommend catheter ablation as a second-line therapy for patients with symptomatic PAF (class I recommendation) or persistent AF (PeAFl; class IIa recommendation) for whom therapy with antiarrhythmic drugs has failed, and for

patients with long-standing PeAF (class IIb indication)[272]. In tandem with symptom control, data from meta-analyses[273-275] and RCTs[268,276,277] show that among patients who did not derive benefit with at least one antiarrhythmic agent, catheter ablation reduces AF recurrence and is markedly more effective in maintaining sinus rhythm than with use of antiarrhythmic therapy.

In selected patients with symptomatic PAF, catheter ablation might be considered as a first-line therapy before trialling antiarrhythmic drugs (class IIa indication). In a 2015 meta-analysis that analysed three RCTs (including a total of 491 symptomatic patients with AF, 98.7% of whom had PAF) catheter ablation was associated with significantly higher freedom from AF recurrence compared with antiarrhythmic drug therapy (risk ratio 0.63, $P = 0.02$) [278]. In patients with tachycardia–bradycardia syndrome, several studies have demonstrated that successful ablation can eliminate reversion pauses and avoid the need for permanent pacemaker implantation[188,279]. In these patients, the presence of reversion pauses is a contraindication for most antiarrhythmic agents and ablation can be considered a first-line therapy[189]. Finally, catheter ablation is also an important first-line option for patients with certain professions such as aircraft pilots, military service personnel and athletes for whom medical therapy can impair performance (discussed below). A summary of the indications for catheter ablation in AF is shown in Figure 1.

Quality of life

Patients with AF report poorer quality of life (QoL) than those with other cardiac conditions (such as coronary artery disease and congestive heart failure) and healthy individuals[5], particularly younger patients (aged <65 years) with PAF[48]. Many of the early RCTs that demonstrated improvement of QoL with catheter ablation used generic scoring systems, such as the 36-item short form health survey (SF-36) or the EuroQol (EQ-5D) questionnaire[280-282]. In these trials, the improvement in QoL was most pronounced at the 3-months follow-up, and in some patients, this improvement was sustained for up to 12 months[280]. In a 2015 meta-analysis of 12 RCTs (total *n* = 1,707)[283], catheter ablation was associated with significant early improvement in QoL compared with medical therapy. However, this benefit was not maintained beyond 9 months of follow-up. Nevertheless, two large multicentre RCTs evaluating long-term QoL outcomes have since been completed. In the CAPTAF trial[284], a significant and sustained improvement in QoL persisted at 12 months for those treated with catheter ablation compared with the medical therapy. This improvement corresponded to a dramatic reduction in AF burden in the ablation group (25% to 5% burden).

However, perhaps the strongest evidence for the benefit of catheter ablation on QoL emerged from the CABANA trial[267]. This large multicentre RCT (*n* = 2,204) used AF-specific QoL assessment tools (the AF effect on quality of life (AFEQT) questionnaire and the Mayo AF-specific symptom inventory (MAFSI)) and thereby overcame the inherent limitation associated with using generic QoL tools, such as lack of specificity and sensitivity to change in AF status[285]. Patients randomized to catheter ablation showed

significant improvement in QoL compared with those receiving antiarrhythmic drugs alone, as assessed by both AFEQT and MAFSI. This maximal benefit of catheter ablation on QoL was seen at 12 months, and the improvement was modestly attenuated at or after 24 months but remained significant. The CABANA investigators suggest that this attenuation could be attributed to a 27.5% crossover from medical treatment to ablation. In support of this explanation, the per-protocol analysis showed that the pattern of late attenuation in QoL benefit was no longer evident.

Heart Failure with Reduced Ejection Fraction

The current decade has seen the emergence of robust data demonstrating significant benefits across a range of outcomes associated with catheter ablation compared with medical therapy in patients with concomitant AF and heart failure and reduced ejection fraction (HFrEF).

Across several registries, catheter ablation has consistently been shown to reduce mortality and risk of ischaemic stroke compared with antiarrhythmic drug therapy[286-288]. Similarly, data from seven RCTs[269,270,289-293] and a meta-analysis of these trials[294] strongly indicate that catheter ablation of AF is superior to pharmacological or pace-and-ablate-based rate control in terms of improvement in left ventricular ejection fraction, exercise capacity and QoL. Table 1a and 1b summarize the data relating to the improvement in left ventricular ejection fraction and other outcomes from RCTs that compare catheter ablation with antiarrhythmic drug therapy in patients with HFrEF. Real world data also support the use of catheter ablation to treat patients with AF and HFrEF[295].

In the 2017 joint consensus document, catheter ablation for AF in patients with congestive heart failure was included in the section on indications for catheter ablation in populations of patients not well represented in clinical trials. The document concluded that "it is reasonable to use similar indications for AF ablation in selected patients with heart failure as in patients without heart failure" (class IIa recommendation, level of evidence B–R). In 2018 after the publication of the CAMERA-MRI[269] and CASTLE-AF[270] trials, the Australian guidelines recommended the use of catheter ablation for symptomatic PAF or PeAF in selected patients with HFrEF (quality of evidence, moderate; strength of recommendation, strong)[296].

Psychological distress

A perhaps unexpectedly large proportion of patients with AF experience substantial psychological distress. In an observational study that aimed to characterize the severity and predictors of distress associated with AF, severe psychological distress was present in 35% of patients referred to a tertiary centre for AF management, with 20% reporting suicidal ideation[46]. Compared with antiarrhythmic drug therapy, catheter ablation significantly reduced the severity of psychological distress and the prevalence of suicidal ideation. Indeed, the most common factor influencing QoL in patients with AF is anxiety related to the disease[297]. Clinicians should recognize potential severe psychological stress when assessing patients with AF and take it into account during the decision-making process. Although severe psychological distress might not be independent of other factors that can impair QoL, cardiac ablation can plausibly be indicated in such patients

experiencing a high level of psychological distress. An ongoing RCT aims to clarify the direct effect of catheter ablation on psychological distress[298].

Cognitive function

AF has been identified in multiple studies as a significant risk factor for cognitive impairment, independent of its effect on stroke risk[299-301]. However, the evidence to date for the benefits of cardiac ablation on cognitive function in patients with AF is less clear. A retrospective study reported that patients undergoing catheter ablation for AF ablation (*n* = 4,212) had a significantly lower risk of dementia than age-matched and sex-matched patients with AF who had not undergone ablation (*n* = 16,848)[302]. However, a subsequent study showed that AF ablation was associated with a 13–20% prevalence of post-procedural neurocognitive abnormalities at long-term follow-up, with increasing left atrial dwell time as the most important predictor[43]. This high prevalence of post-procedural neurocognitive abnormalities was attributed to silent cerebral embolism, which has been extensively reported after AF ablation[40,42,303]. However, in 2019, a prospective case-control study reported that catheter ablation for AF improved neurocognitive function at the 1-year follow-up, particularly in patients with pre-ablation cognitive impairment[304]. Unlike earlier studies, patients undergoing ablation received uninterrupted oral anticoagulation therapy at least 1 month before and 3 months after the procedure, and systemic anticoagulation was performed to maintain an activated clotting time of 350–400s during the procedure. Further studies with a larger sample and long-term follow-up are needed to clarify these mixed findings.

Selected Patient Subgroups

Asymptomatic Patients

Classifying patients with AF as 'asymptomatic' for the purpose of catheter ablation should be undertaken cautiously as this classification can be very subjective and even patients who are 'truly asymptomatic' have ongoing increased risk of stroke, heart failure and death, and might potentially benefit from being in sinus rhythm. Another important point to consider is that patients might simply be unaware of their symptoms but subconsciously limit their physical activity, and thus do not experience any indicators of AF. Observational data show that catheter ablation improves QoL in patients who are asymptomatic, but at the expense of increased risk of inducing post-procedural arrhythmia[305,306].

The 2017 expert consensus statement on catheter and surgical ablation of AF advises that a trial of sinus rhythm can be conducted in patients with asymptomatic PeAF to verify whether they are truly asymptomatic[272]. The document also states that catheter ablation can reasonably be pursued in patients with asymptomatic PAF or PeAF (but not long-standing PeAF) after a careful discussion regarding risks and benefits of the procedure (class IIb recommendation, level of evidence C). A detailed review discussing the pros and cons of catheter ablation in patients with AF who are truly asymptomatic supported this recommendation[307].

Patients with Concomitant Tachycardia–Bradycardia Syndrome

Sinus node dysfunction and AF frequently co-exist[186,308,309]. Several clinical studies have reported that curative AF catheter ablation can abolish or markedly diminish both symptomatic and asymptomatic sinus pauses on AF termination[187,188,279]. These studies have consistently shown catheter ablation to be effective in treating PAF-related tachycardia–bradycardia syndrome in terms of restoration of sinus rhythm without needing permanent pacing, higher rates of sinus rhythm maintenance without need for antiarrhythmic drugs compared with pacemaker implantation plus antiarrhythmic drugs, and lower hospitalization rates related to tachycardia compared with pacemaker implantation. Some data suggest that reverse remodelling of sinus node function can occur after catheter ablation[189]. Indeed, a 13-fold reduction in the percentage of atrial pacing after catheter ablation has been reported in patients with implanted pacemakers for sick sinus syndrome[187]. Guidelines recommend a class IIa indication for catheter ablation in patients with tachycardia–bradycardia syndrome[272].

Elderly Population

Although advanced age is an important risk factor for the development of AF, a paucity of robust data exists on the efficacy and safety of catheter ablation in elderly patients with AF. For the elderly population, clinicians need to take into account factors such as frailty, comorbidities and patient preferences when making a decision regarding the appropriateness of AF ablation[310]. Different studies have used a range of cut-off age points, with some defining elderly patients as those aged ≥75 years[311,312], while others consider age ≥80 years to be elderly[313,314]. In general, data from these studies confirm both the efficacy and safety of catheter ablation in this cohort. However, although

patients aged ≥75 years make up almost 50% of the community burden of AF, they represent <10% of patients undergoing catheter ablation in many centres, confirming the presence of what might be considered appropriate selection bias[315]. Furthermore, long-term outcomes can be still be negatively affected by age. A large registry of patients undergoing AF ablation reported that age >75 years was a significant predictor of mortality on multivariate analysis[316]. Current guidelines suggest that similar indications can be used for AF ablation in selected older patients with AF as for younger patients (class IIa recommendation, level of evidence B–NR).

Athletes

Given that data on the management of athletes with AF are limited, many recommendations are consequently made by extrapolating data from nonathletic populations, and by assessing observational data and expert opinions. Athletes with AF are generally more intolerant to medical therapy than nonathletes[317]. Several observational studies have evaluated the role of AF ablation in this cohort and have consistently demonstrated similar safety and long-term efficacy to nonathletes[318-320]. An early invasive approach with catheter ablation might be reasonable in selected athletes who choose ablation as a first-line strategy and in those who quickly prove intolerant to medical therapy. Reassuringly, athletes who return to vigorous physical activity after ablation showed similar outcomes to athletes who adopt a more sedentary lifestyle[321]. Accordingly, the 2017 consensus guidelines recommend AF ablation as a first-line therapy in athletes owing to the negative effects of medication on athletic performance (class IIA recommendation, level of evidence C)[17].

PVI TECHNIQUES AND TECHNOLOGIES

The earliest demonstration of an AF trigger from within the pulmonary veins by Haissaguerre and colleagues in 1998 was a major milestone in the field of cardiac electrophysiology, revealing a novel mechanistic pathway underlying AF development as well as a new potential target for treatment[51]. Cardiac ablation to isolate the pulmonary veins emerged as a feasible strategy and has significantly evolved over the past two decades from the originally described segmental ostial pulmonary vein ablation[322] to the use of 3D electroanatomical mapping to guide ablation[323] and eventually to wide-area circumferential ablation with verification of conduction block. This latter procedure was demonstrated in a randomized study to be more effective than ostial segmental isolation of each individual pulmonary vein[324], possibly owing to ablation of more proximal trigger sources and associated autonomic denervation[325]. The antral approach also reduced the rates of pulmonary vein stenosis associated with catheter ablation.

PV antral isolation is now widely accepted as the cornerstone of AF ablation techniques and is recommended during all AF ablation procedures (class I indication, level of evidence A)[272]. In patients with PAF, PV antral isolation is associated with a rate of freedom from AF recurrence between 60% and 79%[326-329], and long-term freedom from AF recurrence can reach 77%[330].

For many years, the major stumbling block to attaining long term ablation success was achieving durable PVI[331]. The 2017 consensus document suggested the potential approaches to limiting pulmonary vein reconnection[17] (summarized in Table 2). Although

pulmonary vein reconnection an important issue related to catheter ablation, advances both in radiofrequency ablation (RFA) and cryoablation have made considerable inroads in overcoming this limitation.

Evaluation of lesion size

Although the introduction of contact-force sensing catheters alone did not seem to improve outcomes associated with RFA, the addition of a novel estimate of lesion size (termed ablation index or lesion size index) to evaluate a composite of power, force, stability and duration has resulted in greatly improved outcomes[332,333]. The minimum threshold of the ablation index that was predictive of no PV reconnection was ≥370 for posterior/inferior segments and ≥480 for anterior/roof segments[334]. A meta-analysis of five observational studies showed that the ablation index-guided procedure resulted in a significantly lower incidence of AF, atrial tachycardia and atrial flutter, higher rate of first-pass isolation, shorter fluoroscopy time and shorter total ablation time compared with catheter ablation that did not incorporate the ablation index[335].

The CLOSE protocol was first described by Duytschaever and colleagues in 2018 and involves a novel approach for RFA that encompasses the ablation index (≥400 at the posterior wall and ≥550 at anterior wall), inter-lesion distant markers (≤6 mm apart to ensure lesion contiguity) and catheter stability[336]. The investigators demonstrated that rates of first-pass and adenosine-proof isolation exceeded 95%, with coincident reduction in both procedure and radiofrequency times. In the CLOSE to CURE study[337], 105 patients with PAF with an implanted loop recorder undergoing the CLOSE protocol

ablation approach had a single-procedure freedom from any atrial arrhythmia of 87% at 1 year and 78% at 2 years. After PVI (1.13 ± 0.39 procedures per patient), median atrial arrhythmia burden decreased to 0% at the first and second years of follow-up.

The lesion size index is a proprietary index associated with the use of the TactiCath catheter (Abbott, USA) that combines three different parameters (contact force, ablation time and amount of energy delivered) to guide durable PVI[338]. In a retrospective analysis, mean lesion size index >5.3 was a good predictor of AF freedom at the 1-year follow-up. A larger post-market multicentre prospective study is currently underway to characterize regional differences in lesion size index to achieve durable PVI[339].

Cryoablation

Another widespread approach to isolate pulmonary veins in patients with AF involves the use of a cryoballoon. To date, three large prospective RCTs have compared cryoballoon ablation with RFA in patients with PAF, and have demonstrated that these two approaches are similar in terms of efficacy and safety[329,340,341]. End points such as freedom from all arrhythmias at long-term follow-up, rate of repeat cardiovascular hospitalizations and rate of repeat ablation procedures were also not different between the two approaches. In these RCTs, single-procedure success rates (defined as freedom from any atrial arrhythmia at 12 months) ranged from 52% to 65% depending on the intensity of monitoring (Table 3).

Advances in cryoballoon technology continue to facilitate improved outcomes and shorter procedure times. Time-to-isolation has been demonstrated to be an important

predictor of durable PVI during cryothermal ablation[342]. Compared with earlier iterations, the newest-generation cryoballoon catheter released in 2018 (CB4, Arctic Front Advance Pro, Medtronic Inc.) has a 40% shorter tip length, which enables improved visualisation of pulmonary vein signals to confirm isolation. This improvement was evident in a study assessing the CB4 cryoablation catheter, in which time-to-isolation could be accurately observed in 84.8% of pulmonary veins[343]. An older study had demonstrated that a minimal temperature of ≤–51°C predicted successful isolation and no acute reconnection of pulmonary vein conduction[344]. Achieving isolation within 60 s had a 96.4% negative predictive value for late reconnection. Similar observations were also made in another multicentre study in which time to PVI of ≤60 s and an interval thaw time to 0°C longer than 10 s were predictive of permanent PVI[345].

The duration and dosage of cryoablation for improving outcomes has also been extensively evaluated. Robust data now indicate that a single application of cryoballoon ablation is sufficient to guarantee permanent electrical PVI if the required temperature of −40°C and acute electrical isolation are obtained within 60 s[346]. Numerous studies have confirmed that the long-term outcomes of cryoablation remain similar between patients who underwent a single-freeze procedure compared with those who received a bonus freeze[347]. In the CIRCA-DOSE study[329], no difference in 1-year efficacy was observed between the 2-min freeze procedure and the 4-min freeze procedure, but procedure duration was significantly reduced with the 2-min freeze protocol.

PVI as a sole strategy for PeAF

PVI alone has been effective in treating PeAF. A meta-analysis of 14 studies (total *n* = 956) showed that single-procedure, arrhythmia-free survival at 12 months was 66.7% with PVI alone, with the majority of patients (80.5%) off antiarrhythmic drugs[348]. A subsequent systematic review compared outcomes after PeAF ablation when additional substrate ablation was added to PVI compared with PVI alone[349]. Using PVI ablation as the reference strategy (single-procedure success rate of 57%), the most complex approach (PVI combined with linear ablation and complex fractionated atrial electrogram (CFAE) ablation) was associated with significantly poorer outcomes (single-procedure success rate of 33%; $P < 0.001$), whereas PVI combined with linear ablation and PVI combined with CFAE ablation were also associated with a trend towards reduced efficacy when compared with PVI alone. Finally, the multicentre CRYO4PERSISTENT AF trial[350] involving 101 patients with PeAF undergoing cryoballoon-based PVI reported a single-procedure-associated rate of freedom from any atrial arrhythmia at 12 months of 60.7%[350]. Of these patients in sinus rhythm, only 5.9% were prescribed antiarrhythmic drugs at the end of the follow up.

Nevertheless, in comparison to patients with PAF, long term outcomes in patients with PeAF after catheter ablation have been disappointing and further work is required to understand the underlying mechanisms in order to improve these results. Indeed, given the progressive nature of the substrate in some patients with PeAF, long-term palliation rather than cure might be a more realistic goal for many individuals.

Advances in radiofrequency ablation

In the past 5 years, advances in both RFA and cryoballoon techniques have occurred contemporaneously with the development of other novel energy sources for ablation. Which of these novel energy sources will lead to the most efficient procedure with the best improvement in outcomes is the subject of ongoing evaluation.

High-power, short-duration strategies

To optimize lesion formation and minimize collateral damage, a high-power, short-duration strategy has been evaluated for RFA. By increasing lesion size using resistive heating, high power (40–50 W) might theoretically create a more reliable and irreversible lesion size, whereas the short duration minimizes the risk of collateral damage associated with time-dependent conductive heating. This strategy might be particularly suited to the thin-walled atrium. An in vitro ovine study demonstrated that lesion depth in the atrium with the power settings of 50W, 60W or 70W for 5 s was equivalent to that of 40W for 30 s; however, no steam pops occurred at the higher power settings[351]. For in vivo ablations, all lesions were transmural and lesions at 70W were significantly wider than those created at lower power settings. Another study that sought to evaluate the safety and efficacy of high-power ablation in a swine experimental model and 100 patients referred for PVI demonstrated that a power of 50W for 10 s produced wider lesions with a similar rate of transmurality as using a power of 25W for 20 s[352].

Although no RCTs have been published to date that have evaluated the efficacy and safety profile of this high-power, short-duration strategy compared with conventional

ablation, promising results have been described by several observational studies. Table 4 provides a summary of the studies that have evaluated both the high-power, short-duration approach and very high-power RFA (70W–90W). Despite these promising early data associated with the high-power or very high-power, short-duration strategy, no clear consensus has been established as to the optimum power and duration that maximizes clinical benefit and maintains a high safety profile. Given that major adverse complications associated with catheter ablation, such as stroke, tamponade and atrio-oesophageal fistula formation, occur very rarely, a definitive assessment of the safety of any new ablation technique will require large data sets.

Emerging tools in radiofrequency ablation

Numerous novel radiofrequency catheters have been developed to overcome the limitations of the catheters in current use, such as for use on smaller footprint lesions that currently require prolonged ablation times and carry a risk of injury to neighbouring structures. Early preliminary studies evaluating some of these tools have demonstrated acute procedural success and promising early clinical results, but large-scale studies are still needed to validate their true potential. A summary of the emerging tools for PVI are shown in Figure 2.

Three radiofrequency balloon catheters have been investigated in the past 5 years. The Heliostar catheter, which is compatible with the currently available CARTO 3 3D mapping system (both from Biosense Webster, USA), is a 28 mm spherical, irrigated, compliant radiofrequency balloon catheter that is capable of delivering radiofrequency energy from

all or selected electrodes. Preliminary data from the RADIANCE study[353] showed acceptable short-term success among 39 patients with PAF, but with potentially concerning adverse events, including a 2.6% incidence of phrenic nerve palsy, 7.7% incidence of asymptomatic oesophageal thermal changes and self-resolving silent cerebral embolic events in ~ 20% of patients, as visualized on periprocedural cerebral MRI. A much larger prospective multicentre study is ongoing to clarify the safety and efficacy of this novel multielectrode catheter[354].

The Satake HotBalloon catheter (Toray Industries, Japan) is a 13-F balloon catheter that is deployed through a guiding sheath[355]. The system delivers radiofrequency current at 1.8MHz between a coil electrode inside the balloon and four cutaneous electrode patches, and produces capacitive-type heating in the balloon. In a multicentre RCT involving 143 patients with PAF, success rates at the 9-month follow-up were 59% in the balloon group and 4.7% in the antiarrhythmic drug therapy group (P <0.001)[355]. However, major complications occurred in 15 patients (11.2%), and the incidences of pulmonary vein stenosis and transient phrenic nerve injury were 5.2% and 3.7%, respectively[355]. In a propensity score-matched study, 37 patients undergoing ablation with the hot balloon catheter were compared with 37 patients undergoing cryoballoon ablation[356]. Acute touch-up ablation was required for residual or dormant pulmonary vein conduction in 52% of the hot balloon group versus 24% of the cryoballoon group, highlighting a substantial limitation of this novel technology. Mapping studies indicated that the lesions caused by the hot balloon catheter were smaller than the lesions caused by the

cryoballoon catheter. Nevertheless, AF recurrence did not differ between the two treatment groups at 12 months.

The Luminize-RF (Boston Scientific, USA) is another irrigated single-shot radiofrequency balloon catheter. Preliminary data presented at the European Heart Rhythm Association congress in 2019 showed that the catheter was both safe and effective at 30 days for the treatment of AF[357]. The Luminize-RF catheter has a visual guidance capability from a built-in camera that is intended to provide direct evidence of electrode contact to facilitate tailored ablation. The catheter also has integrated mapping and pacing capabilities, allowing real-time assessment of PVI and phrenic nerve capture. Longer-term data for this new technology are eagerly awaited.

The Sphere-9 catheter (Affera Inc, USA) has an expandable, spheroid-shaped, lattice electrode design with an effective surface area that is 10-fold greater than standard irrigated electrodes, allowing higher energy delivery at a lower current density[358]. In a preclinical model, the lattice catheter created wider lesions with wider linear ablation lines in a shorter timeframe using a very high-power, short duration ablation strategy when compared with a standard irrigated radiofrequency catheter[358]. At 30 days, 100% of the ablation lines created with the lattice catheter remained contiguous compared with only 14% of the lines created with a standard irrigated catheter[358]. Steam pops or collateral tissue damage was not observed. Furthermore, a first-in-human study involving 71 patients with right atrial flutter or AF showed that PVI and linear ablation performed in a point-by-point fashion (T_{max} 73–80°C, range 2–7 s) was clinically feasible with no

major complication at 3 months[359]. The acute success rate for PVI was 98.5%, which was achieved with 2.7 min of RFA. Mitral block was achieved in 100% of patients using a mean of 1 minute of RFA.

Finally, experimental studies have demonstrated the feasibility of direct visualization of ablation lesions using NADH autofluorescence[360,361]. NADH is an endogenous metabolic coenzyme present in all viable cells. RFA results in cell disruption, which causes an acute loss of NADH autofluorescence. Preliminary data on the LuxCath OmniView light-guided catheter (LuxCath LLC USA), an irrigated radiofrequency catheter that is capable of detecting real-time reduction of endogenous NADH fluorescence, highlight its capacity in detecting lesion gaps in 91% of instances[362]. In vivo clinical studies on this prototype catheter are ongoing.

Alternative energy sources for PVI

Endoscopic laser balloon

The endoscopic ablation system (CardioFocus Inc., USA) is a balloon-based ablation system that incorporates a titratable laser energy source and a miniature 2F endoscope that enables an endoscopic view into the target pulmonary vein and ablation under direct visual control. A prospective, multicentre RCT in patients with PAF showed no difference in efficacy between the endoscopic balloon ablation and irrigated point-by-point ablation at the 12 month follow-up[363]. A subsequent RCT comparing this technology with conventional point-by-point wide area PVI in patients with PeAF also showed no differences in efficacy between the two strategies[364]. The complication rates of the two

approaches were also not different. Furthermore, preliminary data on the latest-generation laser balloon ablation system (HeartLight X3, CardioFocus, USA) showed that this novel catheter was as safe and effective as point-by-point PVI, but the procedure duration was markedly shorter[365].

Pulsed field electroporation

Pulsed field ablation uses high voltage electrical pulses for a very short duration (<1 s) to injure tissue via irreversible electroporation[366,367]. Pulsed field ablation is a nonthermal energy modality developed broadly using the concept of direct current ablation that was used for a short period prior to the advent of RFA[368]. Cardiomyocytes have among the lowest electroporation threshold values of any tissue, making this technology uniquely suited to cardiac ablation[369]. This difference in sensitivity between cardiomyocytes and other non-target tissues can potentially limit the risk of collateral damage to the oesophagus and phrenic nerve, which can be injured by RFA and cryoballoon ablation. The efficacy and tissue specificity of pulsed field ablation have been demonstrated in preclinical studies[370-372].

In the first clinical study assessing pulsed field ablation, endocardial PVI using the multispline pulsed field ablation catheter (FARAWAVE, Farapulse Inc., USA) was successful in all 15 patients, with 3.26 ± 0.5 lesions per pulmonary vein, an energy delivery time of <60 s per patient and no procedural complications[373]. Similar safety and efficacy outcomes were reported in a subsequent first-in-human trial that included 81 patients in whom proprietary bipolar pulsed field ablation waveforms were used in either a

monophasic manner (900–1,000 V per application; *n* = 15) or a biphasic manner (1,800–2,000 V per application; *n* = 66)[374]. With sub-second durations of pulsed field ablation pulses, the total time of energy delivery was <3 min per patient and the estimated rate of freedom from arrhythmia at 12 months was 87%.

In summary, preliminary studies indicate that pulsed field ablation is an attractive alternative to PVI, given the shorter procedure time, reduced risk of collateral injury and improved long-term durability. Large scale studies are needed to confirm these benefits and validate its safety profile[358].

ADJUNCTIVE ABLATION STRATEGIES: BEYOND PVI

Over the past 2 decades, a range of adjunctive ablation strategies have been evaluated in an attempt to improve ablation outcomes for those patients who do not respond to PVI alone. In these patients, mechanisms beyond pulmonary vein arrhythmogenesis are critical for the initiation and maintenance of AF. Persistent forms of AF are more likely to involve mechanisms that do not involve the pulmonary vein, and more likely to be observed in the setting of substantial atrial remodelling than paroxysmal forms of AF. Unfortunately, strong evidence to support improved clinical outcomes for any of the adjunctive ablation strategies is lacking.

Non-pulmonary vein triggers

Non-pulmonary vein triggers of AF can be identified in 10–33% of affected patients[375,376]; this variability is attributable to discrepancies in both the adopted definition of an atrial trigger and the induction protocol used between different studies[377]. The definitions of non-pulmonary vein triggers of AF have ranged from repetitive atrial premature depolarizations without definitive AF initiation[378] to reproducible sustained AF triggers[376]. Induction protocols have used increasing doses of isoprenaline with low yield from ≤10 mcg per min and increasing yield when doses >20 mcg per min are used. Numerous anatomical structures have been suggested as sites from which non-pulmonary vein triggers might occur, including the posterior wall of the left atrial, the left atrial appendage (LAA), the superior vena cava, the crista terminalis, the fossa ovalis, the coronary sinus, the ligament of Marshall and adjacent to the atrioventricular valve annuli[376,379-381].

The most challenging aspect of identifying and successfully ablating non-pulmonary vein triggers has been the difficulty associated with accurately localizing a focus when only be a few mappable beats might be present. Deployment of multipolar catheters to identify activation sequences can facilitate the general localization of the site of the trigger, and a number of centres use this approach. However, in view of the inability to achieve precise focus localization in many patients, various isolation procedures have been developed, including those involving the left atrial posterior wall (which might also be responsible for other AF mechanisms), the superior vena cava, the coronary sinus and the LAA.

LAA Isolation

The role of LAA ablation to improve clinical outcomes for patients with AF remains controversial. Although mechanistic data exists to suggest the potential role of the LAA as a trigger of AF[378], the true prevalence of these triggers is hotly debated. A large observational series consisting of 7,129 patients undergoing AF ablation found LAA triggers in only 21 patients (0.3%) and only three patients demonstrated triggers exclusively from the LAA[382]. These data provide a strong argument against routine LAA isolation when PVI alone has been ineffective. However, other studies have consistently demonstrated improved ablation outcomes with LAA isolation, but not with focal LAA trigger ablation[383,384].

The BELIEF study[384] involved 175 patients with long-standing PeAF who were randomized to either extensive atrial ablation or extensive atrial ablation plus appendage isolation. After 1.3 procedures, the rate of success at the 24-month follow-up was 76% when the LAA was isolated and 56% when the LAA was not isolated. Isolation of the LAA can either be performed at the level of the ostium or by larger-area compartmentalization with a roof line, posterolateral mitral isthmus line and an anterior line. The efficacy between these different LAA isolation procedures was similar according to a meta-analysis[385].

The concerns associated with adopting LAA ablation are twofold. First, on the basis of the data from the BELIEF trial[384], achieving complete LAA electrical isolation is technically challenging, requires prolonged ablation even in experienced operators and is associated with a high chance of reconnection. Second, emerging data have implicated a substantial

thrombus risk in the isolated appendage and patients undergoing LAA ablation will generally also require LAA occlusion[386,387]. To date, LAA ablation has not been widely adopted.

Another potentially feasible option is electrical isolation of the LAA by percutaneous ligation, which can be achieved using Lariat device (SentreHEART, USA). This device provides an effective mechanical barrier to thromboembolism during LAA ligation, and can facilitate electrical isolation of the LAA, while obviating the need for anticoagulation. The aMAZE trial[388] is currently underway to address the role of LAA ligation with the Lariat device as an adjunctive therapy in patients with PeAF.

Posterior Wall Isolation

Observational data support the role of LA posterior wall isolation in patients with PeAF[389], but its clinical utility needs to be confirmed in RCTs. Although LA posterior wall isolation is routinely performed in nearly 40% of patients during repeat procedures for non-PAF[272], achieving isolation can be very challenging owing to associated oesophageal heating. In addition, the benefit of posterior wall isolation has not been consistently demonstrated, with numerous RCTs showing mixed results[390-392]. In a meta-analysis of 17 studies (13 involving box isolation, 3 involving single-ring isolation

and 1 using debulking ablation) comprising at total of 1,643 patients (31.3% PAF), the rate of single-procedure freedom from atrial arrhythmia at 12 months was 65.3% overall and 61.9% for patients with PeAF, with an overall low rate of major complications that nevertheless included two atrio-oesophageal fistulas[393]. In this meta-analysis, the RCTs

comparing posterior wall isolation to PVI (3 studies including a total of 444 patients) yielded conflicting results and could not confirm an incremental benefit of posterior wall isolation. A subsequent RCT reported no benefit of posterior wall isolation in patients with PeAF[394]. Further large RCTs are ongoing to determine whether the addition of posterior wall isolation to PVI ablation is more effective than PVI ablation alone.

Rotor Identification and Ablation

The work of Jalife and others have demonstrated that in isolated preparations, high frequency rotors might be responsible for driving AF[395,396]. A range of technologies have been developed in the past 10 years in an attempt to identify rotors as the potential underlying mechanism driving AF and to target these sites for ablation. In a series of papers, Narayan and colleagues described the use of a 64-electrode basket catheter (RhythmView, Abbott Medical, USA) and phase mapping to identify rotors[397-399]. This focal impulse and rotor modulation mapping (FIRM) technique involves targeting temporally stable rotors in the left and right atrium that could be eliminated with ablation at the core of the rotor. A series of observational studies have reported encouraging results[397-399], but other studies were unable to reproduce these results[400-403]. The prospective, randomized REAFFIRM trial[116] did not report any incremental benefit with FIRM-guided ablation when added to standard ablation.

An alternate approach to rotor identification involves the use of a noninvasive body surface potential mapping technique, known as noninvasive electrocardiographic imaging (ECGI). ECGI uses a 252-electrode vest to obtain virtual unipolar potentials

projected on the epicardial atrial surface anatomy of the patient's cardiac CT scan. Using the inverse solution and phase mapping, the system can identify atrial activation patterns. An observational study demonstrated the presence of driver domains within the atria, which are regions where transient rotor activity consisting of a median of 2–3 rotations tend to repetitively reform over time[239]. Driver domains had a particular propensity to be localized at the margin of zones of fibrosis, as identified on cardiac MRI. Ablation at these sites resulted in acute arrhythmia termination in some patients[239]. Patients with PeAF had significantly more driver domains than those with PAF[238]. The subsequent multicentre, observational AFACART study[404] assessed the efficacy of PeAF ablation that targeted ECGI-identified driver domains. The rate of freedom from AF at 12 months with driver domain ablation alone was 77%. These preliminary results will need to be confirmed in a RCT.

A number of other approaches to identify possible rotors have also been evaluated in preliminary observational studies. The CARTOFINDER novel mapping system (Biosense Webster, USA) uses wavelet analysis of unipolar signals recorded from the bipolar electrogram window to generate dynamic 3D propagation maps[129,131,132,405]. Another novel approach to identify drivers of PeAF involves use of the STAR (stochastic trajectory analysis of ranked signals) mapping method[139]. A multipolar catheter is used to determine the proportion of time that an electrode's activation is seen to precede that of neighbouring electrodes in order to determine consistently early sites of activation. Acute preliminary results seem promising[139], but further validation is required.

Complex Fractionated Atrial Electrograms (CFAE's)

Other approaches to identify driver regions involve the analysis of signal characteristics, including a strategy that mapped and ablated complex fractionated atrial electrograms[100]. These signals were described as either highly fractionated, low-voltage (between 0.06 mV and 0.25 mV) potentials or those with a very short cycle length (120 ms) that were considered to identify driver regions[100]. Early data from observational and small RCTs seem to support this approach, and this technique has since been rapidly adopted into clinical practice. However, data from two subsequent large RCTs[108,109] indicated that this approach imparted no additional benefit compared with PVI alone, but is also associated with possible adverse effects. The extensive ablation frequently required to eliminate the complex fractionated atrial electrograms had considerable proarrhythmic consequences that adversely affected clinical outcomes. Dominant frequency has also been used to identify driver domains. Once again, although observational studies showed encouraging results, data from RCT did not show a benefit of this approach over conventional ablation[97,99].

Uncertainty Regarding Mechanisms Underlying PeAF

Notably, the sustaining mechanisms underlying PeAF remains a hotly debated topic, an important point to remember when considering approaches to identify drivers regions and possible rotors. In addition to the presence of rotors, other mechanisms described in preclinical and clinical studies include focal drivers[406] and multiple wave fronts[407-409]. Indeed, these mechanisms are not necessarily mutually exclusive. In the past 5 years, our understanding of the mechanisms underlying AF has been strengthened by accumulating

evidence indicating that the atrium frequently functions electrically as a 3D structure. Simultaneous endocardial–epicardial AF mapping has shown evidence of endocardial–epicardial dissociation with frequent focal breakthroughs[155]. This novel concept in the mechanisms of AF, particularly the non-paroxysmal forms, can certainly explain why mapping and ablation targeted just to the endocardium might result in suboptimal outcomes.

Substrate Identification and Ablation

An alternative approach to identifying ablation sites for PeAF has been to identify the regions of abnormal electrical substrate with the assumption that these areas must be the critical regions responsible for driving AF. Fibrosis identified by cardiac MRI has been shown to be linearly associated with increased AF recurrence after catheter ablation and nonrandomized studies have indicated that ablation of these regions might improve outcomes[237]. However, a major limitation of this approach is that the degree of scar identified depends critically on the threshold used to define the scar[410]. At present, no uniform standard has been developed for the definition of a scar, thereby limiting the reproducibility of the technique. The ongoing, multicentre, randomized DECAAF II trial[411] is testing the hypothesis that ablation of scar detected on cardiac MRI in addition to PVI improves outcomes in patients with PeAF compared with PVI alone.

Finally, abnormal substrates can also be identified using electroanatomic mapping. Kottkamp and colleagues first described this approach using an ablation catheter to identify low-voltage regions in the atrium[412]. Box isolation was performed to eliminate

the potential arrhythmogenic effect of this substrate. Data from outcome studies assessing this approach are needed.

LIFESTYLE MEASURES TO IMPROVE OUTCOMES

Weight Loss

A number of epidemiological studies have drawn attention to the relationship between obesity and increased incidence of AF[413,414]. These epidemiological data are supported by findings from both RCTs and cohort studies that have extensively demonstrated the benefits of a targeted weight loss intervention on AF burden and severity[415-417]. BMI is an important factor in determining outcomes after catheter ablation, with data to support lower rates of freedom from AF in patients with BMI ≥35[418]. In addition, weight loss can prevent progression of PAF to PeAF and can actually result in patients returning to PAF from PeAF, even without ablation[419]. This benefit is directed linked to the degree of weight loss, with the most dramatic improvements seen with a >10% reduction. A meta-analysis identified a 3.1% greater risk of recurrent AF after ablation for every one unit increase in BMI (risk ratio 1.03, 95% CI 1.00–1.07)[420]. Several observational studies have also reported that a BMI ≥30 is independently associated with reduced freedom from AF after ablation[421-423]. Procedural duration and radiation dose were also greater for patients who were overweight or obese, compared with those with a normal BMI[422].

Beyond using traditional methods of diet and exercise to achieve weight loss, surgical weight loss has also been demonstrated to be beneficial in improving outcomes after

catheter ablation[424-426]. An ongoing RCT is currently evaluating whether bariatric surgery or standard weight loss management prior to AF ablation can affect long-term freedom from AF among patients who are morbidly obese[427]. The 2019 focused guideline update on management of patients with AF recommend weight loss combined with risk factor modification for patients with AF who are overweight or obese (class I indication, level of evidence B–R)[428].

Exercise

In patients with AF who are sedentary, increasing physical activity levels has been shown to reduce the risk and burden of AF[429,430]. Data from the CARDIO-FIT study[431] also showed that each one metabolic equivalent incremental gain in fitness corresponded to a 9% reduction in AF recurrence over a 4-year follow-up period. Although these results increase the possibility that exercise training pre-ablation might offer similar benefits by reducing long-term post-ablation arrhythmia recurrences, moderate levels of physical activity have not yet been independently shown to improve ablation outcomes in patients who are sedentary. Importantly, the U-shaped relationship between exercise dose and the relative risk of development AF has been observed. Endurance athletes have a paradoxical fivefold increased risk of AF[432], and physical activity that is very high in intensity and long in duration confers an incremental increase in AF incidence[433]. However, a meta-analysis showed that this risk seems to be sex-specific as intense exercise increases risk of AF in men (OR 3.3) but not in women (OR 0.72)[434].

Treating Sleep Apnoea

A number of studies have indicated an association between moderate-to-severe sleep-disordered breathing and development of AF[435-437]. Furthermore, small studies in patients undergoing either cardioversion or AF ablation have shown that treatment of obstructive sleep apnoea (OSA) with continuous positive airway pressure (CPAP) therapy can improve AF ablation outcomes[438,439]. Given that many patients with severe sleep apnoea are known to have no clinical indicators, the 2017 AF consensus statement recommends screening for signs and symptoms of OSA when evaluating a patient for an AF ablation procedure, and recommends sleep evaluation if OSA is suspected (class Ia indication, level of evidence B–R)[272]. However, this recommendation has been suggested to be made on the basis of data from small heterogenous trials with no consistent diagnostic strategy for OSA nor careful follow-up of CPAP treatment and tolerance among patients[440]. This uncertainty will hopefully be clarified with completion of the ongoing large, multicentre, randomized SLEEP-AF trial[441].

Alcohol Abstinence

Patients with AF who abstain from alcohol have been shown to have better outcomes after catheter ablation than patients who consume alcohol. In 122 consecutive patients with AF undergoing PVI, the rate of arrhythmia-free survival at 1 year after catheter ablation was 81% in non-drinkers, 69% in light-to-moderate drinkers (up to 1 drink per day for women and up to 2 drinks per day for men) and 35% in 'heavy' drinkers (>1 drink per day for women and >2 drinks per day for men)[442]. The effect of alcohol abstinence on arrhythmia recurrence has also been demonstrated in a multicentre, prospective,

controlled trial involving 140 patients (alcohol intake >10 standard drinks per week) who were randomized to alcohol abstinence or to continue their usual habits (>10 standard alcoholic drinks per week)[15]. Participants in the abstinence group successfully reduced their alcohol consumption by 87.5%, with complete abstinence achieved in 61%. The abstinence group had a longer period before recurrence of AF than the control group (HR 0.55) and a significantly reduced AF burden at the 6-month follow-up.

CONCLUSIONS

Catheter ablation is an important and well-established strategy for the management of AF. With advances in technology, the efficacy and safety of the procedure have continued to improve and procedure duration has declined. AF ablation has been shown to reduce AF burden and improve QoL. Although catheter ablation is currently only indicated for symptom control, mounting evidence supports the expansion of its therapeutic role in selected patients. PVI remains the cornerstone approach irrespective of AF type and further investigation is required to determine the most appropriate technique when PVI alone is insufficient. Lifestyle factors that promote AF are increasingly recognized to be important targets in the management of patients with AF.

TABLES AND FIGURES

Table 1a: Randomized studies of catheter ablation in patients with AF and HFrEF

Study (year)	n	Mean LVEF (%)	PeAF (%)	Randomization	Crossovers	Follow-up (months)	Improvement in LVEF CA vs medical therapy	Additional findings	Ref
PABA-CHF (2008)	81	28	48	PVI ± additional ablation *vs* AVNA + CRT	None	6	NR	↑ LVEF, ↑ 6MWT distance, ↑ QoL	289
MacDonald et al (2011)	41	18	100	PVI ± additional ablation *vs* MRC	None	6	4.5 versus 2.8%, *P* = 0.6 (LVEF by CMR); 8.2 *vs* 1.4%, *P* = 0.032 (LVEF by radionuclide imaging)	None	290
ARC-HF (2013)	52	24	100	PVI ± additional ablation *vs* MRC	None	12	11% *vs* 5%, *P* = 0.05	↑ VO_2 max, ↑ QoL, ↓ BNP levels	291
CAMTAF (2014)	50	33	100	PVI ± additional ablation *vs* MRC	None	6–12	8% *vs* 3%, *P* = 0.001	↑ VO_2 max, ↑ QoL, ↓ BNP levels	292
AATAC (2016)	203	30	100	PVI ± additional ablation *vs* amiodarone	None	24	8.1% *vs* 5%, *P* = 0.02	↑ 6MWT distance, ↑ QoL, ↓ Overall mortality, ↓ Unplanned hospitalization	293
CAMERA-MRI (2017)	68	33	100	PVI ± additional ablation *vs* MRC	4.5% to CA, none to MRC	6	18% *vs* 4%, *P* <0.0001	↓ LVESV, ↓ NYHA class, ↓ BNP, ↓ Diffuse fibrosis, Improvements after CA most marked in those without ventricular LGE on preprocedural CMR	269
CASTLE-AF (2017)	363	32	67.5	PVI ± additional ablation *vs* MRC and medical rhythm control	9.8% to CA, 15.6% to MRC	60	8% *vs* 0.2%, *P* = 0.005	↓ Overall mortality, ↓ CV mortality, ↓ HF hospitalization, NNT = 8.3; mortality benefit of CA did not emerge until after 3 years; LVEF gain at 5 years by CA, predominantly driven by CA of PeAF and not PAF; and patients with LVEF ≥ 25% more likely to benefit from CA than those with LVEF<25% (HR 0.48 versus HR 1.36, *P* = 0.01).	270
AMICA (2019)	202	27	100	PVI ± additional ablation *vs* MRC and medical rhythm control	4% to CA, 1.5% to medical management	12	8.8% *vs* 7.3%, *P* = 0.36	↑ 6MWT distance, No change in QoL, No change in BNP levels, ↑ duration of maintaining SR, Negative conclusion driven predominantly by impressive improvement in the medical therapy arm	443

6MWT, 6-minute walk test; AF, atrial fibrillation; AVNA, AV node ablation; BNP, brain natriuretic peptide; CA, catheter ablation; CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronisation therapy; CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LGE, late-gadolinium enhancement; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MRC, medical rate control; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PVI, pulmonary vein isolation; QoL, quality of life; SR, sinus rhythm; VO_2 max, maximum rate of O_2 consumption.

Table 1b: Ongoing randomized studies of catheter ablation in patients with AF and HFrEF

Study (year)	n	Randomization	Follow-up (months)	Ref
RAFT-AF (ongoing)	411	PVI ± additional ablation *vs* MRC and/or AVNA and pacemaker	24	[444]
CONTRA-HF (ongoing)	330	PVI (cryoablation) *vs* MRC and medical rhythm control	12	[445]

Table 2: Recommendations to achieve durable PVI with RFA[a]

Variable	Recommendation	Level of evidence
Contact force of 5–10g	Class IIa	C
Adenosine testing to assess dormant reconnection	Class IIb	B
Loss of capture over ablation line	Class IIb	B
Confirmation of exit block	Class IIb	B

PVI, pulmonary vein isolation; RFA, radiofrequency ablation. [a]According to the 2017 expert consensus statement on catheter and surgical ablation of atrial fibrillation[272].

Table 3: Randomized trials comparing CBA and RFA for PVI

Study (year)	Randomization (n)	Mean follow-up (months)	Outcomes	Main findings	Overall complication rates	Rate of phrenic nerve injury	Ref
FreezeAF (2015)	159 (RFA) 141 (CBA)	12	Freedom from AF, complications	Co-primary end points reached in 70.7% of RFA group and 73.6% of CBA group; CBA was noninferior to RFA	5% RFA *vs* 12.2% CBA, *P* = 0.022	0% RFA *vs* 5.8% CBA, *P* = 0.002	[340]
FIRE AND ICE (2016)	376 (RFA) 374 (CBA)	18	Recurrence of AF, procedure time, fluoroscopy time, complications	1-year Kaplan–Meier event-rate estimates for efficacy: 34.6% for CBA group; 35.9% for RFA group (HR 0.96, *P* <0.001 for noninferiority	12.8 RFA *vs* 10.2% CBA, *P* = 0.24	0% RFA *vs* 0.3% CBA, *P* = 0.5	[341]
CIRCA-DOSE (2019)	115 (RFA) 115 (CBA: 4 min) 116 (CBA: 2 min)	12	Recurrence of symptomatic or asymptomatic atrial tachyarrhythmia	Freedom from atrial tachyarrhythmia: 53.9% of RFA group versus 52.2% of CBA (4 min) group versus 51.7% of CBA (2 min) group (*P* = 0.87); median AF burden reduction: 99.3% of RFA group versus 99.9% of CBA (4 min) group versus 98.4% of CBA (2 min) group (*P* = 0.36); longer procedural duration but shorter fluoroscopy time with RFA compared with CBA	2.6% RFA *vs* 5.2% CBA (4 min) *vs* 6% CBA (2 min)	0% RFA *vs* 1.7% CBA (4 min) *vs* 0.8% CBA (2 min)	[329]

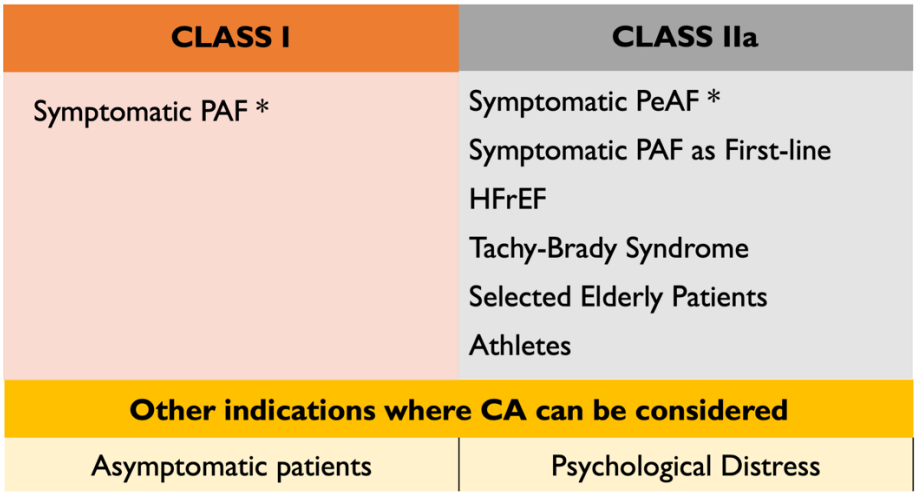
AF, atrial fibrillation; CBA, cryoballoon ablation; RFA, radiofrequency ablation.

Table 4: Overview of studies that assessed the HPSD strategy

Study (year)	Ablation catheter	Power (HPSD group; W)	Duration (s)	n	Mean follow-up (months)	Main findings (compared with standard group with conventional power settings)	Ref
Pambrun et al (2019)	SmartTouch*	40–50	8.5	50 (HPSD group) 50 (standard group)	12	↓ Procedure time, ablation time, energy delivery, duration per RF application ↑ First-pass PVI and fewer reconnections after the 20-min waiting period No change in SR maintenance at follow up, No major complications observed	352
Nilsson et al (2006)	5mm tip, Celsius Thermocool*	45	20	45 (HPSD group) 45 (standard group)	15	↓ PVI time, ↓ Mean fluoroscopy time and radiation dose, ↓ RF application time, ↑ Number of RF applications required for completing PVI, SR in 76% of patients during follow-up, No major complications observed	446
Winkle et al (2019)	NR	45–50	2–15	13,974 (HPSD group) No control arm	Retrospective study	Procedural time was 116 ± 41 min, Complications: Deaths in 0.014% (one stroke-related death and one AEF-related death), pericardial tamponade in 0.24%, PV stenosis in 0.014% and steam pop in 0.014%	447
Vassallo et al (2019)	TactiCath#	45–50	6	41 (HPSD group) 35 (standard group)	12	↓ Left atrial time and RF time, No change in AF recurrence at 6 and 12 months No complications observed	448
Leshem et al (2018)	QDOT Micro*	90	4	20 swine (HPSD group) No control group	None	HPSD resulted in improved lesion-to-lesion uniformity, linear contiguity and transmurality, with a similar safety profile to conventional ablation	449
Barkagan et al (2018)	QDOT Micro*	90	4	3 swine (HPSD group) 3 swine (control group)	None	HPSD ablation resulted in improved linear continuity, shorter ablation time and a safety profile similar to conventional ablation	450
Kottmaier et al (2020)	FlexAbility SE#	70	5–7	97 (HPSD group) 100 (standard group)	12	Freedom from AF (83.1 in HPSD group *vs* 65.1% in control group, *P* <0.013) ↓ Mean RF time (12.4 ± 3.4 min *vs* 35.6 ± 12.1 min, *P* <0.001) ↓ Procedural time (89.5 ± 23.9 min *vs* 111.15 ± 27.9 min, *P* <0.001) No major complications	451
Reddy et al (2019)	QDOT Micro*	90	4	52 (HPSD group) No control arm	3	Total procedure time of 105.2 ± 24.7 min, Total fluoroscopy time of 6.6 ± 8.2 min 94.2% of patients in SR at follow up, Complications: pseudoaneurysm (1.9%), asymptomatic thromboembolism (1.9%), silent cerebral emboli (12%) No deaths, stroke, AEF or PV stenosis.	452
Q-FFICIENCY (ongoing)	QDOT Micro*	90	4	277	12	*NR*	453

* Product of Biosense Webster, USA; #, Product of Abbott, USA; AF, atrial fibrillation; AEF, atrio-esophageal fistula; HPSD, high-power, short-duration; NR, not reported; PVI pulmonary vein isolation; RF, radiofrequency; SR, sinus rhythm.

Figure 1: Summary of indications for catheter ablation in atrial fibrillation

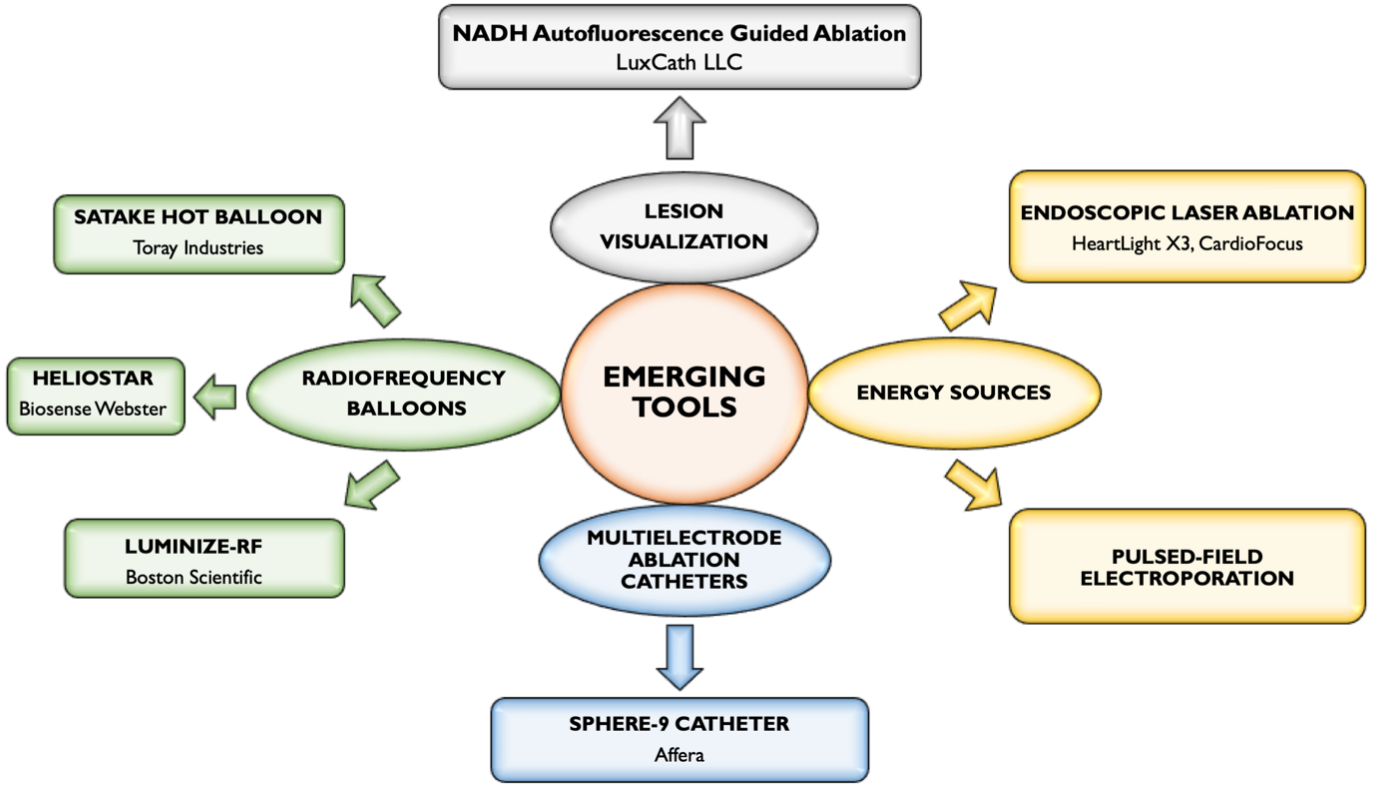


CLASS I	CLASS IIa
Symptomatic PAF *	Symptomatic PeAF * Symptomatic PAF as First-line HFrEF Tachy-Brady Syndrome Selected Elderly Patients Athletes
Other indications where CA can be considered	
Asymptomatic patients	Psychological Distress

* Refractory to medical management; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; HFrEF, heart failure with reduced ejection fraction

Figure 2: Emerging tools for pulmonary vein isolation

The figure summarizes the latest technological advancements that have led to the development of newer catheters and alternative energy sources for performing pulmonary vein isolation.



CHAPTER – 3

CLINICAL IMPACT OF ROTOR ABLATION IN ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW

INTRODUCTION

In the past decade, atrial fibrillation (AF) ablation has played a major role in the management of paroxysmal (PAF) and persistent AF (PeAF), with a greater efficacy for maintenance of sinus rhythm (SR) compared with pharmacological therapy[454]. However, both single and multiple procedure outcomes remain sub-optimal in patients with PeAF[455]. For many patients even durable pulmonary vein isolation (PVI) alone is insufficient, reflecting the presence of AF mechanisms within the body of the atrium. In the absence of a clear understanding of these putative mechanisms various atrial substrate approaches have been utilised but to date none have been confirmed as adding significant benefit over PVI alone[109]. Most recently both basic and clinical mapping studies have suggested that AF may be maintained by drivers in the atrium, most commonly in the form of localized rotors[456,457]

However, not all mapping studies have observed drivers as the mechanism underlying AF and reported outcomes of focal impulse and rotor modulation (FIRM) ablation have been variable.

Our objective is to undertake a systematic review of the medium-term outcomes of rotor ablation in AF.

METHODOLOGY

Search strategy & study eligibility

We performed a comprehensive literature search of EMBASE, PubMed, Medline, and the Cochrane-controlled Trials Register in August 2017. The search was restricted to English language studies involving humans. Key search terms were 'rotors', 'ablation' and 'atrial fibrillation'. Only published manuscripts with medium-term outcome data (minimum 5-months follow-up) for rotor ablation were included in the meta-analysis. Conference abstracts were excluded. For publications from the same group, only the latest publication was used. The search strategy is summarized in Figure 1.

Definition(s) of Rotor Ablation

Majority of studies used FIRM mapping (RhythmView, Abbott Medical) to identify rotors. This technique involves computational analyses of recordings from both atria, using a direct-contact 64-electrode basket catheter (FIRMap or Constellation). Rotors, defined as sequential clockwise or counterclockwise activation contours (isochrones) around a centre of rotation emanating outward to control local AF activation[399], are displayed as a movie projected on a 2D grid representing the endocardial surface of the atrium of interest.

In an alternate approach to detect rotors, Haissaguerre and colleagues have recently reported the use of body-surface phase mapping[458]. With this technique, mapping is performed using a 252-electrode vest and unipolar electrograms from torso potentials which are reconstructed during each cycle using mathematical algorithms and projected on a biatrial shell. Driver domains identified prior to the procedure were targeted for ablation during the procedure.

Only outcomes from studies using FIRM mapping (RhythmView, Abbott Medical), were included in the meta-analysis.

Data extraction & outcomes

337 eligible abstracts were identified and exported into EndNoteX8 referencing software. Study selection, assessment for validity, and extraction of data were performed by two independent reviewers (RP, AV). Another investigator (JK) was consulted if 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.

Eleven published manuscripts were included in this review after various exclusions (Figure 1). No randomized studies have yet been reported. The patient characteristics of included studies are listed in Table 1. The primary outcome was medium-term arrhythmia-free survival after initial procedure. Patients were included in separate analyses for paroxysmal or persistent AF. Arrhythmia events included a composite of AF,

atrial flutter or atrial tachycardia > 30 seconds (s). The definition of post-PVI blanking period and use of anti-arrhythmic drugs (AAD) were left to individual study design. If on-antiarrhythmic and off-antiarrhythmic success rates were reported, off-antiarrhythmic data were used.

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 these Kaplan–Meier data. Study estimates and confidence intervals (CI) were subsequently pooled using a random effects model based on logit transformed proportions. Statistical analysis was performed using the Comprehensive Meta-Analysis software, Version 3(Biostat). Heterogeneity was assessed using an I^2 statistic, with I^2 > 50% indicative of significant heterogeneity and >75% considered 'high'**.** A high level of inconsistency reduces the confidence of recommendations about treatment. Potential publication bias was assessed using funnel plots and these were then confirmed using Egger's test. In all statistical analyses, P< 0.05 was considered significant.

RESULTS

FIRM-guided ablation in Paroxysmal AF

Three observational studies reported clinical outcomes of FIRM-guided ablation in PAF in 24 patients[459], 9 patients[403], and 64 patients[398]. A vast majority of patients in these cohorts also underwent PVI after FIRM ablation.

The Indiana University FIRM registry[398] included 64 patients and reported a 95% single procedure 1-year freedom from AF and 77% single procedure 1-year freedom from all atrial arrhythmias (AT) in this cohort. 48% of these patients had undergone a prior AF ablation. Of note, there was a disparity between acute termination and long-term outcomes in this cohort with only 59% acute termination post-ablation.

In contrast, in a multicentre experience of 24 patients[459] the 12-month freedom from AF was only 25%. Notably, 26% of the cohort had severe left atrial (LA) enlargement which may have contributed to reduced efficacy. Using FIRM mapping, all PAF patients were shown to have rotors or focal sources (mean 2.0±1.0) although less in number compared to PeAF patients.

A comparably poor outcome with 100% AF recurrence was also noted in 9 patients with PAF despite undergoing PVI plus FIRM ablation[403].

Rotor ablation as a sole strategy for paroxysmal AF

The only study investigating the efficacy of rotor ablation as a stand-alone procedure for PAF was by Berntsen et al[401] in twenty-seven patients. Acute termination to SR was noted in 19% and in a further 27% the cycle length was prolonged >10%. At follow-up after 15.2±3.9 months, AF episodes ≥30 minutes and ≥60 minutes were noted in 85% and 78% respectively. Among the patients monitored with the implanted monitors (63%), the target AF burden of <1% was achieved only in 12%.

Overall, the pooled estimate of single-procedure freedom from AF in PAF from the four studies comprising 166 patients was 37.8% (95% CI 5.6%-86.3%) at a mean follow-up of 13.8±1.8 months (Figure 2). There was a significant and very high level of heterogeneity among published studies (I^2 = 93.8).

FIRM-guided ablation in non-paroxysmal AF

A total of ten studies have reported outcomes of FIRM ablation in PeAF. The majority of these patients have undergone PVI in addition to FIRM ablation. Only one study has reported outcomes of FIRM ablation as a stand-alone procedure in non-paroxysmal AF.

In the largest series[398] (52 patients PeAF and 54 LPeAF), the 1-year single procedure freedom from AF following FIRM guided ablation plus PVI (in 95%) was 83% and 82% respectively. Freedom from all AT was reported at 75% and 57% respectively. The same group previously reported an 81.5% freedom from AF at 1 year in PeAF (30% on AAD's) in 55 patients (7 with LPeAF)[460].

The CONFIRM study[399] reported single procedure freedom from AF of 82.4% (freedom from all AT of 70.6%) after a median follow-up of 273 days. After a median 890 days of follow-up in this cohort, freedom from AF was 77.8% [21 of 27] after 1.2±0.4 procedures (median 1; IQR: 1 to 1); significantly higher than in a conventional ablation group (38.5% [25 of 65], p=0.001). After a single procedure alone, freedom from AF was also higher for FIRM-guided than conventional therapy for patients undergoing first ablation (75.0% [15

of 20] vs. 30.2% [16 of 53], p<0.001) and all patients (66.7% [18 of 27] vs 27.7% [18 of 65], p<0.001)[397].

Favourable outcomes were also reported by three other small single-centre studies[17,461,462] in a collective cohort of 91 patients (33 PeAF, 48 LPeAF) who demonstrated stable rotors on mapping. At 6-months, freedom from AF was 80% and 73.2% in two studies[461,462]. Both studies reported a very low acute rate of termination to SR(<10%). In 25 patients (15 PeAF), Tilz et al[17] reported a single-procedure freedom from atrial tachyarrhythmia of 52% in the entire cohort at 13±1 months follow-up.

In the multicentre report by Buch et al[459] a modest 57.5% were free of AF at 18±7 months follow-up after a single procedure. Stable rotors were identified in all patients. 77% of patients had PVI following FIRM ablation in the entire cohort (paroxysmal and persistent AF patients). In a cohort of 43 patients (34 PeAF), Steinberg et al[403], observed a 21% freedom from recurrent AF (12% free of AF off AAD's) at 16 months follow-up. More recently, in 27 patients with PeAF, Balouch et al[463] reported a 12-month freedom from AF/AT in 45.5%.

Rotor ablation as a sole strategy for non-paroxysmal AF

Gianni et al[402] enrolled 29 PeAF patients (31% LPeAF), in whom FIRM mapping revealed a mean of 4±1.2 rotors per patient (62% LA, 38% Right atrium (RA)). At 5.7±3.7 months follow-up, single procedure freedom from AF/AT without AAD's was 17%.

Overall, the pooled estimate of single-procedure freedom from AF in non-paroxysmal AF from the ten studies was 59.2% (95% CI 41.4%-74.9%) at a mean follow-up of 12.9±6 months (Figure 4). However, there was a significant and high level of heterogeneity among the ten published studies (I^2 = 88.3%) (Figures 4, 5).

Patient population, ablation approach and follow-up methodology

There were no obvious systematic differences in the patient populations which might account for the wide variation in the reported outcomes (Table 1). When comparing studies with success rate >50% with those <50% there were no clinically relevant differences in: Mean patient number (36 vs 29), age (61.5 vs 61.4 yrs), atrial size (48.9 vs 44.8mm), patients with prior ablation (56 vs 55%), duration of AF since diagnosis and left ventricular ejection fraction (LVEF) (53 vs 55%).

The ablation approach and duration did demonstrate some variation (Table 2). While most studies targeted the rotor core of approximately 1-2 cm radius, wider ablation lesions were delivered to the core and surrounding area in several studies reporting higher success rates[403,462]. Similarly, studies reporting success rates of >50% had longer total ablation times than those with success rates under 50% (48±13 vs 34±7 minutes) (Table 2). However, for the small number of studies reporting rotor ablation time separately, this seemed similar across the studies (Table 2). No studies reported the actual area of ablation from a 3D map estimate.

Approaches to post-ablation documentation of AF recurrences varied considerably but were rigorous in the majority of studies. These included regular ECG, regular holter monitors (24 hour, 3 day or 7 day), event-recorders or implanted loop recorders. There were no systematic differences and indeed studies reporting higher success rates frequently used rigorous monitoring.

Finally, the proportion of patients on AAD's after the blanking period varied between studies from 0 to 25.6% (Table 2). However, the prevalence of AAD's use was not systematically different between studies reporting a success rate over 50% versus those with success rate under 50%.

Safety associated with rotor ablation

The overall major complication rate as a percentage of all the patients included in the studies reporting complications was 3.4%. Ten studies reported complications in 17 patients which included 6 cardiac tamponades, 4 heart failure exacerbations needing hospitalisation, 2 pseudo-aneurysms, 1 groin bleed needing transfusion, 1 transient ischemic attack, 1 heart block, 1 epidural hematoma and 1 fatal atrio-oesophageal fistula. In addition to these procedure-related complications one patient developed self-limiting urinary bleeding following traumatic catheterisation that prolonged hospitalisation. Drawing inferences from the complications from FIRM ablation are challenging as many patients also had additive ablations (PVI) and whether all complications are attributable to FIRM ablation alone is unclear.

DISCUSSION

In the current systematic review, using FIRM-guided rotor ablation, the overall pooled estimate of single-procedure AF free survival at approximately 1 year was 37.8% for PAF and 59.2% for non-paroxysmal AF. However, these pooled estimates alone hide the fact that heterogeneity (I^2) was significant and high at approximately 94% and 90% in PAF and PeAF respectively indicating the wide variation in reported efficacy. These variations could not be simply explained by differences in patient population, ablation approach or follow-up methodology. This lack in consistency raises important questions regarding the overall efficacy of FIRM ablation and indicates that further studies are warranted to ascertain whether this technology will have a future routine clinical role. Interestingly, in patients with PAF where PVI is the cornerstone ablative strategy, additional FIRM guided ablation resulted in a suboptimal outcome at one year suggesting the possibility of pro-arrhythmic effects of rotor ablation.

A number of factors need consideration when interpreting the results of FIRM guided ablation in this analysis. Limitations in signal acquisition have been reported with the current basket technology[464,465] . This was largely a result of spline bunching and poor atrial coverage with variable electrode contact resulting in suboptimal endocardial atrial maps and associated complexities in map interpretation. In the study by Oesterlein et al aiming to quantify the catheter deformation and endocardial coverage and the effect of catheter size and electrode arrangement using an in silico basket model, it was concluded that interspline distances of more than 20 mm are common, leading to a coverage of less than 50% of LA surface. In our most recent experience the overall mean percentage of

the LA surface area mapped by the basket catheter was 22±6% with no significant improvement with the use of a deflectable sheath. Furthermore, there was regional variation with preferential coverage of the lateral wall and absence of contact with the septum. This will greatly impact the anatomic distribution and prevalence of observed rotors and no doubt will have a major impact on outcomes.

The wide variability in the outcomes could have also resulted from the potential inaccuracies associated with the 2D-phase mapping technique used to identify rotors which works on several anatomical assumptions. Electrodes of the basket catheter are assumed to be located uniformly in an 8x8 evenly spaced grid which is not a true reflection of the actual electrode positioning in 3D space. It also fails to allow for the considerable variations in LA anatomy between patients. Pathik et al recently described a novel 3-D phase mapping technique whereby phase is projected onto patient-specific 3-D LA geometry which takes into account the relative 3-D locations of the basket catheter electrodes and the complex curved surfaces of the LA in both the interpolation and visualization of the data. Using this methodology, rotors demonstrated using 2D phase mapping were not observed in corresponding 3D phase maps in the same patient, time segment and anatomical site[466].

Finally, it is also arguable that PVI performed in the majority of patients across all but two studies was a major determinant of a successful outcome. Nevertheless, it is unlikely for it to have contributed to the large variance in the observed outcomes given its widespread implementation as an additional ablation strategy in these studies.

Prospective randomised studies are required before rotor ablation can be considered to have routine clinical benefit.

Limitations

This review included several studies with follow-up <12-months despite current guidelines recommending a minimum of 12- months objective follow-up in all AF ablation patients. The possibility of the 'small-size effect' was considered, however all of these studies had experienced operators with the individual centres abiding by the established mapping protocol. Finally, this analysis is restricted to studies using only FIRM-guided rotor ablation and cannot be extrapolated to other recent technologies (CARTOFINDER, ECGi) used for detecting localised sources.

CONCLUSION

The current analysis indicates a wide variability in reported outcomes from procedures using FIRM guided ablation technology to target rotors. There are no clear differences between the studies that might account for these striking differences. In this context, this approach needs to be questioned and further information from ongoing prospective randomised controlled studies is required before the efficacy of the technique can be confirmed or refuted.

TABLES AND FIGURES

Table 1: Patient and study characteristics of the studies reviewed

Article	N	Type of AF enrolled	Age (years)	Duration of AF since diagnosis	Prior ablations (%)	Left atrial size (mm)	Left ventricular ejection fraction (%)	Hypertension (%)	Diabetes (%)	Sleep apnea (%)	Coronary artery disease (%)
Buch et al[459]	43	24 PAF 19 PeAF	61±11	7.3±5.4years	67	-	59±6.4	-	-	-	-
Steinberg et al[403]	43	9 PAF 34 PeAF	64.3±10.9	80.8±64.8 months	72	44±7	53.6±7.3	64.3	26.2	23.8	-
Miller et al[398]	170	64 PAF 52 PeAF 54 LPeAF	59±12	-	43	52±10	47±10	-	-	-	-
Berntsen et al[401]	27	27 PAF	55±12	6.2±4.4 years	30	42±5	93% normal LVEF	7	7	-	7
Miller et al[460]	78	23 PAF 48 PeAF 7 LPeAF	61.3±10.1	-	48.7	56 ±9	47±10	-	-	-	-
Narayan et al[399]	36	7PAF 29PeAF	63±9	52 (38–110) months	42	48±7	53±15	-	-	-	-
Sommer et al[461]	20	2 PAF 18 PeAF	60.9±7.6	68.5±51.1 months	50	45.9±4.9	55.2±8	75	-	-	-
Spitzer et al[462]	58	10 PeAF 48 LPeAF	62.2±9.4	4.1±3.1 years	100	47±6	57±9	82.8	19	-	19
Tilz et al[17]	25	10 PAF 15 PeAF	63±9	-	-	45±5	58±7	48	-	-	-
Balouch et al[463]	27	23 PeAF 4 LPeAF	64.4±9	4.3±4 years	51.9	46±8	53±4.1	66.6	3.7	26	-
Gianni et al[402]	29	20 PeAF 9 LPeAF	62.4±10.3	36 (4–72) months	-	47(43–50)	55	82	14	24	10

LPeAF: Long-standing persistent atrial fibrillation PAF: Paroxysmal atrial fibrillation, PeAF: Persistent atrial fibrillation

Table 2: Procedural and outcome data of the studies reviewed

Article	Mapping	Average sources	Ablation approach	Targets	Rotor ablation time, min	Total RF time, min	Fluoro time, min	Follow-up for AF recurrence detection/Blanking period†	Outcome, %		Complications (%)
									Freedom from AF with or without AAD	Freedom from all atrial arrhythmias	
Buch et al[459]	Constellation	2.0±1.0(LA) 0.6±0.8(RA)	FIRM+PVI (77%)	Core (1-2cm radius)	-	39±18	55±24	Symptoms/ECG (1, 3, 6, 12 and then 6 monthly)	30 (PAF) 57.5 (PeAF)	21	9.3
Steinberg et al[403]	Constellation (67.4%) FIRMap (32.6%)	1.3±0.7(LA) 0.6±0.6(RA)	FIRM+PVI (90.6%) Linear ablation (9.3%) CFAE (4.6%)	Core+2cm^2	19.9±11.2	27.8±13		Symptoms/trans-telephonic monitoring (1, 3, 12mo)	21	12	2.2
Miller et al[398]	Constellation (25.8%) FIRMap (74.2%)	2.0±1.3(LA) 1.8±1.3(RA)	FIRM+PVI (95%)	Core+2-8cm^2	-	56±14	25±13	ECG/Event monitors/14.1 % implanted device. AAD in 1.1%	87	70	3.5
Berntsen et al[401]	FIRMap	3.0±1.1	FIRM	Core (1-2cm radius)	20±9	25.4 ±9.5	74±34	Symptoms/ECG/3-daysHolter/63% loop recorders interrogation (1, 3, 6 and then 6 monthly). AAD ceased at 3mo	22.2	-	3.7
Miller et al[460]	Constellation	2.3±0.9	FIRM+PVI	Core of 2cm^2	16.6±11.7	-		Symptoms/Event monitors. AAD continued in 25.6%	80.5	71.4	0
Narayan et al[399]	Constellation	2.1±1.0 (74%LA, 26%RA)	FIRM+PVI	Core	16.1±9.8	57.8	-	Symptoms/7-day Events monitor/Implanted device (3,6, 9, 12, 18, 24mo). AAD in 14.7%	82.4	70.4	6
Narayan et al[397]	Constellation	2.1±1.0 (74%LA, 26%RA)	FIRM+PVI	Core	16.1±9.8	57.8	-	Symptoms/7-day Events monitor/Implanted device (3,6, 9, 12, 18, 24mo). AAD in 14.7%	77.8	66.7	6
Sommer et al[461]	FIRMap	3.05±1.4(LA) 1.15±0.7(RA)	FIRM+PVI	Core+surrounding area	-		18.1±4	7-day ambulatory ECG after 2mo blanking-period. AAD ceased by 2 mo	80	-	0
Spitzer et al[462]	FIRMap	3.0±1.6	FIRM+PVI	Core+surrounding area (mean 3.4±1.9cm^2)	-	30±15	26±9	Symptoms/ECG/7-day Events monitor(1, 3, 6, 12mo). AAD in 7.7%	80.8	76.9	5.2
Tilz et al[17]	FIRMap	3.0 (range 1-4)	FIRM+PVI	Core+surrounding 2cm^2	15.4 (median)	-	28 (range 24-38)	72-hrs Holter (1, 3, 6, 12mo). AAD in 16%	-	52	4
Balouch et al[463]	FIRMap	2.9±1.2	FIRM +PVI	Core+surrounding area (mean 3.1±1.6cm2)	-	44.3	60±11	Symptoms/Holter (3, 6, 12mo). AAD in 11.1%	38.5	-	--
Gianni et al[402]	FIRMap	4±1.2	FIRM	Core	-	35±16	-	ECG/7-days Holter. AAD in 10.3%	28	-	0

AAD: Anti-arrhythmic drug therapy, CFAE: Complex fractionated atrial electrograms, mo: months, PAF: Paroxysmal atrial fibrillation, PeAF: Persistent atrial fibrillation PVI: Pulmonary vein isolation, RF: Radiofrequency.
† Blanking period 3-mo unless stated otherwise

Figure 1: Flow diagram of included studies for primary outcome

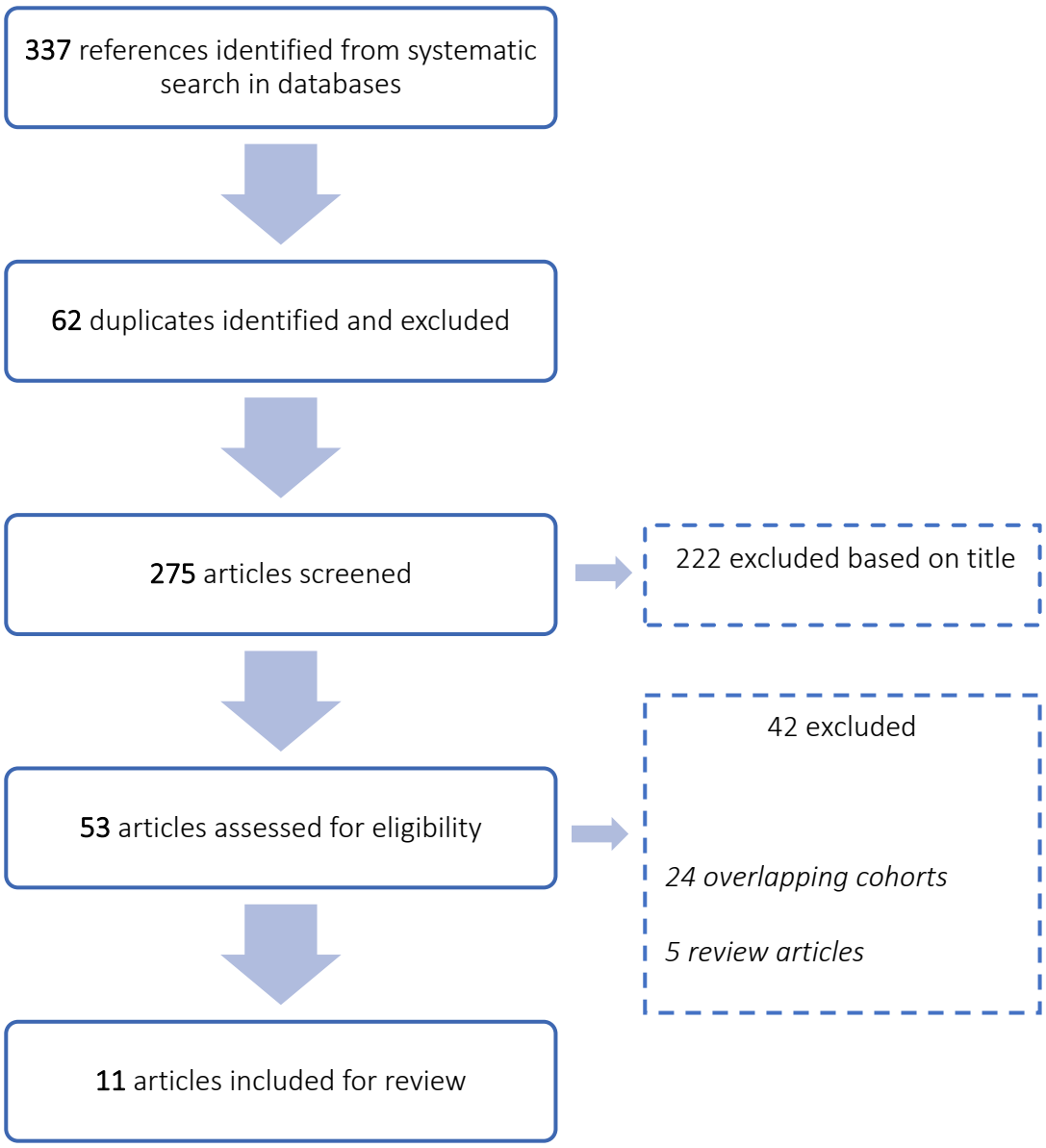


Figure 2: Pooled estimate of AF-free survival after FIRM ablation in PAF

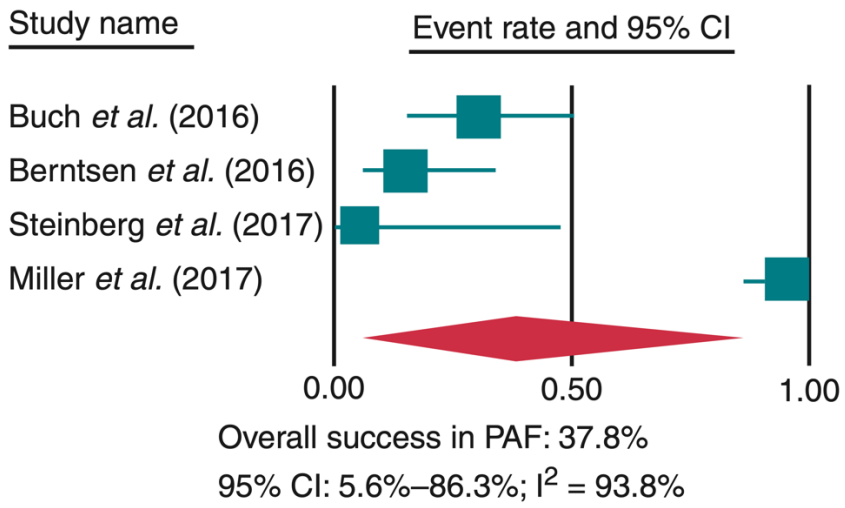


Figure 3: Funnel plot of AF-free survival after FIRM ablation in PAF

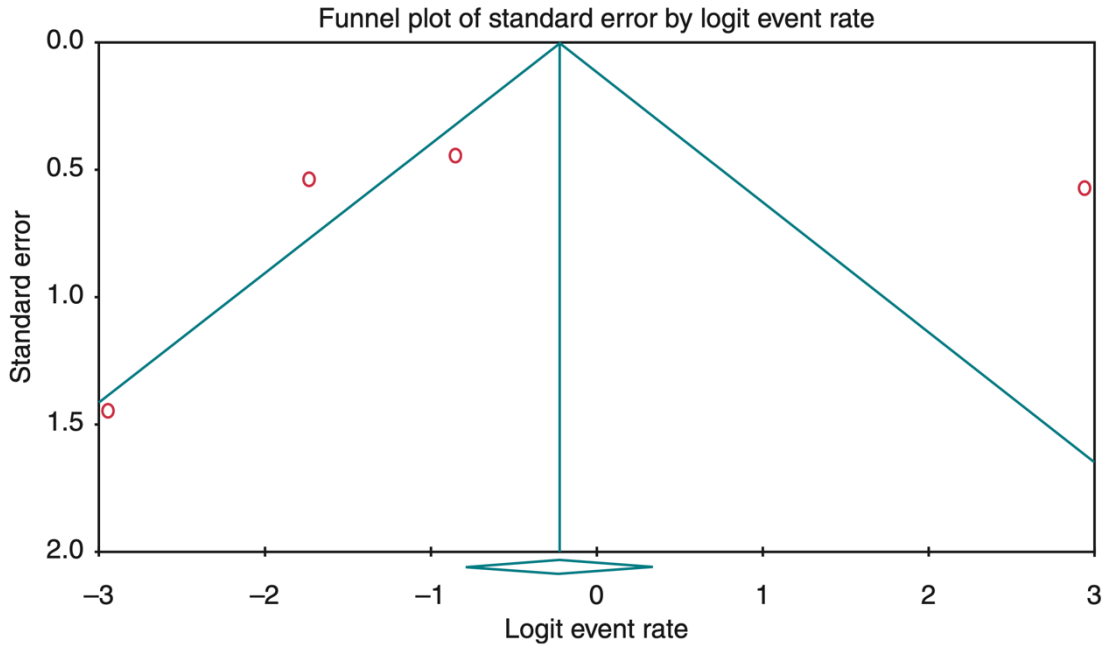


Figure 4: Pooled estimate of AF-free survival after FIRM ablation in non-paroxysmal AF

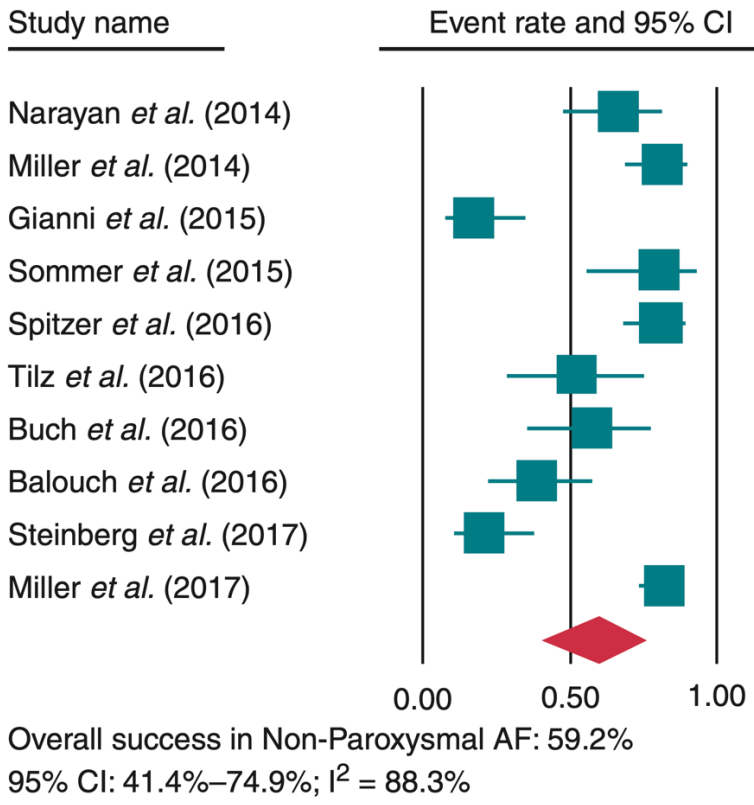
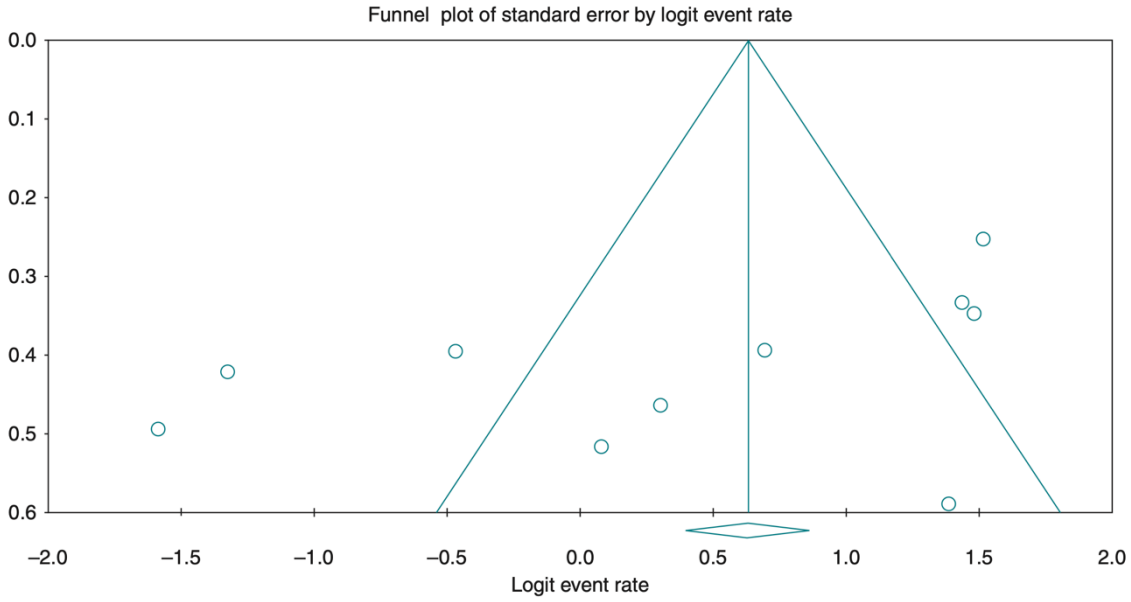


Figure 5: Funnel plot of AF free survival after FIRM ablation in non-paroxysmal AF



CHAPTER – 4

FUNCTIONAL ATRIAL ENDOCARDIAL-EPICARDIAL DISSOCIATION IN PATIENTS WITH STRUCTURAL HEART DISEASE UNDERGOING CARDIAC SURGERY

INTRODUCTION

Atrial excitation is increasingly being recognized as a 3-dimensional process which may play an important role in maintenance of persistent AF. Regional right atrial epicardial-endocardial dissociation was demonstrated more than two decades ago [149] in an animal study where differences in the activation sequence correlated with the underlying anatomic architecture. High density epicardial mapping studies in persistent AF have also shown longitudinal dissociation of muscle bundles within the atrium presumably as a result of extensive atrial remodelling and development of fibrosis [123,154]. These epicardial mapping studies observed the presence of focal atrial activations which were hypothesised to represent endocardial-epicardial breakthrough. More recently, simultaneous epicardial-endocardial high-density mapping of AF in humans showed evidence of right atrial endocardial-epicardial dissociation during persistent AF [155]. Recent mapping studies also suggest the presence of endocardial-epicardial dissociation during sinus rhythm but the nature of this has not been fully explored [467].

In the current study we used simultaneous epicardial and endocardial phase mapping to characterise the functional properties of atrial endocardial-epicardial dissociation in sinus rhythm and during programmed stimulation.

METHODOLOGY

Study population

Patients undergoing cardiac surgery for ischemic and/or valvular heart disease at Royal Melbourne Hospital, Melbourne, Australia were included. Patients with a history of catheter ablation for atrial arrhythmias were excluded. All patients gave written, informed consent prior to the surgery and the study protocol was approved by the research and ethics committee of Melbourne Health.

Data acquisition

Following median sternotomy and prior to cardiopulmonary bypass, simultaneous epicardial and endocardial mapping of the lateral right atrium was performed using two Advisor™ HD Grid catheters (Abbott, St. Paul, Minnesota, USA) one each for the epicardial and endocardial surfaces of the RA. Each HD grid catheter represents a 4x4 electrode array (3mm interelectrode distance) having four 2.5F splines on its distal tip with each spline containing 4 platinum-iridium electrodes that were used for recording unipolar electrograms. Epicardial mapping was achieved by positioning of the grid catheter over the lateral wall of the RA covering the trabeculated region between the crista terminalis and the tricuspid annulus. Simultaneously, endocardial mapping was performed by

manually inserting the catheter through the 9F introducer into the right atrium via an incision in the right atrial appendage. Both the grid catheters were anchored proximally to maintain alignment and adequate contact confirmed by assessing real-time signal quality. The steerable nature of the HD Grid catheter allowed manoeuvring of both the catheters to ensure good contact without compromising alignment. CENTRAL ILLUSTRATION (A) and (B) show the illustration and an example photo of the mapping methodology used.

Atrial epi- and endocardial unipolar electrograms were simultaneously recorded using the EnSite Precision™ Cardiac Mapping System (Abbott, St. Paul, Minnesota, USA). EGM's were sampled at 1kHz and a filtering set to 0.1-500Hz. The sternal retractors were used for unipolar reference. A quadripolar catheter (Supreme™ 5F JSN, Abbott, St. Paul, Minnesota, USA) was used for pacing from the epicardial posterior RA and after determining pacing threshold, the pacing stimulus was set at 1.5 times the threshold. Rhythm recordings were made in the following sequence after confirming satisfactory catheter stability and adequate signal quality: (i) sinus rhythm (ii) continuous pacing for 30 seconds at 600 ms (iii) continuous pacing for 30 seconds at 400 ms, (iv) during programmed extra-stimulation at drive cycle of 400 ms incrementing the S_1S_2 interval (10 ms steps) from below atrial ERP to the first atrial capture beat 10 ms greater than ERP. Recordings were made from the propagation pattern of this beat.

Data Analysis

Analysis of each electrogram was performed offline using our custom-made software. Filtered unipolar EGM's were exported for signal processing (phase and activation analyses).

Phase analysis

Phase analysis was performed using MATLAB version R2018a (MathWorks Inc., Natick, Massachusetts, USA). Sinusoidal recomposition and instantaneous phase analysis have previously been described in detail [468] and can be summarized in the following steps: 1) electrogram is transformed using sinusoidal recomposition; 2) Hilbert transformation of the recomposed sinusoids; 3) followed by calculation of instantaneous phase. Far-field signals were digitally subtracted from the raw EGMs' using a template-matching algorithm before sinusoidal recomposition [469]. Signal phase at each location of the endocardial surface was compared to phase timing at the nearest location on the opposing epicardial surface during each rhythm. Dynamic phase maps were displayed on schematic diagrams of grid catheters and phase dispersion between epicardial and endocardial surfaces were calculated. A negative phase difference indicated that the endocardial activation preceded the epicardial surface while a positive difference indicated the converse. Comparisons of phase dispersion were then made between sinus rhythm, pacing drive at 600 ms and 400 ms and PES.

Activation analysis

Activation analysis was performed using a customized algorithm on MATLAB version R2018a (MathWorks Inc., Natick, Massachusetts, USA). After digitally subtracting far-field ventricular EGM's using a template-matching algorithm, local activation times of both the epicardial and endocardial surfaces were determined from the maximum deflection of every unipolar EGM on each electrode. All automated electrogram analyses were visually verified by two independent electrophysiologists to ensure accurate annotation of activation times. These activation times were displayed on schematic diagrams of the grid catheters as an activation time map. For all activation sequence maps, the differences between epicardial and endocardial activation times were calculated, and comparisons were made between each rhythm recording.

Wavefront propagation pattern

All wavefronts were analysed for endocardial-epicardial propagation symmetry. The entry and exit sites of each activation on the endocardial and epicardial grid were compared to determine this during sinus rhythm, pacing drive and PES. Activations were also carefully studied to identify any focal breakthroughs.

Signal fractionation

Electrogram morphology was analysed semi-automatically in MATLAB R2018a (MathWorks Inc., Natick, Massachusetts, USA) [470]. Electrograms with injury potentials were excluded from analysis. Based on previous work on unipolar EGM fractionation in sinus rhythm [467], we classified EGM's based on the number of deflections as there is no

uniform classification for grading unipolar electrogram morphology. Bipolar EGM's were defined based on previously described criteria [471]. All automated electrogram analyses were visually verified to ensure accurate classification of EGM's. Activation times of these fractionated EGM's were manually corrected if automated annotation were incorrect. Comparisons of the burden of fractionated EGM's were then made between the three rhythms. All fractionated EGM's defined by the algorithm were manually verified by two independent electrophysiologists with good interobserver agreement (κ: 0.9; 95% CI: 0.7 to 1.0).

Definitions

Endocardial-Epicardial Dissociation

We defined endocardial-epicardial dissociation as difference in phase or activation times ≥20ms between nearest electrodes on opposing surfaces of the atrium. Although there is no universally accepted definition of endocardial-epicardial dissociation a recent study mapping atrial fibrillation [155] used comparable criteria.

Electrogram fractionation

Data on criteria for fractionation on unipolar EGM's is limited and no standard criteria have been established for this. Based on a previously published mapping study on unipolar EGM's [467] we defined unipolar electrograms with ≥3 deflections as fractionated. An example of a fractionated EGM is shown in Figure 1.

Statistical analysis

Statistical analyses were performed using MINITAB (version 18, Minitab Inc., State College, Pennsylvania, USA). Continuous variables are displayed as mean ± SD or median (IQR). Categorical variables are presented as a number and percentage. The student-t-test, or its non-parametric equivalent, Mann-Whitney U test when appropriate was used for comparison of continuous variables. Fisher's exact test was used for the comparison of nominal variables. Kappa statistic was used to examine interobserver agreement. A p-value of <0.05 was considered significant.

RESULTS

Baseline characteristics

We included sixteen patients (12 men; 60.5±4.1years) who underwent cardiac surgery for coronary artery bypass grafting (n=7), mitral valve surgery (n=3), aortic valve replacement (n=4) and tricuspid valve surgery (n=1). One patient underwent bypass grafting and aortic valve replacement for concomitant severe aortic stenosis. A minority of patients (n=3) had a history of paroxysmal AF and all these patients had enlarged left atrium based on echocardiogram criteria. In total, LA enlargement was present in 6 (37.5%) patients in the entire cohort. Patients with history of AF had larger volumes than those without although this did not achieve statistical significance (76±14 vs 48.3±11.3 ml/m^2 BSA, p = 0.075). Clinical characteristics of the study population are provided in Table 1.

Functional Endocardial-Epicardial Dissociation

Phase mapping

A total of 10,724 EGMS's were analysed (1186 in SR, 7525 in pacing drive and 2013 in PES) with a mean of 670 EGM's per patient. Overall, 96.8% of the EGM's were deemed to be of adequate quality for analysis. The mean CL during sinus rhythm in our cohort was 900±120 ms. During SR, 90%±0.2% of epi-phase values were equal to or within 20 ms of the paired endo- phase value consistent with synchronous activation. However, with pacing drive at 600 ms, 400 ms and PES, this significantly reduced to 77.6%±0.4% ($p<0.0001$), 74.2%±0.8% ($p<0.0001$) and 66%±0.8% ($p<0.001$), respectively. Between 600 ms and 400 ms cycle lengths of pacing drive, there was no significant differences in endocardial-epicardial dissociation (22.4% vs 25.8%, $p = 0.084$). CENTRAL ILLUSTRATION (C), demonstrates the increasing functional dispersion of endocardial-epicardial phase timing while moving from sinus to pacing drive and PES. Supplementary Table 1 shows percentages of dissociated activations in each patient during SR, pacing at 600 ms, 400 ms and PES.

Activation mapping

Analysis of the activation maps showed 92.2% of the activations were synchronous during SR and in comparison to this, a significantly less number of activations were synchronous during pacing drive at 600 ms CL (74.6% vs 92.2, $p<0.0001$), 400 ms CL (72.3% vs 92.2%, $p<0.0001$) and PES (70.5% vs 92.2%, $p<0.0001$). The proportion of dissociated activations also differed significantly between pacing drive at 600 ms and 400 ms with increased dissociation with the latter (Figure 2A).

Of the minority of activations that were dissociated during sinus rhythm, 59.7% showed earlier activation of the endocardium while the remaining 40.3% showed earlier activation of the epicardium.

Wavefront directionality

Endocardial-epicardial wavefront directionality of the 10,724 activations showed marked differences between SR, pacing drive and PES. CENTRAL ILLUSTRATION (D) shows isochronal maps of atrial activations progressive function endocardial-epicardial dissociation and wavefront asymmetry with pacing drive (400 ms) and PES when compared with sinus activation. During SR, 87.5% of wavefront propagations demonstrated endocardial-epicardial propagation symmetry. Figure 3 and Online Video 1 show an example of sinus rhythm activation with endocardial-epicardial propagation symmetry during simultaneous endocardial-epicardial mapping of the RA. The wavefront enters at A1 electrode and following a diagonal trajectory (white dashed arrows) exits at D4 electrode on both the endocardial and epicardial grid catheters. The isochronal map also shows the symmetrical propagation of the wavefront on both surfaces.

Endocardial-epicardial wavefront directionality was more frequently asymmetrical during PES and pacing drive (600 ms and 400 ms) compared to during sinus rhythm (48.8% vs 34.8 vs 12.5% respectively, p=0.033). Figures 4, Online video 2 shows and example of asymmetrical activation during epicardial pacing drive at 400 ms cycle length in the same patient. The wavefront is seen entering the epicardial grid at A2 electrode and follows a direct course diagonally (white dashed arrows) and exits at C4 electrode while in the endocardial

grid the wave-front enters at A2 and A3 electrodes and follows an asymmetrical course to exit at D1 electrode. Figure 5, Online Video 3 shows an example of asymmetrical activation during epicardial premature extra-stimulation in the same patient. The wavefront directionality is markedly different with propagation from A1 to D4 electrodes diagonally (white dashed arrows) on the epicardial grid and a circuitous propagation in the opposite direction on the endocardial grid proceeding from D1 to D4 electrodes (yellow dashed arrows). The isochronal map also represents the markedly different wavefront propagation patterns between the two surfaces.

Electrogram fractionation:

Unipolar electrograms

Using the semi-automated algorithm, 39.5% of the EGM's during sinus rhythm satisfied the definition for fractionation. The overall proportion of fractionated EGMs' significantly increased from 39.5% in SR to 50.2% during PES ($p<0.0001$), but not during pacing drive (40.1%, $p = 0.325$). However, no differences were observed in the proportion of fractionated EGM's recorded on the epicardial vs the endocardial surface in sinus rhythm, during pacing at 600 ms and 400 ms cycle lengths or with PES (Figure 6).

Bipolar electrograms

When compared to sinus rhythm, fractionation was significantly higher during pacing drive at 600 ms (Endo: 38.4% vs 28.9%, $p=0.002$; Epi:42.1% vs 29.9%, $p = 0.002$), 400 ms (Endo: 44% vs 28.9%, $p=0.0012$; Epi: 44.3% vs 30.1%, $p<0.0001$) and during PES (Endo: 48.9% vs 28.9%, $p<0.0001$; Epi: 54% vs 28.9%, $p<0.0001$). Overall, more bipolar EGM's on

the epicardial surface were fractionated than the endocardium during PES (54.1% vs 48.9%, p = 0.023).

Analyses of fractionation across the two orthogonal planes (vertical and horizontal) were also performed on EGM's from a total of 24 bipoles each on the endo- and epicardium respectively. This demonstrated that horizontal bipole electrodes configurations had higher degree of fractionation than vertically oriented bipoles during PES (Endocardium: 51.4% vs 46.4%, p=0.0284; Epicardium: 58.1% vs 48.9%, p = 0.001).

Subgroup analyses:

Functional dissociation was also compared in the subgroups of patients based on LA size and history of AF.

The proportion of functionally dissociated activations did not differ between patients with enlarged LA (n=6) and those without, during sinus rhythm (10.3% vs 9.3%, p = 0.393), pacing at 600 ms CL (26.4 vs 24.3%, p = 0.192), 400 ms CL (28.5% vs 26.2%, p = 0.167) and premature extra-stimulation (29.3% vs 27.4%, p = 0.507).

Among the patients with enlarged LA, those who also had a history of AF had a significantly larger proportion of functionally dissociated activations than those without history of AF during pacing drive (@ 600 ms CL: 29.9% vs 23.1%, p = 0.0008; @400 ms CL: 30.9% vs 25.4%, p = 0.031) and premature extra-stimulation (33.8% vs 23.8%, p = 0.0410) but not during sinus rhythm (13.2% vs 9.2, p = 0.165)

DISCUSSION

Simultaneous high density endocardial-epicardial mapping of the right atrium in the presence of structural heart disease revealed the following key findings:

1) Significant functional electrical dissociation (as evidenced by phase dispersion, activation timing differences and differences in wave-front directionality).
2) Proportionally more fractionated unipolar EGM's during PES and pacing drive when compared to sinus rhythm in both the epicardial and endocardial layers

This study provides compelling evidence for the first time, of the 3-Dimensional nature of functional atrial substrate.

The concept of functional dissociation was first demonstrated in the isolated atrium of normal dogs by Schuessler et al [149]. Regional endocardial-epicardial dissociation was observed in certain parts of the atrium and the dispersion of time differences increased after premature stimulation compared with sinus rhythm. Differences in the activation sequence correlated with the underlying anatomic architecture with the largest differences in activation times between the epicardium and endocardium in those regions of the atrium where pectinate muscles ran below the epicardial surface. Discordant activation was also found in regions where the atrial wall thickness was <0.5 mm and correlated with transmural differences in fibre orientation. Subsequent in vivo studies have also demonstrated endocardial-epicardial dissociation. In a study in goats with varying AF duration, Eckstein et al demonstrated that dyssynchronous activity

increased progressively from 17% during acute AF to 68% after 6 months of AF [151] Dissociation was more pronounced in thicker parts of the atrial wall. The increase in dissociation was due to progressive uncoupling between the epicardial layer and the endocardial bundles and resulted in increasing stability and complexity of the AF substrate.

In humans, high density epicardial mapping studies in persistent AF have also shown longitudinal dissociation of muscle bundles within the atrium presumably as a result of extensive atrial remodelling and development of fibrosis [123,154]. These epicardial mapping studies observed the presence of focal atrial activations which were hypothesised to represent endocardial-epicardial breakthrough. A study of perfused human right atria from explanted diseased hearts using both optical mapping and MRI defined anatomy of muscle bundles demonstrated that complex atrial microstructure caused significant differences between endocardial and epicardial activation. In this study, pinacidil-induced AF was driven by intramural re-entry anchored to fibrosis-insulated atrial bundles [472]. More recently, simultaneous epicardial-endocardial high-density mapping of AF in humans undergoing cardiac surgery demonstrated evidence of right atrial endocardial-epicardial dissociation during persistent AF [155]. In that study a clamp made of 2 rectangular electrode arrays was inserted into an incision in the right atrial appendage. Recordings of 10 seconds of AF were analysed with demonstration of asynchronous endo-epicardial activation in a high proportion of maps. In this study, the majority of focal fibrillation waves could be attributed to endo-epicardial excitation. Recent mapping studies also suggest the presence of endocardial-epicardial dissociation

during sinus rhythm [467]. In that study, a significantly higher proportion of epicardial-endocardial dissociation was demonstrated in sinus rhythm in the superior RA than in the mid and inferior RA (57% vs 19% vs 12%). The authors attributed the fibrous case surrounding the sinus node and the thickness of the anisotropic terminal crest to this regional variation and susceptibility of the superior RA to delays in activation and consequent dissociation.

In the current study we extend these observations by demonstrating for the first time, the functional nature of endocardial-epicardial dissociation in the human atrium. While our study demonstrated that for the most part activation was synchronous during sinus rhythm, wave-front propagation and activation timing became markedly dyssynchronous during pacing and PES with the observation that endocardial and epicardial wavefronts could occur in opposite and frequently markedly circuitous directions. This highly functional nature of the atrial substrate in humans with structural heart disease may in part explain why so many mapping studies have observed the instability of atrial activation patterns during persistent AF. The patients with history of AF and enlarged LA had significantly more functional dissociation than those without history of AF in our cohort. Although this number is small in our cohort, the study also highlights that even in early stages of remodelling, functional epicardial endocardial dissociation produces an environment suitable for the maintenance of atrial arrhythmias.

Van der Does et al previously demonstrated that endocardial-epicardial dissociation contributes to electrogram fractionation during sinus rhythm mapping [467]. By correlating

fractionation to spatial activation patterns, they demonstrated that remote activation was responsible for most fractionated deflections in sinus rhythm. As in the current study, fractionation was similar when comparing the endocardial with the epicardial recordings. We extend these observations by demonstrating that with increasing functional endocardial-epicardial dissociation, fractionation also increases presumably due to recording of more dyssynchronous far-field activations.

Limitations

We have demonstrated functional endocardial-epicardial dissociation in the lateral right atrium when pacing from the epicardial aspect of the right atrium. Whether this exists in other anatomic regions and when pacing from the endocardium could not be addressed by the current protocol. The findings of the current study are also confined to the RA only. While it might be anticipated that the electrophysiological properties of the LA would be similar to that of RA, simultaneous endocardial-epicardial mapping of LA was not performed.

CONCLUSION

Simultaneous endocardial-epicardial mapping of the right atrium in the presence of structural heart disease shows novel evidence of functional electrical dissociation along with increased signal complexities and conduction slowing. This study provides compelling evidence of the 3-dimensional nature of functional atrial substrate and may in part explain the propensity for development of atrial fibrillation in this cohort.

TABLES AND FIGURES

Table 1: Baseline characteristics

Number of Patients	16
Age in years, mean±SD	60.5±4.1
Gender, n (%)	
Males	12 (75)
Females	4 (25)
BMI, mean±SD	33.7±3.5
History of Atrial Fibrillation, n (%)	3 (18.7%)
Diabetes mellitus, n (%)	11 (68.7)
Hypertension, n (%)	12 (75)
Cerebrovascular accident, n (%)	1 (6.2)
Underlying cardiac disease, n (%)	
Coronary artery disease	8 (50)
Aortic Stenosis	4 (25)
Aortic Regurgitation	1 (6.2)
Mitral regurgitation	2 (12.5)
Mitral Stenosis	1 (6.2)
Tricuspid Regurgitation	1 (6.2)
Left atrial dilation n (%)	6 (37.5)
Impaired Left ventricular function, n (%)	7 (43.75)

CENTRAL ILLUSTRATION: Simultaneous endocardial-epicardial mapping of the right atrium. Illustration (A) and photograph (B) of simultaneous epicardial and endocardial mapping of the RA lateral wall using two HD grid catheters is shown along with an epicardial quadripolar pacing catheter (orange). SVC: superior vena cava, IVC: inferior vena cava, RAA: right atrial appendage, RA: right atrium, RV: right ventricle, AO: aorta. (C) Phase mapping showing increasing dispersion of signal phase between the epicardial and endocardial surfaces with progression from sinus rhythm (SR) to pacing and programmed stimulation (PES). (D) Isochronal maps of an activation showing increasing functional dissociation with circuitous wavefront propagation, conduction slowing (isochronal crowding) and marked wavefront propagation asymmetry (yellow dot arrows) with progressive change from SR to pacing to PES.

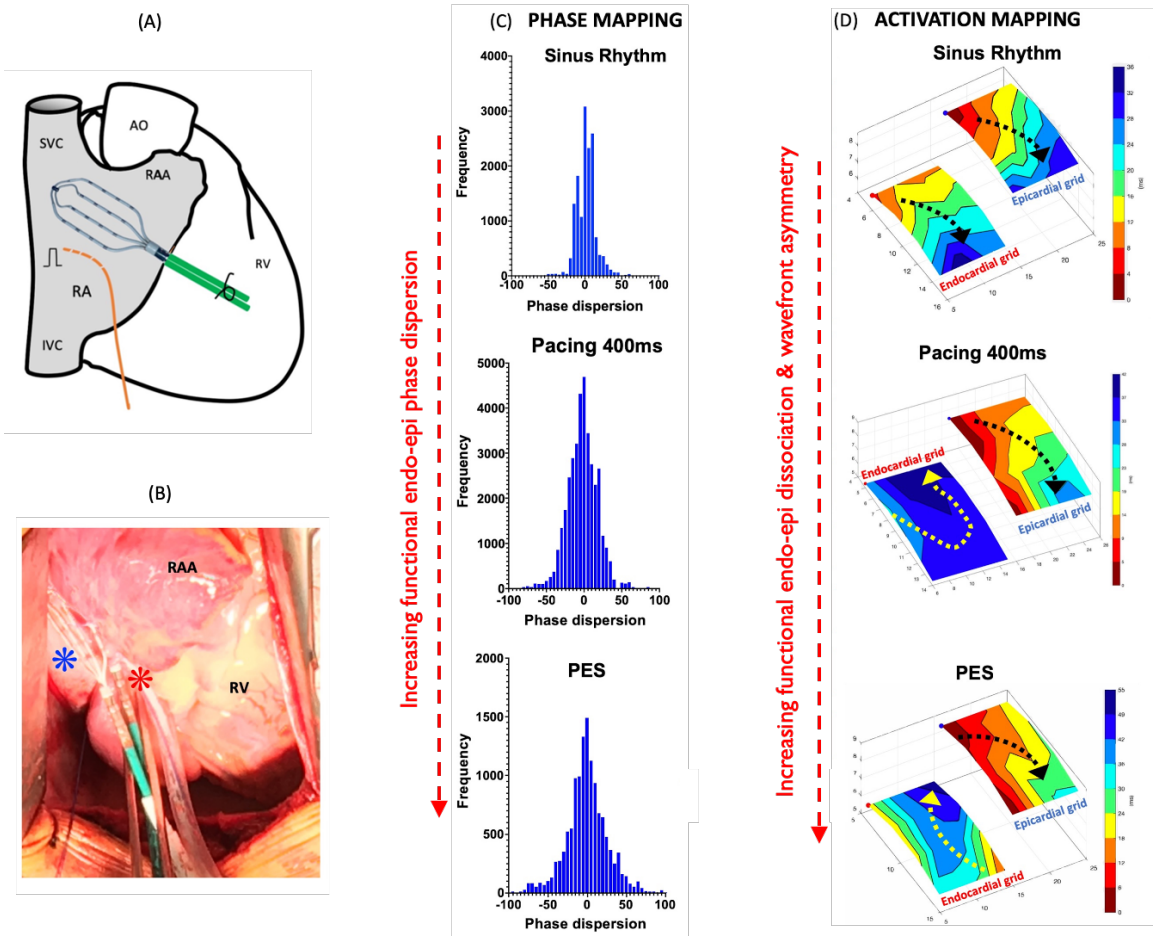


Figure 1: Examples of normal and fractionated unipolar electrograms. Asterisks (∗) correspond to peak-to-peak amplitude marks - where two asterisks indicate one deflection. Circles (○) indicate the local activation time (defined by the deflection with maximum peak to peak amplitude)

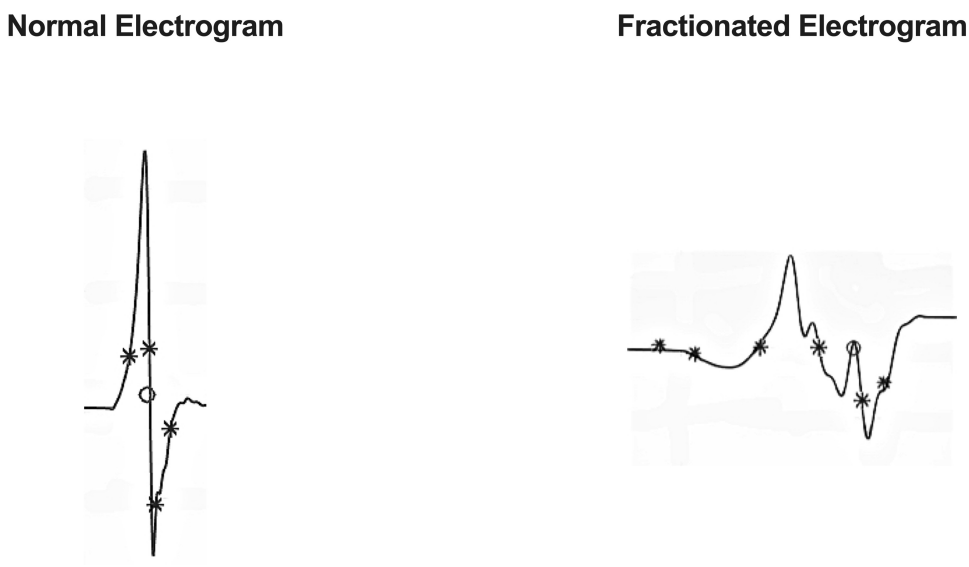


Figure 2: Functional endocardial-epicardial dissociation on activation mapping. (A) Bar diagrams showing the percentages of synchronous and dissociated activations with comparisons between sinus rhythm, pacing drive (600 ms and 400 ms) and premature extra-stimulation. (B) Bar diagrams showing the proportion of epicardial and endocardial exits among the dyssynchronous activations with comparisons between sinus rhythm, pacing drive (600 ms and 400 ms) and premature extra-stimulation showing preferential epicardial exits during premature extra-stimulation.

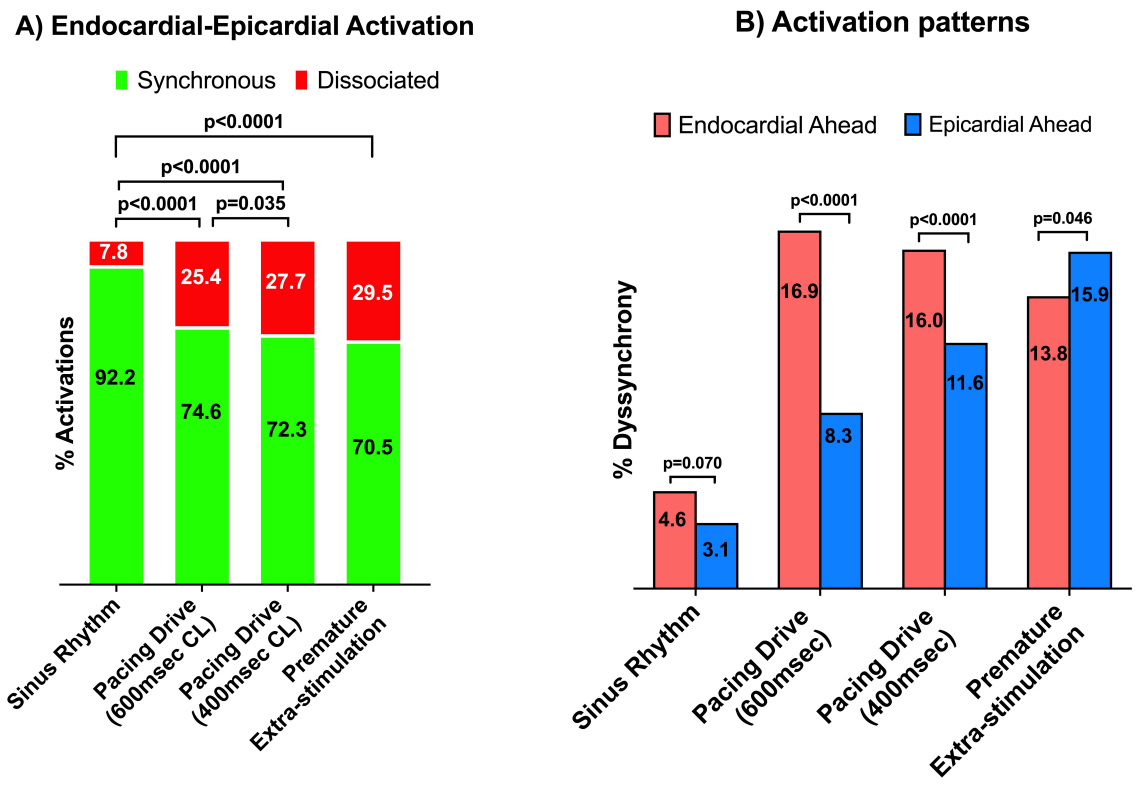


Figure 3: Example of a sinus rhythm atrial activation with simultaneous endocardial-epicardial mapping. **(A)** Shows atrial unipolar electrogram morphology with instantaneous phase and activation peaks at each electrode of the endocardial (red) and epicardial (blue) HD grid catheters. **(B)** Histogram of the proportion of synchronous and dissociated activations based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface. **(C)** and **(D)** Propagation and isochronal maps showing symmetric endocardial-epicardial wavefront propagation with the wavefront entry at A1 electrode and following a diagonal trajectory (white dashed arrows) exits at D4 electrode on both the endocardial and epicardial grid catheters.

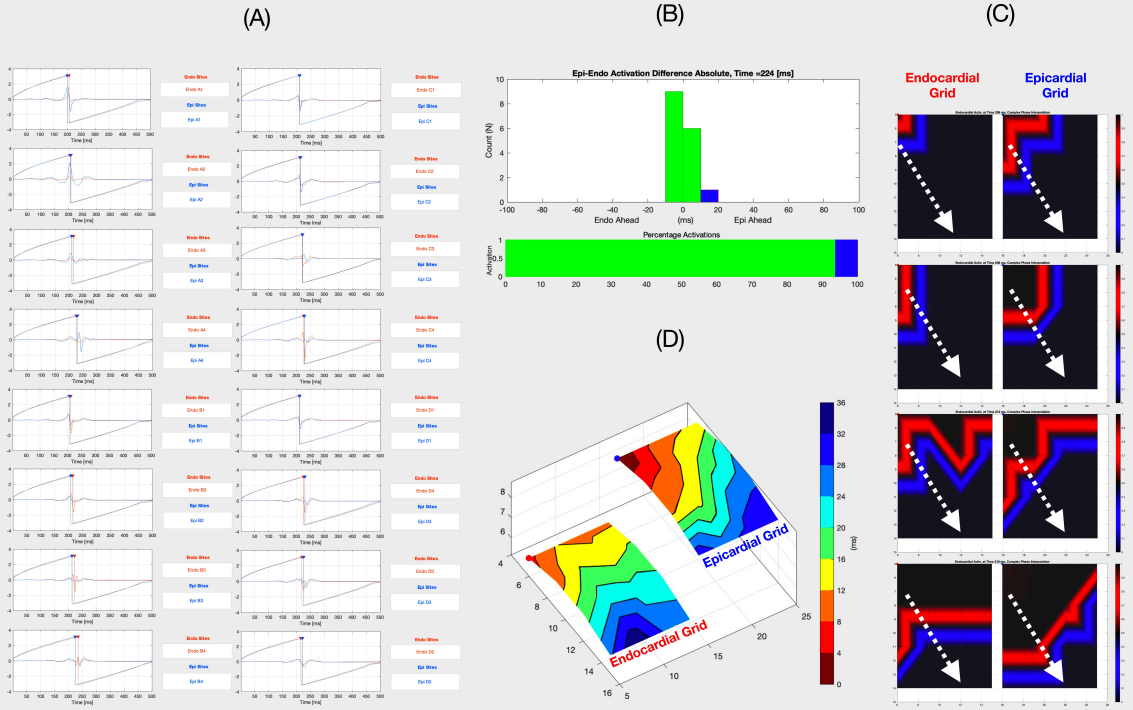


Figure 4: Example of atrial activation with simultaneous endocardial-epicardial mapping during epicardial pacing drive at 400 ms cycle length in the same patient. **(A)** Shows atrial unipolar electrogram morphology with instantaneous phase and activation peaks at each electrode of the endocardial (red) and epicardial (blue) HD grid catheters. **(B)** Histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface. **(C)** and **(D)** Wavefront propagation map and isochronal map showing the wavefront entering the epicardial grid at A2 electrode and follows a direct course diagonally (white dashed arrows) and exits at C4 electrode while in the endocardial grid the wave-front enters at A2 and A3 electrodes and follows an asymmetrical course to exit at D1 electrode.

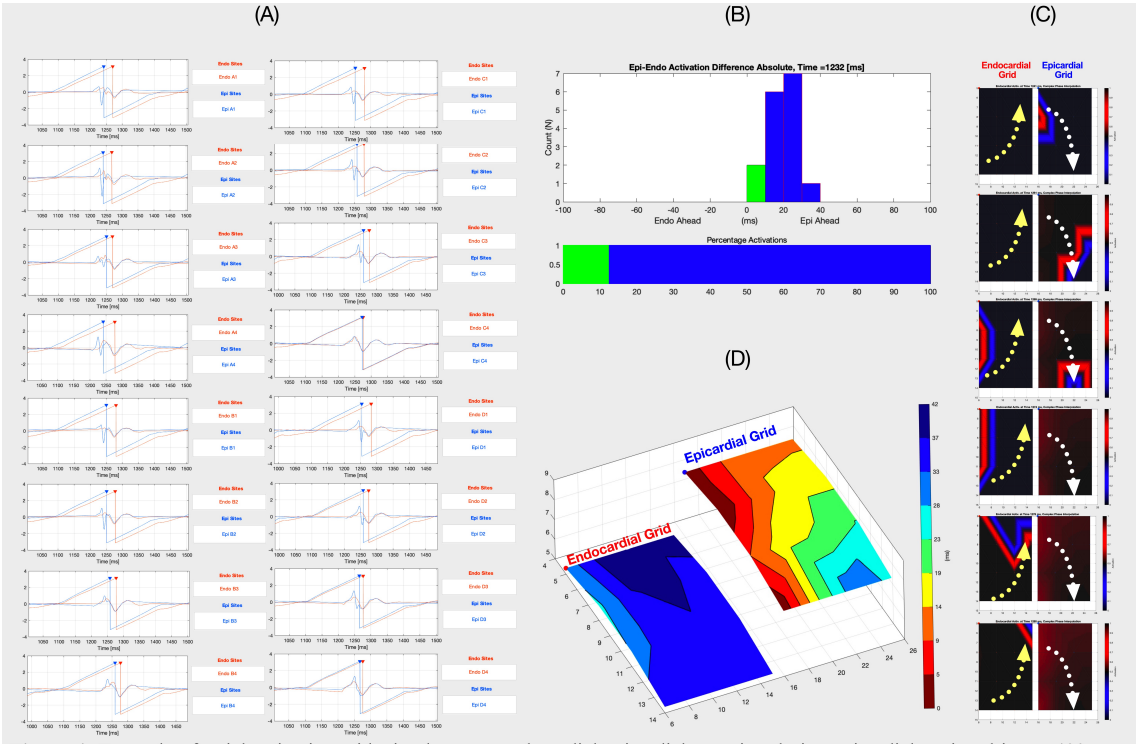


Figure 5: Example of atrial activation with simultaneous endocardial-epicardial mapping during premature extra-stimulation in the same patient. **(A)** Shows atrial unipolar electrogram morphology with instantaneous phase and activation peaks at each electrode of the endocardial (red) and epicardial (blue) HD grid catheters. **(B)** Histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface. **(C)** and **(D)** propagation and isochronal maps showing markedly asymmetric wavefront directionality with propagation from A1 to D4 electrodes diagonally (white dashed arrows) on the epicardial grid and a circuitous propagation in the opposite direction on the endocardial grid proceeding from D1 to D4 electrodes (yellow dashed arrows).

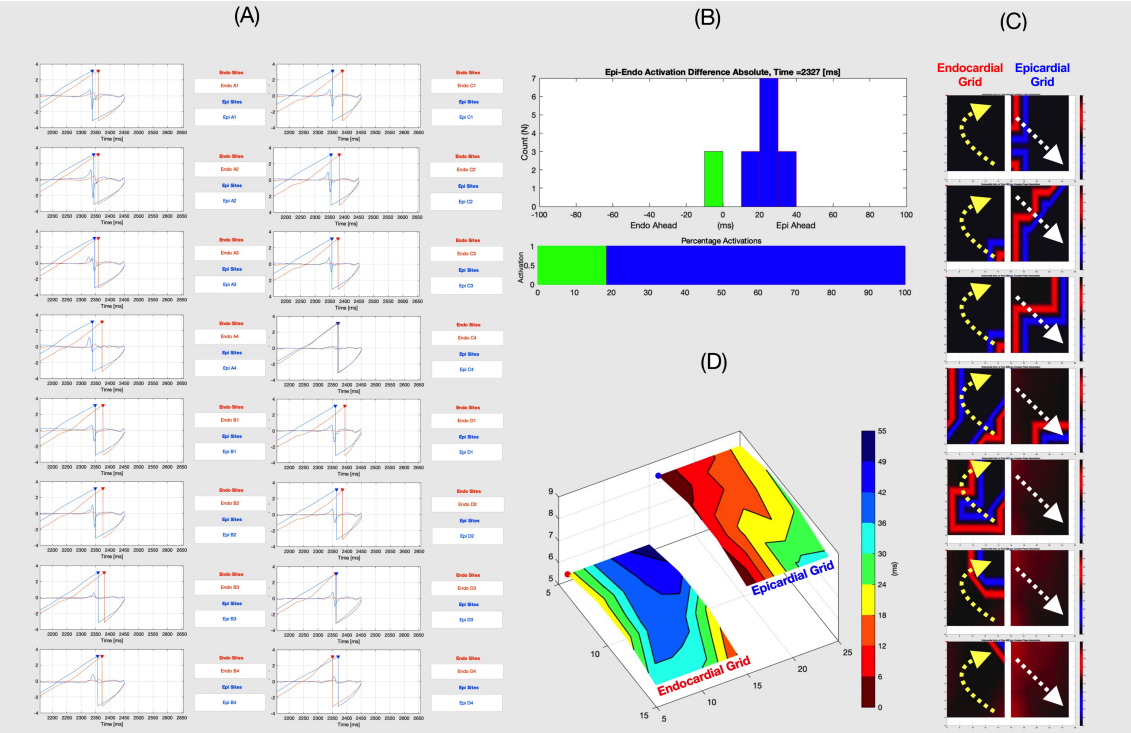
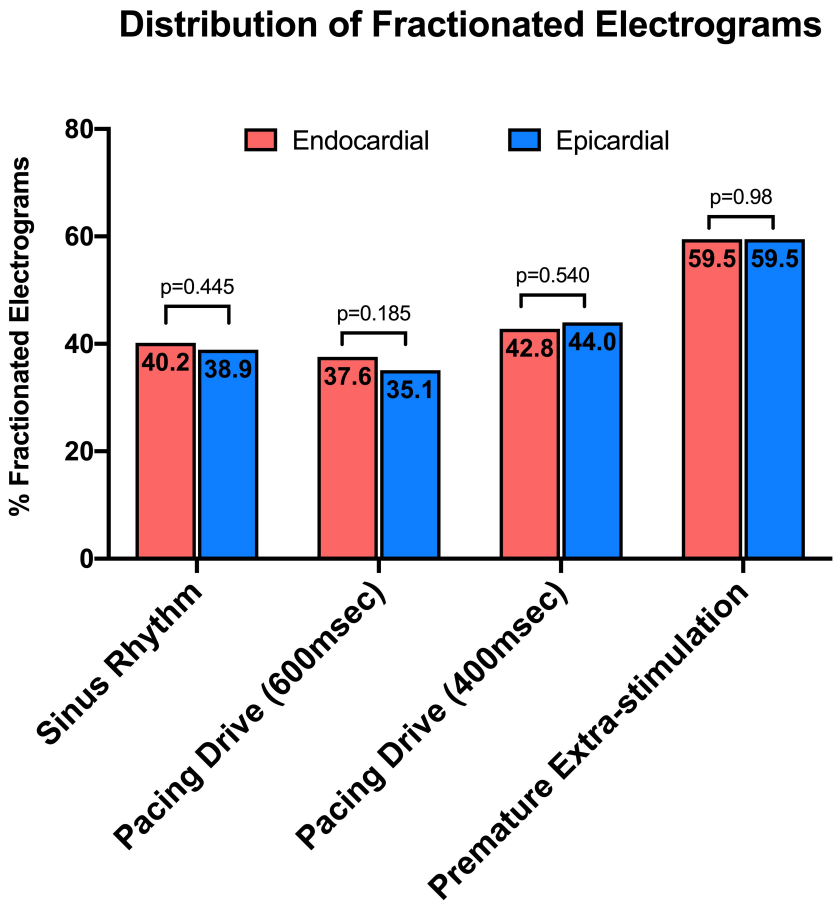


Figure 6: Bar diagrams showing distribution of fractionated electrograms on endocardial and epicardial surfaces. Significant increase in proportion of fractionated EGM's during PES is seen.



SUPPLEMENTARY MATERIAL

Table 1: Percentage of dissociated activations in each patient during sinus rhythm, pacing at 600 ms, 400 ms and during premature extra-stimulation with simultaneous endocardial-epicardial phase mapping.

Patient	SR	Pacing (600 ms)	Pacing (400 ms)	PES
Patient 1	10.26	21.37	25.47	33.25
Patient 2	10.02	23.85	26.74	34.90
Patient 3	10.21	22.45	26.85	32.20
Patient 4	9.84	22.04	26.35	33.60
Patient 5	11.23	21.92	25.92	35.00
Patient 6	10.25	22.61	27.05	34.95
Patient 7	9.97	23.35	24.65	34.60
Patient 8	9.63	22.86	26.93	34.58
Patient 9	10.10	21.50	25.85	32.90
Patient 10	10.85	22.15	26.17	34.00
Patient 11	9.78	21.85	24.75	33.65
Patient 12	11.23	22.95	25.45	35.08
Patient 13	10.29	22.25	24.15	33.05
Patient 14	10.73	21.95	24.30	31.90
Patient 15	9.91	24.05	26.15	34.90
Patient 16	9.70	22.35	24.80	33.30

SR, sinus rhythm; PES, premature extra-stimulation; ms, milliseconds

Online Video 1: Atrial activation with simultaneous endocardial-epicardial mapping during sinus rhythm. Dynamic propagation and isochronal maps showing symmetric wavefront propagation on endocardial and epicardial surfaces (white arrows) with synchronous activation.

Online Video 2: Atrial activation with simultaneous endocardial-epicardial mapping during epicardial pacing drive at 400ms cycle length in the same patient. Dynamic propagation and isochronal maps showing asymmetric wavefront propagation on endocardial surface (yellow dashed line) with dissociated activation.

Online Video 3: Atrial activation with simultaneous endocardial-epicardial mapping during epicardial premature extra-stimulation in the same patient. Dynamic propagation and isochronal maps showing asymmetric wavefront propagation on endocardial surface (yellow dashed line) with dissociated activation.

CHAPTER – 5

ENDOCARDIAL-EPICARDIAL PHASE MAPPING OF PROLONGED PERSISTENT ATRIAL FIBRILLATION RECORDINGS: HIGH PREVALENCE OF DISSOCIATED ACTIVATION PATTERNS

INTRODUCTION

The mechanisms underlying human persistent atrial fibrillation (PeAF) remain incompletely understood. Putative mechanisms have included multiple wavelet re-entry [473], single or multiple stationary or wandering rotors [85] and the presence of extra-pulmonary vein driving foci [376,474]. These mechanisms may not be mutually exclusive and may potentially co-exist in the same patient.

Recently, endocardial-epicardial dissociation (EED) has been recognised in certain anatomic regions of the atrium. Dissociation has both functional [475] and anatomic components [472] and has been described to play a role in 3-dimensional transmural rotors and in multiple dissociated wavelet break-through. A recent human study using simultaneous high-density endo-epicardial activation mapping of 10-seconds of AF [155] also revealed evidence of EED and regions of focal breakthrough.

In the current study, we performed simultaneous endo-epicardial phase mapping to facilitate analysis of more prolonged AF recordings in patients with PeAF undergoing

cardiac surgery. We aimed to characterise the degree of EED, to describe the simultaneous wave-front patterns and to analyse potential 3D driver characteristics.

METHODS

Study population

Patients with non-paroxysmal AF undergoing cardiac surgery for ischemic and/or valvular heart disease at Royal Melbourne Hospital, Melbourne, Australia were included. Patients with a history of catheter ablation for atrial arrhythmias were excluded. All patients gave written, informed consent prior to the surgery and the study protocol was approved by the research and ethics committee of Melbourne Health.

Data acquisition

Data acquisition for simultaneous endo-epicardial phase mapping has been described previously [475]. In brief, mapping of the antero-lateral right atrium (RA) was performed following median sternotomy and prior to cardiopulmonary bypass using two 16 electrode grid mapping catheters (Advisor™ HD Grid, Abbott, St. Paul, Minnesota, USA) with 3 mm inter-electrode spacing, one each for the epicardial and endocardial surfaces. Both the grid catheters were anchored proximally to maintain alignment and adequate contact confirmed by assessing real-time signal quality. Atrial epi- and endocardial EGM's (unipolar and bipolar) were simultaneously recorded using an electroanatomic mapping system (EnSite Precision™, Abbott, St. Paul, Minnesota, USA). EGM's were sampled at 2kHz and unipolar electrogram filtering set to 0.1-500Hz and bipolar electrogram filtering 30-500Hz. The sternal retractors were used for unipolar reference.

Data Analysis

Analysis of EGM's was performed offline using our custom-made software. Filtered EGM's (unipolar and bipolar) of 2-minutes continuous AF were exported for signal processing.

Phase analysis

Phase analysis was performed using MATLAB version R2018a (MathWorks Inc., Natick, Massachusetts, USA). Sinusoidal recomposition and instantaneous phase analysis have previously been described in detail [468] and can be summarized in the following steps: 1) digital subtraction of far-field ventricular signals from the filtered unipolar EGM's using a template-matching algorithm; 2) electrogram is then transformed using sinusoidal recomposition; 3) Hilbert transformation of the recomposed sinusoids; 4) calculation of instantaneous phase.

To determine endo-epicardial phase dispersion, signal phase at each location of the endocardial surface was compared to phase timing at opposing electrode location on the epicardial surface. Using the epicardial signal as reference, this was performed using a series of "Phase-Shift-Time-Windows" of interest which were created around each epicardial moment of activation time point (SUPPLEMENTARY MATERIAL: Figure 1). The width of the "Phase-Shift-Time-Window" was 200ms, centred around the moment of epicardial activation. The signal cross-correlation MATLAB function (Xcorr) was used to determine the phase difference between the epicardial phase signal compared to the matched endocardial phase signal. Phase dispersion was calculated in this manner for every activation in the 2-min of continuous AF. A negative phase difference indicated that

the endocardial activation preceded the epicardial surface while a positive difference indicated the converse.

We assessed for EED based on the difference in phase value between opposing endo-epi electrode pairs of ≥20ms, ≥30ms and ≥40ms but resorted to define EED as difference in phase value ≥20 ms between opposing endo-epi electrode pairs. Although there is no universally accepted definition of EED, we used this strict criterion based on prior comparable studies [155,475].

Wave front propagation patterns

Dynamic phase maps of 2-minutes continuous AF were displayed on schematic grid's for WF pattern analysis. Phase maps were analysed for potential drivers and agreement in WF patterns between endocardial and epicardial surfaces at each instance. As previously described[124], propagation patterns were classified as follows:

- Single wavefronts (SWF): Earliest activity at a discrete electrode site with subsequent linear activation of >3 adjacent electrodes at least 2 adjacent electrodes wide
- Multiple wavefronts (MWF): were defined as the presence of ≥2 simultaneous WF activating in a linear fashion.
- Focal activity: Repeated (at least 3 consecutive activations) earliest activation at a discrete electrode site in the centre of the grid catheter with centrifugal spread.
- Rotational Activity: Rotating WF with ≥ 2 revolutions

- Disorganized Activity: Any propagation pattern that did not fulfil the criteria for a WF or activations that occurred as isolated beats dissociated from activation of adjacent electrodes

Signal fractionation

Electrogram morphology was analysed in MATLAB R2018a (MathWorks Inc., Natick, Massachusetts, USA) using the semi-supervised clustering technique [470] based on the number of deflections and the percentage of sample duration it occupies. As previously published [471], bipolar EGM's with ≥5 deflections occupying at least 70% of sample duration were deemed complex and fractionated. An example of a complex fractionated bipolar EGM is shown in Figure 1. All fractionated EGM's defined by the algorithm were manually verified by two independent electrophysiologists and inter and intra-observer agreements were assessed.

Statistical analysis:

Statistical analyses were performed using MINITAB (version 18, Minitab Inc., State College, Pennsylvania, USA). Continuous variables are displayed as mean ± SD or median (IQR). Categorical variables are presented as a number and percentage. The student-t-test, or its non-parametric equivalent, Mann-Whitney U test when appropriate was used for comparison of continuous variables. Fisher's exact test was used for the comparison of nominal variables. Kappa statistic was used to examine interobserver agreement. Temporal heterogeneity in endo-epicardial dissociation was assessed using repeated measures ANOVA. A p-value of <0.05 was considered significant.

RESULTS

Baseline characteristics

We included fourteen patients (9 men; 64.5±4.8years) who underwent cardiac surgery for coronary artery bypass grafting (CABG) (n=6), mitral valve surgery (n=6), aortic valve replacement (n=1) and tricuspid valve surgery (n=1). Majority of the patients had LSPeAF (71.4%) and all had bi-atrial dilatation with a mean LA volume of 55±19.7 ml/m^2 BSA. The mean AF cycle length was 178±97 ms. Clinical characteristics of the study population are provided in Table 1. Baseline characteristics did not differ between patients undergoing surgery for ischemic heart disease and valvulopathy as shown in Table 2.

Endocardial-Epicardial Dissociation

Simultaneous endocardial-epicardial phase mapping of 2-min continuous AF revealed 49.7% of activations to be synchronous. Of the dissociated activations (50.3%), activation was more often earlier on the endocardium compared to the epicardium (29.2 vs 21.1%, p = 0.0001). EED showed significant correlation with LA volume (Spearman rho 0.60, 95% CI 0.07 - 0.85, p=0.028). The prevalence of dissociated activations did not differ significantly between patients undergoing CABG and valve surgery (50.2±5.2% vs 49.6±6.8%, p=0.873). Figure 2 shows the wide phase dispersion and the overall preferential activation in the 2-min continuous AF analysed. SUPPLEMENTARY MATERIAL: Table I shows the proportion of dissociated activations with the criteria of 30ms and 40ms.

Temporal Heterogeneity in Activation

Analysing preferential activation in 10-seconds aliquots, there was marked temporal heterogeneity in the preferential activation ($p<0.0001$). Within the 2-min mapped segment, endocardial activation occurred prior to epicardial activation in 7/12 10-seconds segments while in 5/12, the epicardium occurred earlier than the endocardium. Figure 3 shows the dot plots and means of preferential activation during each 10-second aliquot.

Wavefront Propagation Patterns

Across 14 patients, a total of 7,845 activation patterns were evaluated. WF propagation patterns were highly heterogeneous with multiple unstable patterns transitioning from one to another on the endocardial and epicardial surfaces in all patients. Figure 4 shows the overall prevalence of the various activation patterns on the endocardium and epicardium in the cohort. Figure 5 shows the distribution of the WF patterns on the endo and epicardial surfaces on a per patient basis.

The commonest WF patterns observed on simultaneous endo-epicardial AF mapping were disorganised activity which was more prevalent on the epicardium than the endocardium (Endo: 41.3% vs Epi: 46.8%, $p=0.0194$) and single WF (Endo: 31.3% vs Epi: 28.1%, $p=0.129$). Among the SWF, 76% displayed symmetrical WF directionality. MWF accounted for a minority of activations (Endo: 5.4% vs Epi: MWF 5.9%, $p=0.204$) and all comprised of two wavefronts colliding to dissipate as a SWF. SUPPLEMENTARY MATERIAL: Video 1-3 show examples of single wave front, disorganised activity and multiple wave front respectively.

Transient rotational activity was observed in 22% on the endo and 19.2% on the epicardium. The median number of revolutions per instance was 2 and their mean duration was 590±140 ms. All rotational activations were highly unstable and none of them sustained for ≥ 3 revolutions. SUPPLEMENTARY MATERIAL: Videos 3-5 show examples of rotational activity independently occurring on the endo and epicardial surfaces (Video 4), only on the epicardium (Video 5) and only on the endocardium (Video 6). In 4/14 patients (28.5%) transient rotational activations were recurrent at the same site with a mean recurrence 1.75±0.4 per patient. Recurrences of rotational activity maintained the same orientation during all instances. SUPPLEMENTARY MATERIAL: Figure II shows an example each of recurring unstable rotations on the endocardium and epicardium respectively.

In 2/14 patients (9% maps), rotational activity appeared to show transmural migration. In all of these instances (n=6), the rotational activity migrated from the epi- to the endocardium. Figure 6 shows an example of epicardial-endocardial migration of rotational activity. A clockwise rotation is seen between D2-D3 electrodes on the epicardium at 21061 ms which migrates to the endocardium at 21125 ms before dissipating as a single wave front at 21351 ms. SUPPLEMENTARY MATERIAL: Video 7 shows this example on dynamic phase maps Videos 6 shows an example of such apparent transmural migration of rotational activity from the epicardial to the endocardial grid.

Occasionally, isolated instances of focal activations were observed during the 2-min of persistent AF (Endo: 1.2%, Epi: 1.6%). All these activations were single and non-

sustained. Figure 7 shows two such examples on isochronal maps, one each on the endocardium and the other on the epicardium.

Furthermore, dynamic phase maps showed apparent earliest activation sites near the peripheral electrodes on the grid in all patients (Endo: 6±2.3%, Epi: 8±1.1%) but none satisfied the criteria for a focal driver. SUPPLEMENTARY MATERIAL: Figure III shows two isochronal maps of such peripheral sites of apparent earliest activation.

Comparing WF patterns between patients with coronary artery disease (CAD) and those with valvular heart disease (VHD), no differences were observed in the distribution of the different WF's except disorganized activity which was more prevalent in patients with VHD on the endo- and epicardium (CHD vs VHD: Endo – 38.1 vs 44.9%, p=0.003; Epi – 43.5 vs 49.8%, p=0.005). SUPPLEMENTARY MATERIAL: Figure IV shows the distribution of Endo-Epicardial WF patterns based on underlying cardiac disease. Disorganized activity was also more common on the epi than the endocardium in both subgroups (Endo vs Epi: CAD - 38.1 vs 43.5%, p=0.01, VHD - 44.9 vs 49.8%, p=0.03). SUPPLEMENTARY MATERIAL: Table II shows Endo-Epicardial WF Pattern comparisons between the CAD and VHD patients

Endocardial-Epicardial Wave front Discordance

During the 2-min continuous AF, although phase dispersion defined as a ≥20ms difference in activation timing was present in 50%, when we evaluated endo-epi wave front propagation patterns, these were discordant in 68.3±4.0%. Among different activation patterns, the proportion of wave front discordance was highest during

transient rotational activity (83.1±7.8%) followed by multiple WF (71.3±4.5%). Single WF showed maximal concordance with 54±8.1% of WF occurring symmetrically on the endo and epicardial surfaces.

Electrogram Fractionation

Overall, bipolar EGM fractionation was present significantly more frequently in the epicardium than on the endocardium (61.2% vs 51.6%, $p < 0.0001$). Regardless of the site of occurrence, rotational activations were associated with more fractionation than single WF (Endo: 44.1% vs 30.7%, $p<0.0001$; Epi: 49.8% vs 36.8%, $p<0.0001$).

DISCUSSION

In the current study we use simultaneous endo-epi phase mapping to characterise the activation patterns, EED and potential drivers during prolonged human persistent AF recordings. The key findings of this study are:

1. Significant functional EED (50.3%) with marked temporal heterogeneity.
2. Discordant endo-epicardial wave front patterns with multiple unstable wave-fronts transitioning from one pattern to another on both the endo- and epicardial surfaces in all patients.
3. Unstable rotational activity with endo-epi dissociation during the majority of observed rotations (i.e. rotational activity in 1 layer was usually not accompanied by a simultaneous rotation in the opposite layer) and possible transmural migration of rotational activations in 2 patients.

4. A higher prevalence of complex EGMs during more complex activation patterns such as rotational activity.

EED in AF was postulated as important to the mechanism sustaining AF more than two decades ago [149]. The role of underlying atrial architecture and structural remodelling on the development of EED has been elegantly described in animal studies [153,476]. Allessie and co-workers first inferred the presence of EED during human AF from epicardial mapping studies [123]. More recently, direct evidence of EED in humans was demonstrated by de Groot et al [155] who performed intraoperative endo-epicardial mapping of the RA wall using a customised high-density mapping plaque. Dyssynchronous activations ranged between 0.9 and 55.9% without preference for either side.

In the current study using simultaneous endo-epicardial phase mapping in patients with PeAF, approximately 50% of all activations showed EED. The observation that EED is transient indicates a significant functional component consistent with prior pacing studies [475]. While activations were preferentially earlier on the endocardium overall, within the 2-minutes of continuous AF mapped, there was significant temporal heterogeneity with preferential activation transitioning between the endo and epicardial surfaces when comparing each 10-second aliquots. Frequent transitioning of preferential activation between the myocardial layers of the atrium is indicative of the highly dynamic 3-dimensional nature of the pathophysiology and could explain why attempts at mapping exclusively from either surface may fail to identify potentially important drivers. The presence of extensive EED during persistent AF creates a functional and anatomic

substrate for localised re-entry and also increases the functional surface for fibrillation waves to coexist. Either mechanism might contribute to the stabilization of AF.

Unlike prior endo-epi mapping studies we did demonstrate a significant percent (approximately 20% of activation patterns) of rotational activity even at the mapped site in the RA. These rotations were transient (median number of rotations was 2) and tended to recur repeatedly during a 2-minute epoch. The reason for the discrepancy in the observation of rotational activation during endo-epi mapping is unclear but may relate to the differences in mapping techniques between studies. A prior mapping study suggested that phase mapping might create the appearance of a phase singularity when activation mapping indicated 2 passive wavefronts moving in opposite directions along a central line of block [477]. Nevertheless, the finding of transient rotational activity is consistent with other phase mapping and activation mapping studies [124,238,469,478]. These have been designated driver domains and have been considered to play a potential role in the stabilisation of AF. However, whether these are active drivers or passive patterns has not been established and cannot be answered by the current study.

Consistent with prior data [124,478], WF patterns were highly dynamic transitioning from one to another on both endo and epicardial surfaces. It is also noteworthy that nearly 70% of WF showed endo-epi discordance with the highest its prevalence of WF discordance among organised activations like rotations and multiple WF. Prior studies [155,479], have found a much higher incidence of focal activations than observed in the current study. These focal activations have predominantly been thought to represent endo-epi breakthrough sites rather than true focal drivers and rarely show sustained rapid and

repetitive firing. In contrast to previous demonstrations of focal breakthroughs as a consequence of EED, isolated focal activations from the central electrodes of the grid catheters were only sparsely observed (~ <2%) without preference for endo or epicardium. The limited number of central electrodes on the HD grid and the strict criteria for focal activation may have artificially reduced the observation of focal breakthroughs as seen in the current study.

Interestingly, in two patients, transmural migration of rotational activity was seen. While there is a possibility for this to be a result of two independent activation events one each on either myocardial surface of the atrium, the observation was consistently present in six instances all of which showed the rotation to migrate from the epi to the endocardium. This novel finding further reinforces the concept that there is a 3-dimensional substrate underlying the mechanisms of AF.

Consistent with prior studies, the current study indicated that electrogram complexity is associated with more complex wave-front activation patterns where fractionation may be associated with wavefront curvature and collision.

Limitations

Mapping of the LA was not undertaken due to the ethical issues and thromboembolic risks of mapping the endocardial LA and whether the results of this study could be extrapolated to the LA remains uncertain. It is also unclear if there is regional variation in endo-epicardial dissociation and driver distribution as in our study we restricted mapping to the anterolateral RA. The finite surface area of the HD grid catheter could have masked

the true prevalence of focal activity in our cohort as criteria-based detection warranted that earliest activation occur only in the central four electrodes of the grid catheter to enable demonstration of centrifugal spread. The finite number of mapping electrodes also precludes accurate phase singularity analysis and has limited spatial coverage. Patients with surgical disease may have more complex atrial substrates that may not reflect the mechanism of AF in paroxysmal or recent persistent AF patients.

CONCLUSION

Simultaneous endocardial-epicardial phase mapping of human PeAF shows compelling evidence for functional EED with activation discordance. The dominant patterns over prolonged recordings were single wave fronts and disorganized activity. However, transient rotational activity comprised approximately 20% of patterns and also demonstrated dissociation between the endo- and epicardial layers. Such complex 3D-interactions provide insight into why endocardial mapping alone may not fully characterise the AF mechanism.

TABLES AND FIGURES

Table 1: Patient characteristics

Age in years, mean±SD	64.5±4.8
Gender, n (%)	
Males	9 (64.2)
Females	5 (35.8)
Type of AF, n (%)	
Early persistent AF	2 (14.2)
Long standing persistent AF	10 (71.4)
Permanent AF	2 (14.2)
Duration of AF in months, mean±SD	18.2±11
Anti-arrhythmic drugs/Rate controllers, n (%)	
Beta-blockers	11 (78.5)
Calcium channel blockers	2 (14.2)
Digoxin	3 (21.4)
Sotalol	1 (7.1)
BMI, mean±SD	33.7±3.5
Diabetes mellitus, n (%)	8 (57.1)
Hypertension, n (%)	14 (100)
Underlying Cardiac Disease, n (%)	
Coronary artery disease	6 (42.9)
Valvular Disease	8 (57.1)
Aortic Stenosis	1
Mitral regurgitation	5
Mitral Stenosis	1
Tricuspid Regurgitation	1
Echocardiogram	
Bi-atrial dilatation, n (%)	14 (100)
LA volume in ml/m^2, mean±SD	55±19.7
Impaired LV function, n (%)	6 (42.8)
LVEF 45-55%	4 (28.5)
LVEF 35-45%	2 (14.2)

AF, atrial fibrillation; SD, Standard deviation; BMI, Body mass index; LA, Left atrium; LV, Left ventricle; EF, Ejection fraction.

Table 2: Baseline characteristics: CABG vs Valve Surgery

Patient Characteristic	CABG (n=6)	Valve surgery (n=8)	P value
Duration of AF, months	20.6±14.9	15.8±7.0	0.442
BMI	33.1±6.4	32.3±6.5	0.826
LA volume, ml/m^2	57.6±20.3	52.6±17.9	0.638
LV Ejection fraction, %	49.1±9.1	56.2±6.4	0.443

Values shown are mean ± SD. CABG, coronary artery bypass grafting; AF, atrial fibrillation; BMI, body mass index; LA, left atrium; LV, left ventricle

Graphic Abstract: Endocardial-epicardial phase mapping of prolonged persistent AF recordings

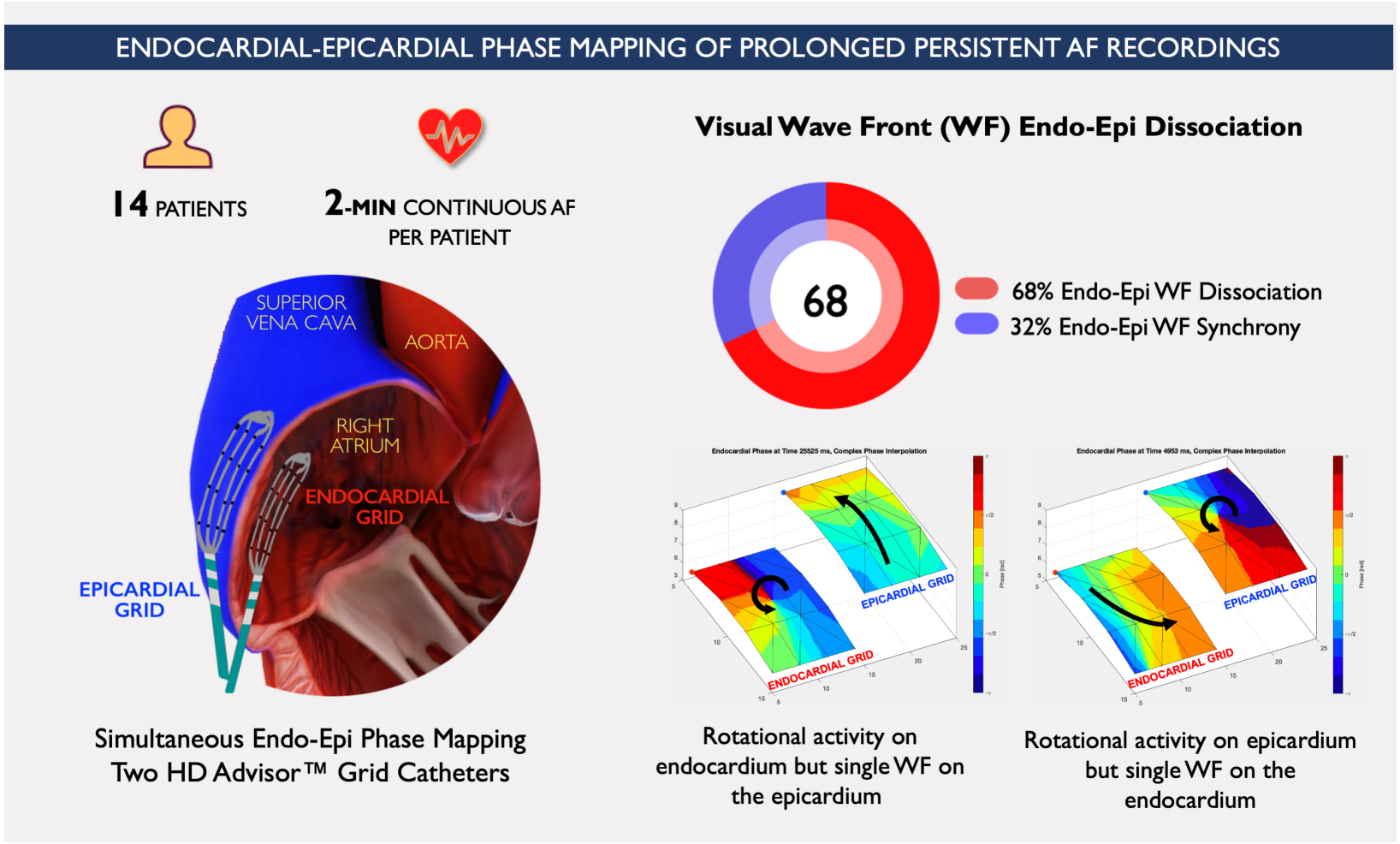


Figure 1: Examples of fractionated bipolar EGM. Asterisks (*) correspond to peak to peak amplitude marks - where two asterisks indicate one deflection. Circles (o) indicate the local activation time (defined by the deflection with maximum peak to peak amplitude)

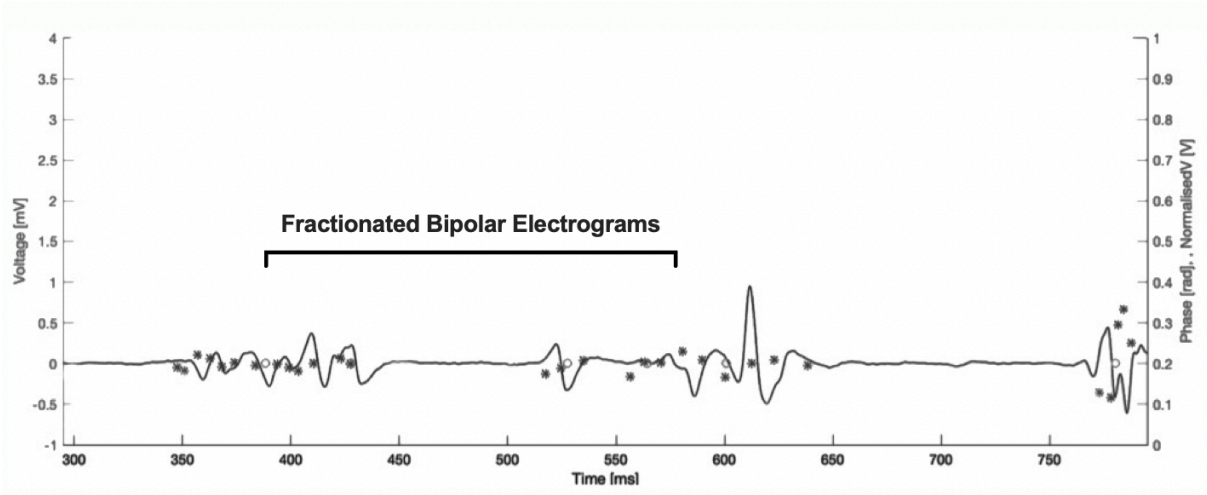


Figure 2: Phase dispersion on simultaneous endocardial-epicardial phase mapping of human persistent AF. Figure shows the frequency histograms of phase dispersion and the overall prevalence of endo-epicardial dissociation

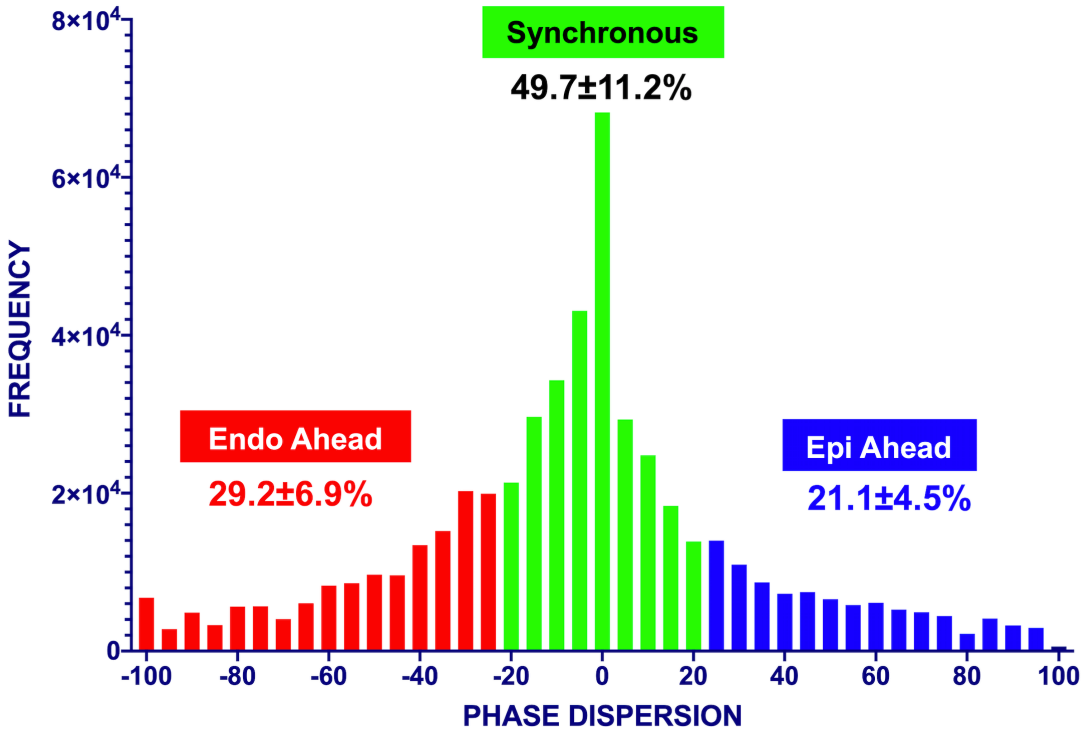
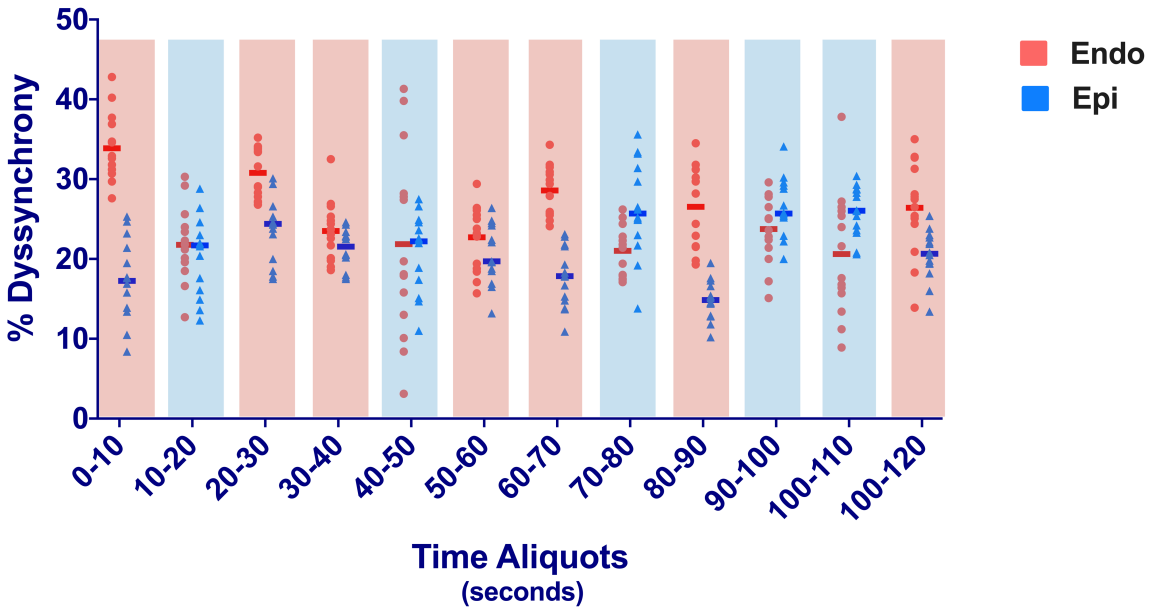
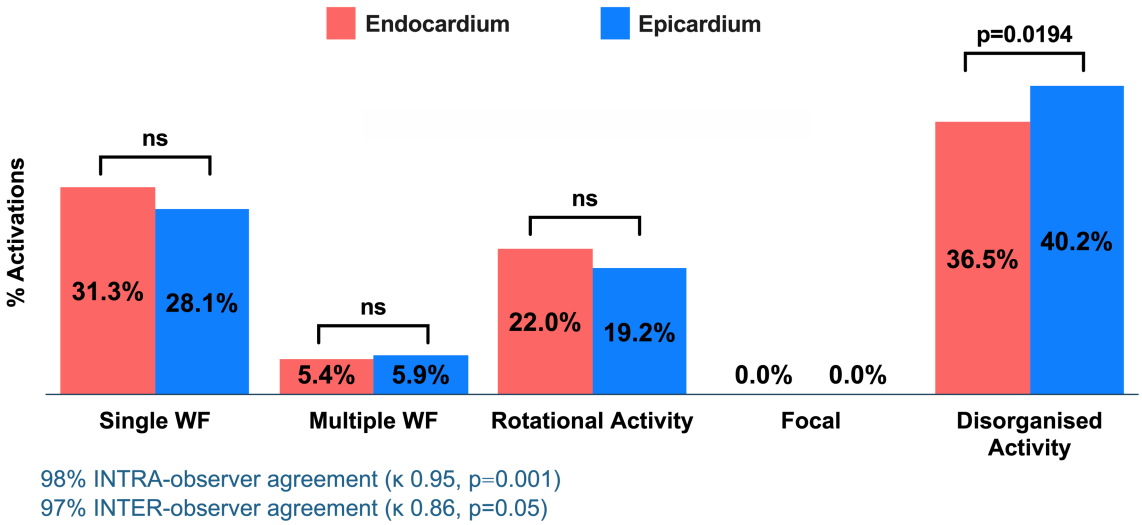


Figure 3: Temporal heterogeneity in endocardial-epicardial dissociation. Dot plots and means of the incidence of dissociated activations where endocardium vs epicardium is activated earlier in respect to the other within each of the 10-second aliquots of the continuous 2-minute duration mapped. Bars shaded in light red denote time segments where endocardial activation was preferentially earlier than the epicardium and those shaded in light blue represent time segments where epicardium was ahead of the endocardium.



One-way Repeated Measures ANOVA; F (6.076, 78.99) = 10.82, p<0.0001, Geisser-Greenhouse's ε=0.2642

Figure 4: Distribution of wave front propagation patterns on simultaneous endo-epicardial AF phase mapping. Bars represent the overall prevalence of wave front types on the endocardium (red) and epicardium (blue). Disorganised activity was the predominant pattern and was significantly more on the epicardium than the endocardium. WF, wave front.



98% INTRA-observer agreement (κ 0.95, p=0.001)
97% INTER-observer agreement (κ 0.86, p=0.05)

Figure 5: Wave front patterns in individual patients. Stacked bar diagrams represent the heterogenous distribution of wave front patterns on the endocardium (Panel A) and epicardium (Panel B) in individual patients.

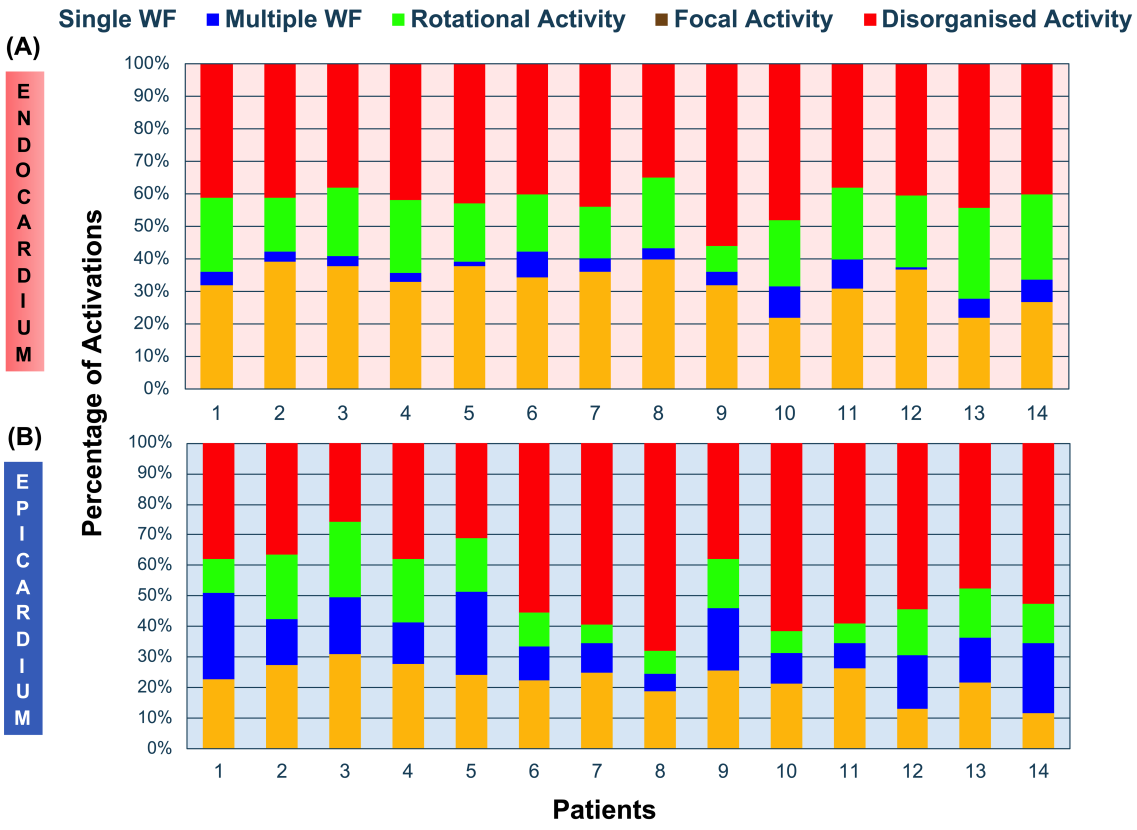


Figure 6: Transmural migration of rotational activity. An example of epi-endo migration of rotational activity is shown. A clockwise rotation is seen between D2-D3 electrodes on the epicardium at 21061 ms which migrates to the endocardium at 21097 ms before dissipating as a single wave front at 21351 ms. Online Video 7 shows this example on dynamic phase maps

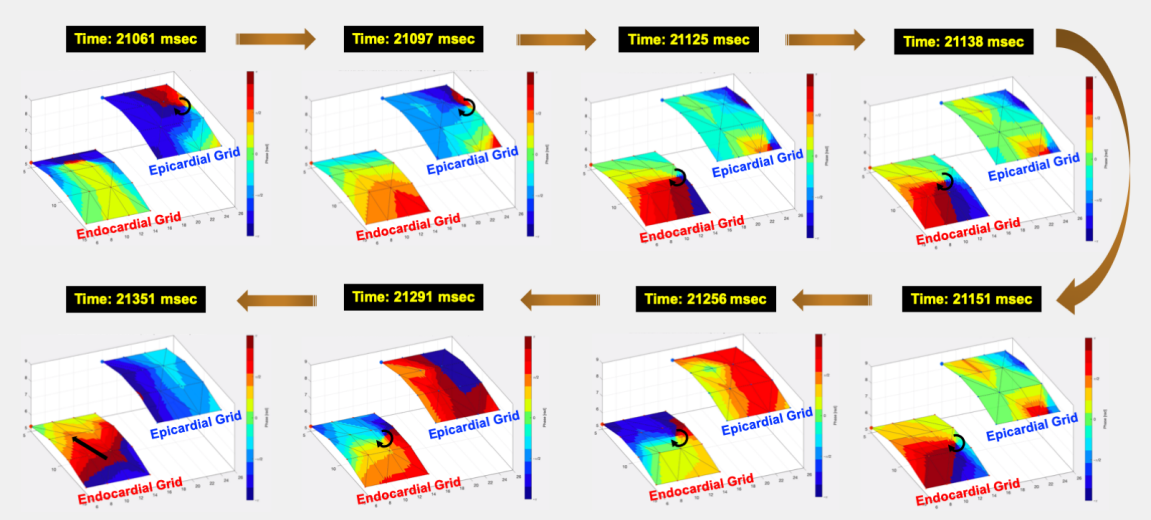
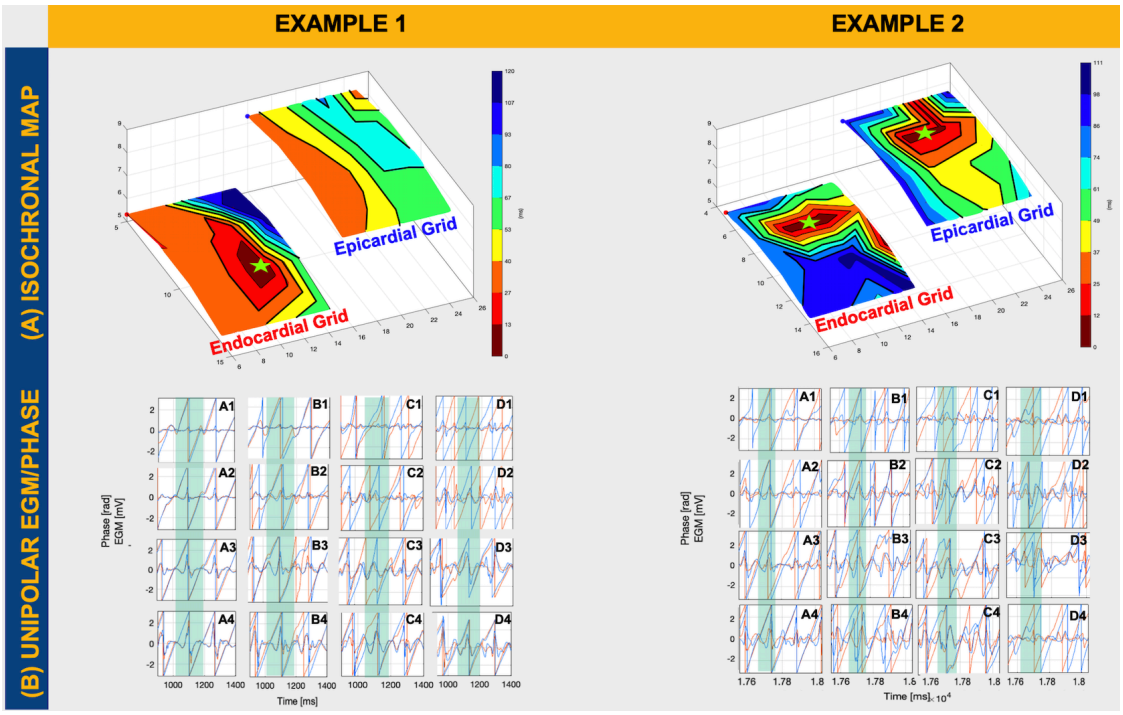


Figure 7: Examples of non-sustained focal activations during simultaneous endo-epi phase mapping of persistent AF. *Panel (A)* shows isochronal maps and *Panel (B)* represent the corresponding unipolar EGM and phase for the activation (respective EGM/Phase segments shaded in light green). In example 1, earliest activation is observed at the C3 electrode (green star) on the endocardium followed by centrifugal spread of the activation on the endocardium only. The epicardial activation is dissociated with no focal activity at the corresponding site. In example 2, simultaneous focal activations are seen on the endo- and epicardial surfaces over C2 electrode followed by centrifugal spread on both surfaces. EGM, Electrogram.



SUPPLEMENTARY MATERIAL

Table I: Endocardial-Epicardial Dissociation based on difference in phase values between opposing endo-epicardial electrode pairs.

Criteria for Endo-Epicardial dissociation	% Dissociated Activations	% Endocardial Ahead	% Epicardial Ahead
Difference ≥20ms between opposing endo-epi electrode pairs	50.3	29.2	21.1
Difference ≥30ms between opposing endo-epi electrode pairs	37.4	22.1	15.3
Difference ≥40ms between opposing endo-epi electrode pairs	28.6	17.0	11.6

ms, milliseconds

Table II: Endo-Epicardial Wave Front Patterns based on Underlying Cardiac Disease

Wave front Patterns (%)	Coronary artery disease			Valvular Heart Disease		
	Endo	Epi	P value	Endo	Epi	P value
Single WF	32.8	29.3	0.10	29.8	26.7	0.13
Multiple WF	4.4	5.2	0.32	5.9	6.3	0.66
Rotations	20.6	18.6	0.28	24	20.2	0.04
Disorganised Activity	38.1	43.5	0.01	44.9	49.8	0.03

WF, Wave fronts

Figure I: *Panels (A) and (B)* show sample unipolar EGM's and phase of 2-seconds of AF recorded at A3 electrode on the endocardial (red) and epicardial (blue) grid catheters. *Panel (C)* shows the time lag of the endocardial phase with reference to that of epicardium within the windows of interest (centered 200 ms around each epicardial phase crossing point (orange bar)). A negative phase-shift indicates that endocardial phase preceded epicardial phase and a positive phase-shift indicates that the epicardial phase preceded that of the endocardium. EGM: Electrogram, AF: Atrial fibrillation

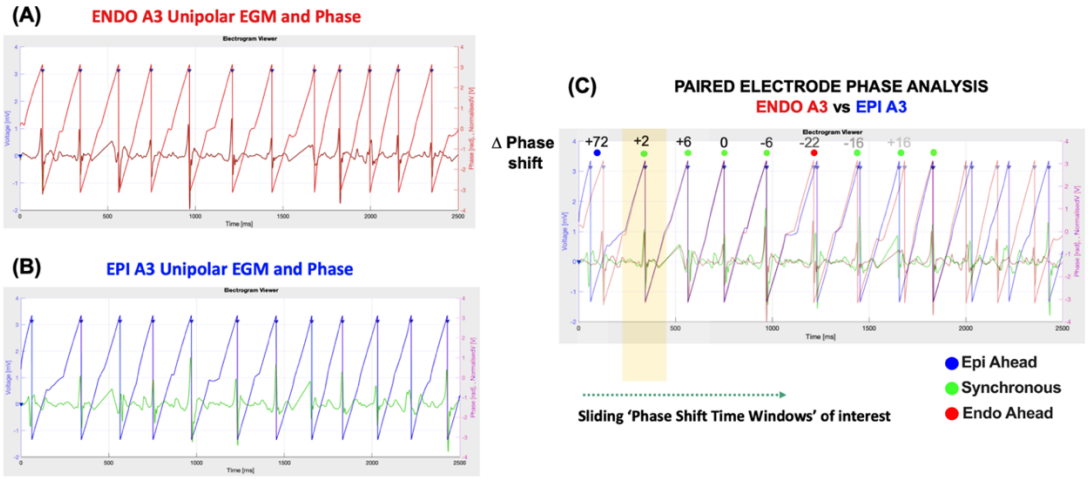


Figure II: Recurrence of Unstable Rotational Activity: Figures (A) and (B) show an example of recurrent counter-clockwise rotation on the endocardium between A2-B2 electrodes at 13070 and 18398 milliseconds respectively. Figures (C) and (D) show an example of recurrent counterclockwise rotation on the epicardium near B2 electrode at 1089 and 14188 milliseconds respectively.

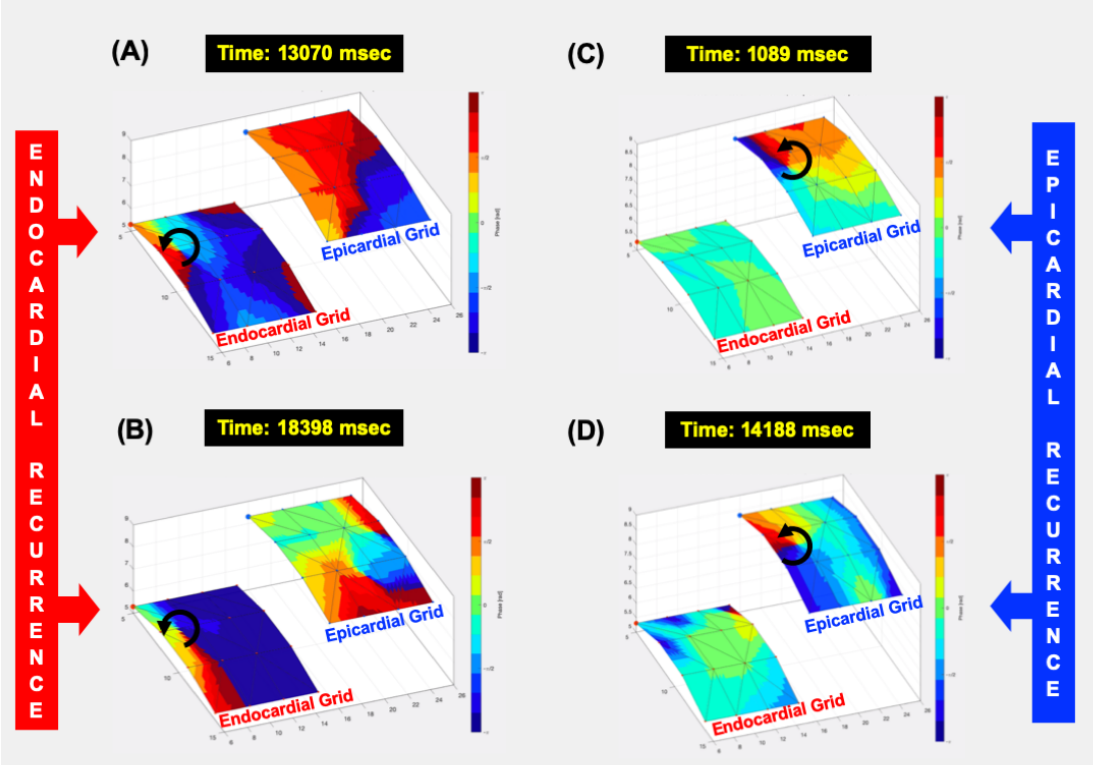


Figure III: Apparent Focal Activations during Simultaneous Endo-Epi Phase Mapping of Persistent AF. Isochronal maps (A) and (B) show examples of apparent focal activations (asterisks) on the endocardial grid catheters. Earliest activation appears to arise from a focal site on D2 electrode in map (A) and A1 electrode in map (B) respectively. Such activations were not classified as focal as accurate site of origin and centrifugal spread of activation could not be established.

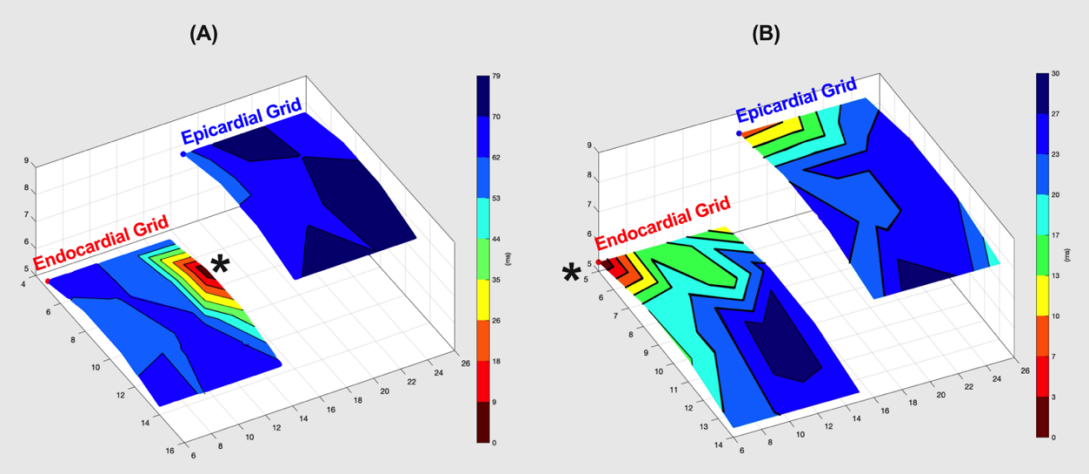
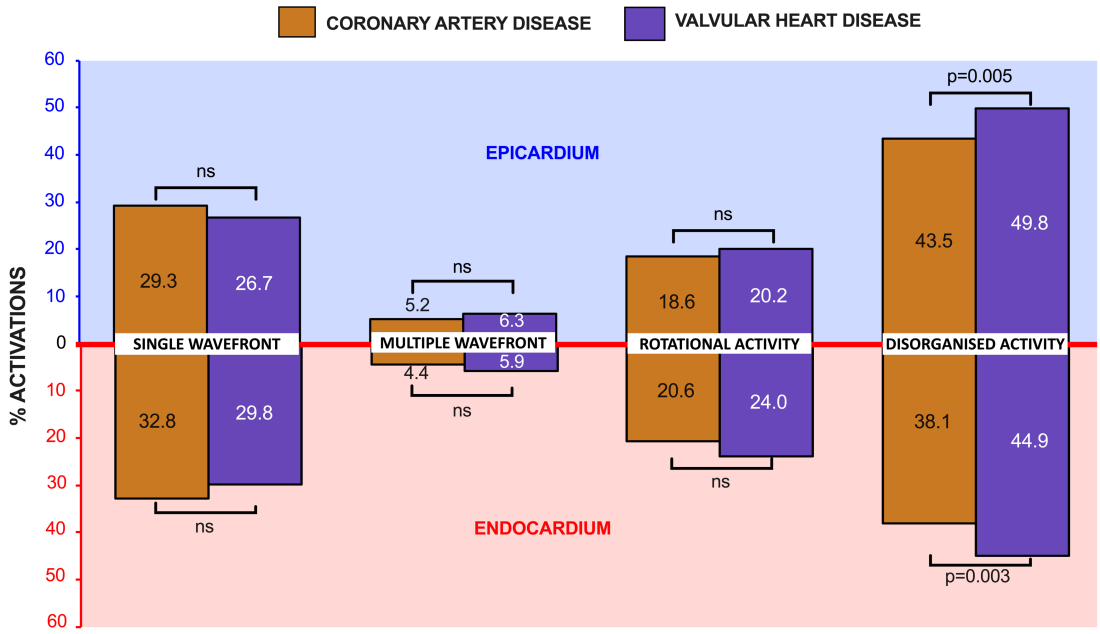


Figure IV: Distribution of Endocardial-Epicardial Wave Front Patterns based on Underlying Cardiac Disease. Bars represent percentage of activations of individual wave fronts on the endocardium (panel shaded in red) and epicardium (panel shaded in blue). ns, not significant.



VIDEO I: Example of a Single Wave Front during simultaneous Endo-Epi Phase Mapping of Persistent AF. Panel (A) shows dynamic phase map of persistent AF with a single broad wave front with asymmetric wave front propagation directionality (black arrows). On the endocardial grid the wave front starts at A1 electrode and courses diagonally towards D4 electrode and on the epicardial surface the wave front courses vertically from the superior to the inferior aspect of the grid. Panel (B) shows concurrent 'live stream' histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface.

VIDEO II: Example of Disorganized Activity on Simultaneous Endo-Epi Phase Mapping of Persistent AF. Panel (A) shows dynamic phase map of persistent AF with disorganized activity both on the endo and epicardial surfaces. Wave front patterns observed here did not satisfy the criteria for either linear, rotation or focal activity. Panel (B) shows concurrent 'live stream' histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface.

VIDEO III: Example of a Multiple Wave Front Pattern during simultaneous Endo-Epi Phase Mapping of Persistent AF. Panel (A) shows dynamic phase map of persistent AF where two wave fronts (black arrow) are seen on the epicardial grid which collide (green star) to dissipate as a single broad wave front that courses from D1 towards A4 electrode. Simultaneously on the endocardium, the phase map shows an unstable rotational activity

(moving from the centre of the grid towards B1/C1 electrodes) and a single broad wave front with directionality from A1 towards D2/D3 electrodes. Panel (B) shows concurrent 'live stream' histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface.

VIDEO IV: Example of a Transient Rotational Activity on Simultaneous Endo-Epi Phase Mapping of Persistent AF. Panel (A) shows dynamic phase map of persistent AF where two independent rotational activations are observed, one each on the endocardium (counterclockwise) and the other on the epicardium (clockwise). Panel (B) shows concurrent 'live stream' histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface.

VIDEO V: Example of a Transient Rotational Activity on the Endocardium. Panel (A) shows dynamic phase map of persistent AF wherein a rotational activity is seen on the endocardium while the epicardium is seen to have dissociated heterogenous wave front activations. Panel (B) shows concurrent 'live stream' histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface.

VIDEO VI: Example of a Transient Rotational Activity on the Epicardium. Panel (A) shows dynamic phase map of persistent AF wherein a rotational activity is seen on the epicardium while the endocardium is seen to have dissociated heterogenous wave front activations. Panel (B) shows concurrent 'live stream' histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface.

VIDEO VII: Example of a Transmural Migrating Rotational Activation. Panel (A) shows dynamic phase map of persistent AF wherein the rotational activity on the epicardium (black arrow) migrates to the endocardium (green arrow) before dissipating as a single wave front. Panel (B) shows concurrent 'live stream' histogram of the proportion of synchronous and dissociated activation based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface.

CHAPTER - 6

SIMULTANEOUS EPICARDIAL-ENDOCARDIAL MAPPING OF THE SINUS NODE IN HUMANS WITH STRUCTURAL HEART DISEASE: IMPACT OF OVERDRIVE SUPPRESSION ON SINO-ATRIAL EXITS

INTRODUCTION

The sinus node (SAN) is a collection of specialised cells situated at the junction of the superior vena cava (SVC) and right atrium (RA) in the epicardial sulcus terminalis and extending a variable distance along the long axis of the crista terminalis inferiorly[480,481]. Human mapping studies have suggested an extensive integrated sinus pacemaker complex with dynamic variation in site of earliest activation[383,482,483].

Recent studies utilising integrated intramural optical mapping combined with 3D histologic reconstruction in isolated preparations have demonstrated the 3-dimensional nature of the SAN; multiple pacemaker sites and multiple preferential sino-atrial conduction pathways (SACP) exist with both endocardial and epicardial exits. With suppression of one pacemaker or conduction pathway, activation of a subsidiary pacemaker with conduction over an alternate pathway maintains SAN function[484,485]. This redundancy of pacemakers and conduction pathways results in a robust system resistant to failure.

Sick sinus syndrome remains the most common indication for bradycardia pacing and usually occurs in the context of advanced SAN and atrial remodelling[483,486-488]. In this setting, atrial arrhythmias frequently coexist and pauses most usually occur immediately following AF termination[489]. Although the 3-dimensional nature of atrial conduction has been demonstrated in isolated preparations, the relative importance of endocardial and epicardial SAN exits and how these are modified by overdrive suppression in the intact atrium has not been evaluated.

In this study, we used simultaneous endocardial and epicardial phase mapping of the SAN during sinus rhythm (SR) and following overdrive suppression to further characterise the preferential nature of sinoatrial conduction in humans with SHD undergoing cardiac surgery.

METHODOLOGY

Study population

Patients undergoing cardiac surgery for ischemic and/or valvular heart disease at Royal Melbourne Hospital, Melbourne, Australia were included. Patients with a history of catheter ablation for atrial arrhythmias were excluded. All patients gave written, informed consent prior to the surgery and the study protocol was approved by the research and ethics committee of Melbourne Health.

Data acquisition

Following median sternotomy and prior to cardiopulmonary bypass, simultaneous epicardial and endocardial mapping of the supero-lateral RA near the SVC-RA junction and overlying the sulcus terminalis was performed using two Advisor™ HD Grid Mapping catheters (Abbott, St. Paul, Minnesota, USA) one each for the epicardial and endocardial surfaces as previously described[475]. Each HD grid catheter represents a 4x4 electrode array (3mm interelectrode distance) having four 2.5F splines on its distal tip with each spline containing 4 platinum-iridium electrodes that were used for recording unipolar electrograms. Epicardial mapping was achieved by positioning of the grid catheter over the superior-lateral aspect of the RA covering the sulcus terminalis immediately at and below the SVC-RA junction (Supplementary Figure 1, intra-operative photograph). Simultaneously, endocardial mapping was performed by manually inserting the catheter through a 9F introducer into the right atrium via a small atrial incision. Both grid catheters were anchored proximally to maintain alignment and adequate contact confirmed by assessing real-time signal quality. The steerable nature of the grid catheter allowed manoeuvring of both the catheters to ensure good contact without compromising alignment.

Atrial epi- and endocardial electrograms (uni and bipolar) were simultaneously recorded using the EnSite Precision™ Cardiac Mapping System (Abbott, St. Paul, Minnesota, USA). EGM's were sampled at 2kHz and a filtering set to 0.1-500Hz. The sternal retractors were used for unipolar reference. A quadripolar catheter (Supreme™ 5F JSN, Abbott, St. Paul, Minnesota, USA) was used for pacing from the epicardial posterior RA and after

determining pacing threshold, the pacing stimulus was set at 1.5 times the threshold. Rhythm recordings were made in the following sequence after confirming satisfactory catheter stability and adequate signal quality: (i) SR at baseline (ii) SR after continuous pacing for 30s at 600ms and (iii) SR after continuous pacing for 30s at 400ms

Data Analysis

Analysis of each EGM was performed offline using our custom-made software. Filtered EGM's (unipolar and bipolar) were exported for signal processing.

Phase analysis

Phase analysis was performed using MATLAB version R2018a (MathWorks Inc., Natick, Massachusetts, USA). Sinusoidal recomposition and instantaneous phase analysis have previously been described[468] in detail and can be summarized in the following steps: 1) electrogram is transformed using sinusoidal recomposition; 2) Hilbert transformation of the recomposed sinusoids; 3) followed by calculation of instantaneous phase. Far-field signals were digitally subtracted from the raw EGMs' using a template-matching algorithm before sinusoidal recomposition.

Dynamic phase maps displayed on schematic grid catheters were used to activation exit sites and wavefront propagation. Activation exit sites were defined based on the location of the earliest site on the endo and epicardial grid catheters as *(a)* ***Cranial*** (along A1 to D1 electrodes) *(b)* ***Mid*** (along A2 to D2 or A3 to D3 electrodes) or *(c)* ***Caudal*** (along A4 to D4 electrodes) as shown in Figure 1. For analysis of regional differences in activation exits,

the three rhythms which are defined as (a) $SR_{baseline}$: Five sinus beats at the beginning of the entire recording sequence, (b) $SR_{post\text{-}pace\ 600}$: The first two sinus beats after continuous pacing for 30s at 600ms and (c) $SR_{post\text{-}pace\ 400}$: The first two sinus beats after continuous pacing for 30s at 400ms . When activation exits changed between baseline and post-overdrive suppression, dynamic phase maps were examined beyond the first sinus beat to determine if activation exits returned to those observed at baseline.

To determine endo-epicardial phase dispersion, signal phase at each location of the endocardial surface was compared to phase timing at opposing electrode location on the epicardial surface. A negative phase difference indicated that the endocardial activation preceded the epicardial surface while a positive difference indicated the converse. Endocardial-epicardial dissociation (EED) was determined by (a) comparing regional differences in distribution of activation exits and (b) assessment of endo-epi wavefront propagation sequence and (c) difference in phase value $\geq$20ms between opposing endo-epi electrode pairs as previously published[475].

Signal fractionation

Bipolar EGM morphology was analysed semi-automatically in MATLAB R2018a (MathWorks Inc., Natick, Massachusetts, USA)[470]. EGM's with injury potentials were excluded from analysis. All automated EGM analyses were visually verified to ensure accurate classification of EGM's. Comparisons of the burden of fractionated EGM's were then made between the 3 rhythms. All fractionated EGM's defined by the algorithm were

manually verified by two independent electrophysiologists with good interobserver agreement (κ: 0.9; 95% CI: 0.7 to 1.0).

Statistical analysis:

Statistical analyses were performed using MINITAB (version 18, Minitab Inc., State College, Pennsylvania, USA). Continuous variables are displayed as mean ± SD or median (IQR). Categorical variables are presented as a number and percentage. The student-t-test, or its non-parametric equivalent, Mann-Whitney U test when appropriate was used for comparison of continuous variables. Fisher's exact test was used for the comparison of nominal variables. Kappa statistic was used to examine interobserver agreement. A p-value of <0.05 was considered significant.

RESULTS

Baseline characteristics

We studied sixteen patients (12 males; 60.5 ± 4.1years) who underwent cardiac surgery for ischemic heart disease or valvulopathy. None of the patients had symptomatic SAN dysfunction. Mean LA volume of the cohort was 58±12.4 ml/m^2. A minority of patients (n=3) had a history of paroxysmal AF. Baseline characteristics of the study population are presented in Table 1.

Sinus Node Exits: Baseline versus Post Overdrive Suppression

A total of 149 activations were analyzed (9.3±1.4 per patient). The mean cycle length during $SR_{baseline}$ was 902±126ms. The corrected sinus node recovery time (cSNRT) was longer during $SR_{post\text{-}pace\ 400}$ than $SR_{post\text{-}pace\ 600}$ (394±98 vs 351±69ms, p=0.047).

During $SR_{baseline}$, 87.5% activations exited from the cranial segment of the grid catheters. Of the remaining, 6.2% exited from the mid and 6.3% from the caudal segments. All activation exits were unicentric during each of the five consecutive beats analyzed in all the patients and were matched between the endocardium and epicardium.

Following pacing at 600ms, there was a caudal shift in some exit sites on both the endocardium (12.5%) and epicardium (18.7%). This resulted in a significant reduction in the frequency of cranial exits immediately post pacing at 600ms ($SR_{post\text{-}pace\ 600}$ vs $SR_{baseline}$: Endo 75% vs 87.5%, p=0.046; Epi 68.8% vs 87.5%, p=0.002). On the endocardial surface, shift occurred to the mid plaque segment in 6.25% and to the caudal segment in 6.25%. On the epicardium all shift in exit sites occurred to the caudal segment. Activations that exited from the mid and caudal segments during $SR_{baseline}$ did not change during $SR_{post\text{-}pace\ 600}$.

Similarly, with overdrive suppression in $SR_{post\text{-}pace\ 400,}$ the frequency of cranial exits decreased compared to $SR_{baseline}$ due to caudal shift of some exit sites following pacing. This was significant for epicardial exits ($SR_{post\text{-}pace\ 400}$ vs $SR_{baseline}$: 68.7% vs 87.5%, p=0.0034) but not for endocardial exits ($SR_{post\text{-}pace\ 400}$ vs $SR_{baseline}$: 81.2% vs 87.5%, p=0.335).

Figure 2 shows examples of isochronal maps where activation exits shift from the cranial segment at baseline to caudal segments following pacing at 600ms and 400ms.

Endocardial-Epicardial Dissociation

Activation exits

During $SR_{baseline}$, all activation exits sites matched on the endocardium and epicardium in the cranial, mid and caudal segments as shown in the Figure 3.

Following pacing at 600ms, activations exits demonstrated evidence of dissociation between epicardium and endocardium. This was more marked in the caudal segment (Endo vs Epi: 12.5 vs 25%, p=0.028) than the cranial (Endo vs Epi: 75 vs 68.8%, p=0.43) and mid segments (Endo vs Epi: 12.5 vs 6.2%, p=0.15).

Following pacing at 400ms, there was increasing EED in the distribution of activation exits in the caudal (Endo vs Epi: 12.5 vs 31.2%, p=0.001) and mid segments (Endo vs Epi: 6.2 vs 0%, p=0.028) while cranial segment exits showed a non-significant trend to dissociation (Endo vs Epi: 81.3 vs 68.8%, p=0.07).

The distribution of exit sites within each segment between the endocardial and epicardial surfaces during $SR_{baseline}$, $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$ is shown in the Figure 3.

Wavefront Propagation Sequence

Wavefront propagation sequence over the endocardium and epicardium showed marked differences between $SR_{baseline}$, $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$. During $SR_{baseline}$, 93.7% of wavefront propagations were symmetrical on the endocardial and epicardial surfaces. This reduced to 85.7% during $SR_{post\text{-}pace\ 600}$ (p=0.015) and 76.1% of wavefronts during $SR_{post\text{-}pace\ 400}$ (p=0.006). These changes reflected the dynamic variations in activation exits described in the prior section and the resultant change in wavefront propagation. Figures 4-6 and Supplementary Videos 1-3 show dynamic phase maps and endocardial-epicardial phase dispersion of activation during $SR_{baseline}$, $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$ from Patient 3. Supplementary Figure 2 shows a summary of endocardial-epicardial wave front directionality during $SR_{baseline}$, $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$.

Phase Dispersion

Overall, comparing phase values between paired endo-epi electrodes showed that during $SR_{baseline}$ 90.7% of the activations were synchronous. This significantly reduced to 84.7% during $SR_{post\text{-}pace\ 600}$ (p<0.0001) and 80.9% during $SR_{post\text{-}pace\ 400}$ (p<0.0001).

Of the dissociated activations, there was no preference for either side of the atrial myocardium during $SR_{baseline}$ (Endo Ahead vs Epi Ahead: 4.4% vs 4.9% , p=0.168) but with overdrive suppression, a larger proportion were earlier on the endo- than the epicardium (Endo Ahead vs Epi Ahead: 9.4% vs 5.9%, p<0.0001 [$SR_{post\text{-}pace\ 600}$]; 11.5% vs 7.6%, p<0.0001 [$SR_{post\text{-}pace\ 400}$]). Figure 7 shows the phase dispersion and preferential conduction during $SR_{baseline}$, $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$.

Recovery Post-Overdrive Suppression

Activation exits and wave front propagation patterns returned to baseline in all patients in 4.5±1.6 beats during $SR_{post\text{-}pace\ 600}$ and 4.8±2.1 beats during $SR_{post\text{-}pace\ 400}$. The time taken for recovery was longer during $SR_{post\text{-}pace\ 400}$ compared to $SR_{post\text{-}pace\ 600}$ (6.3 vs 5.3 s, p=0.021). Supplementary Video 4 shows dynamic phase maps during $SR_{baseline}$ and the impact of overdrive suppression of sinus node after continuous pacing @ 400ms in Patient 14. In this example, the endo-epicardial phase maps show the multi-centric breakthroughs and asymmetric endo-epi wave front propagation seen during $SR_{post\text{-}pace\ 400}$ abruptly change to unicentric activation and symmetric endo-epicardial wavefront propagation after 9 beats (10.5 seconds).

EGM Fractionation

Compared to $SR_{baseline}$, bipolar EGM fractionation was significantly higher during $SR_{post\text{-}pace\ 600}$ ($SR_{post\text{-}pace\ 600}$ vs $SR_{baseline}$: Endo 36.2% vs 28.9%, p=0.006; Epi 34.2% vs 29.9%, p=0.044) and $SR_{post\text{-}pace\ 400}$ ($SR_{post\text{-}pace\ 400}$ vs $SR_{baseline}$: Endo 37.1%vs 28.9%, p=0.0032; Epi 35.0% vs 29.9%, p=0.002) . Supplementary figure 3 shows an example of sinus node activation showing increased bipole electrogram fractionation post overdrive pacing at 600ms ($SR_{post\text{-}pace\ 600}$) and 400ms ($SR_{post\text{-}pace\ 400}$) compared to sinus rhythm at baseline ($SR_{baseline}$).

DISCUSSION

Simultaneous endocardial-epicardial phase mapping of human SAN in patients with SHD at baseline and post overdrive suppression revealed the following key findings:

1) Predominant cranial exits with symmetrical activation sites on the endocardial and epicardial surfaces during $SR_{baseline}$.
2) Post-pacing caudal shift in the activation exits with marked asymmetry in endocardial-epicardial exit sites consistent with multicentricity and redundancy of sino-atrial conduction. Differential epi-endo break out sites resulted in asymmetry of subsequent wave-front propagation.
3) As a result, there is significant post-pacing EED of activation resulting in an increased prevalence of complex electrograms.

These findings demonstrate the complex and dynamic 3D nature of sino-atrial conduction in the intact human heart, confirming studies in isolated preparations.

Dynamics of Sino-Atrial Conduction

Seminal work by Boineau et al[490-492] demonstrated that during SR, atrial breakthroughs occur well beyond the length of the SAN complex. They postulated that the multicentricity of the SAN may be due to either impulses originating at a single site exiting through multiple pathways or the presence of multiple pacemaker foci. Indeed, animal and human studies from recent high-resolution optical mapping integrated with 3D

histological analyses[484,485] have shown that atrial activation patterns can result from intramural SAN excitation waves exiting via distinct SACP's.

In a recent classical study in ex-vivo human hearts, Li et al[484] used optical mapping to characterise the nature of intranodal pacemakers and sinoatrial conduction pathways. They demonstrated that in the presence of adenosine or overdrive pacing a dominant pacemaker or SACP could become suppressed. When this occurred other intramural pacemakers and SACPs would activate. Thus, SR was rescued by 2 independent fail-safe mechanisms for automaticity and conduction. In the current study in intact human hearts, using simultaneous endocardial and epicardial mapping, we were unable to definitively determine whether change in activation site following overdrive suppression represents intramural shift of the pacemaker site or change in SACP. Nevertheless, our results in the intact human heart support the findings of the study in the ex-vivo heart in that sino-atrial exit sites can be dramatically altered on endocardium and epicardium as a result of the perturbation produced by pacing. It is probable that episodes of atrial fibrillation would have a similar effect.

Epi-Endo Dissociation

The current study also indicates a mechanism by which epicardial endocardial dissociation may become manifest. Recent studies have described the functional nature of epicardial-endocardial dissociation[475]. In the current study, differential epi-endo sino-atrial exits created wavefronts propagating in different directions and resulted in significant dissociation between the layers.

Unicentric or Multicentric Origin

In the classical studies by Boineau et al, the normal human pacemaker was shown to be an extensive complex with integrated multicentric activation[490,492]. However, studies in patients with advanced SHD have demonstrated that this multicentricity can be lost as atrial remodelling advances[483,493]. In studies using optical mapping of the coronary perfused human SAN, Fedorov et al[494] demonstrated that during SR intranodal activation was unicentric. With atrial overdrive pacing however, they observed shifts in the site of atrial breakthroughs, multifocal breakthroughs, sinus slowing and a 2-fold slowing of SAN conduction velocity. Interestingly, multifocal breakthroughs abruptly switched back to their baseline findings of superior unifocal breakthrough within one minute after pacing was stopped. In the current study, in patients with SHD undergoing cardiac surgery, all sinus origins were unicentric at baseline with the majority initially demonstrating a matching exit site on epicardium and endocardium. This may reflect both the presence of significant SHD as previously published but may also in part be due to the fact that the mapping grid did not cover the full extent of the pacemaker complex. However, as in the study by Federov and co-workers[494], overdrive pacing produced differential multicentric endocardial and epicardial exits with complete recovery within 12 seconds in all patients.

Limitations

Mapping of SAN was performed based on anatomic landmarks and it is possible that mapping catheter did not encompass the entire SAN region in all patients. As a consequence, the extent of multicentricity of SAN activations may have been missed.

Although we performed simultaneous mapping of the epicardium and endocardium, in the intact human heart it is not possible to map the intramural portions of the sinus node other than in an explanted heart[494].

Clinical Implications

The current study in the intact heart of patients with SHD confirms the presence of multiple differential endocardial and epicardial sino-atrial exits and hence the redundant structure of the pacemaker complex. This is consistent with prior data demonstrating that clinical sinus node dysfunction only occurs in the setting of advanced atrial structural remodelling.

CONCLUSION

In the current study, we performed simultaneous epicardial-endocardial mapping of the human sinus node in the intact heart to further characterise the 3-dimensional characteristics of sinus node function and the impact of overdrive suppression. Following overdrive suppression there was a tendency to caudal shift in exits, differential and hence multicentric endo-epi breakthroughs, asymmetrical wavefront propagation associated with endo-epicardial dissociation and increased EGM fractionation.

TABLES AND FIGURES

Table 1: Baseline Characteristics

Number of Patients	16
Age in years, mean±SD	60.5±4.1
Gender, n (%)	
Males	12 (75)
Females	4 (25)
BMI, mean±SD	33.7±3.5
History of Atrial Fibrillation, n (%)	3 (18.7%)
Diabetes mellitus, n (%)	11 (68.7)
Hypertension, n (%)	12 (75)
Cerebrovascular accident, n (%)	1 (6.2)
Underlying cardiac disease, n (%)	
Coronary artery disease	8 (50)
Aortic Stenosis	4 (25)
Aortic Regurgitation	1 (6.2)
Mitral regurgitation	2 (12.5)
Mitral Stenosis	1 (6.2)
Tricuspid Regurgitation	1 (6.2)
Left atrial dilation n (%)	6 (37.5)
Impaired Left ventricular function, n (%)	7 (43.75)

BMI, body mass index; SD, standard deviatioN

Graphic Abstract: Sino-atrial conduction and impact of overdrive suppression in intact human heart

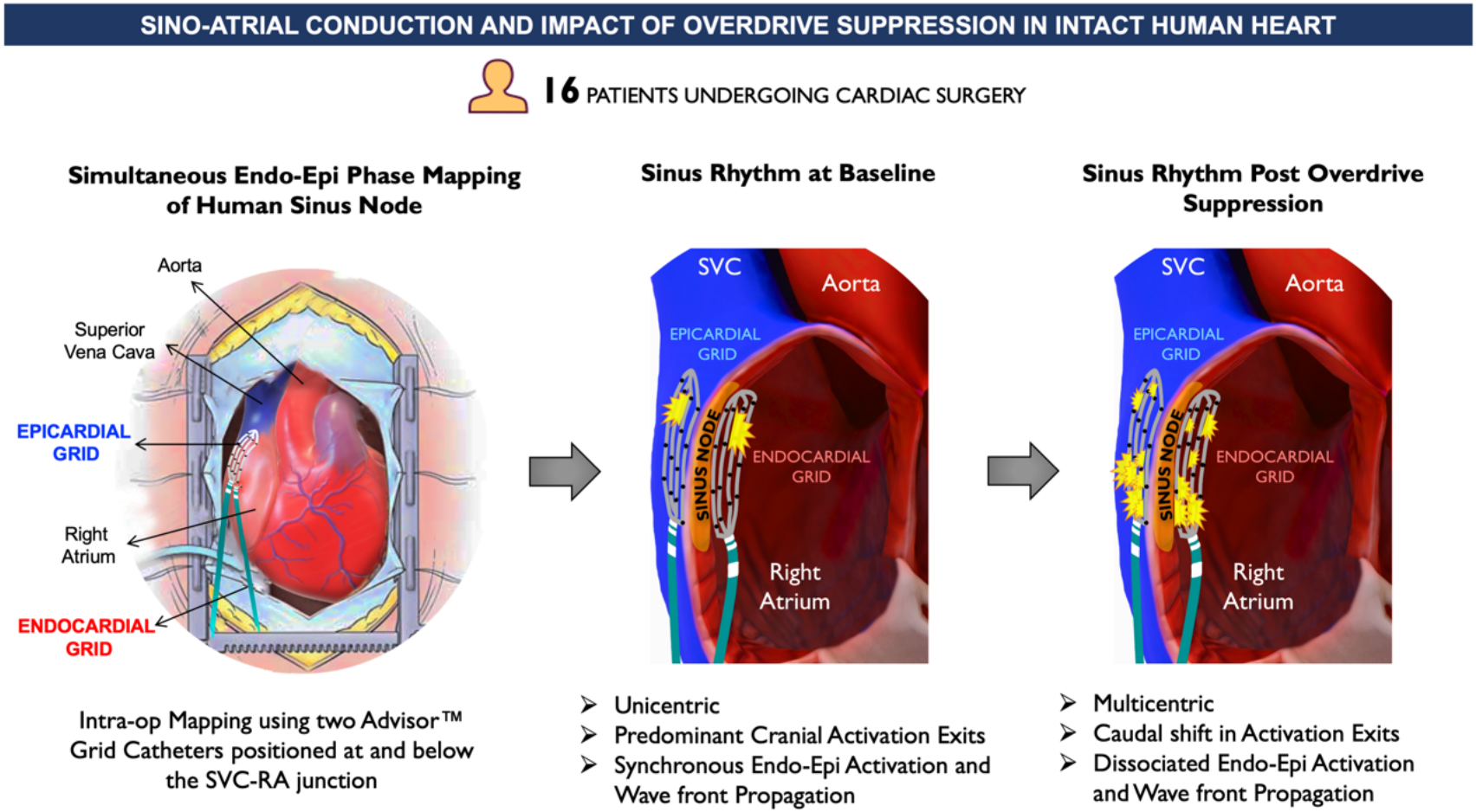


Figure 1: Illustration of the activation exit segments on grid catheters. Simultaneous endocardial-epicardial mapping of the human SA node was performed using two Advisor™ HD grid mapping catheters positioned over the supero-lateral RA wall at and below the SVC-RA junction as shown in the illustration. Activation exit sites were defined based on the location of the earliest site on the endo and epicardial grid catheters as cranial (anywhere along A1 to D1 electrodes), mid (anywhere along A2 to D2 or A3 to D3 electrodes) or caudal (anywhere along A4 to D4 electrodes). IVC, inferior vena cava; SA, sino-atrial; SVC, superior vena cava; RA, right atrium; RV, right ventricle.

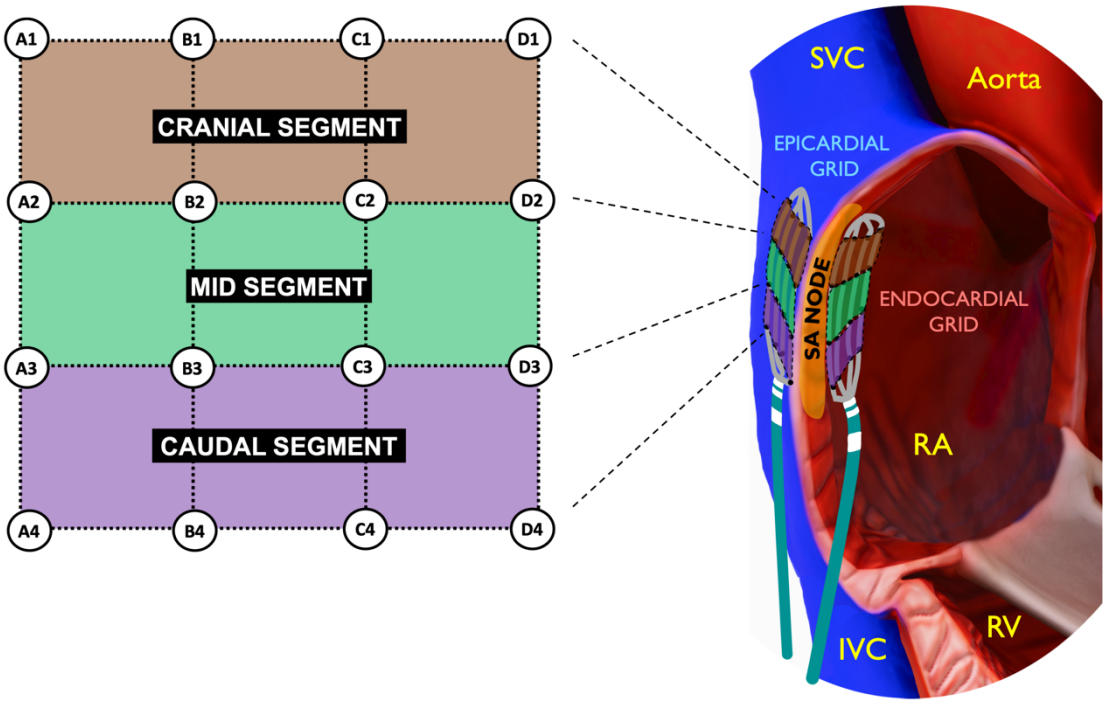


Figure 2: Sinus activation exit (☆) and wave front propagation (black arrows) shifts post overdrive suppression

Isochronal maps of sinus activations in the three patients (1, 3 and 14) with caudal exit shifts are shown. In Patient 1 (*Row 1*) activation exits from D1 on endocardial and epicardial surfaces during $SR_{baseline}$ but shifts to D4 (endocardial and epicardial) during $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$. Wave front directionality is symmetrical on the endocardial and epicardial surfaces during all three rhythms. In Patient 3 (*Row 2*) activation exits at A1 on endocardial and epicardial surfaces but shifts to A3 (endocardial) and D3 (epicardial) during $SR_{post\text{-}pace\ 600}$ and to A3 (endocardial) and D4 (epicardial) during $SR_{post\text{-}pace\ 400}$. Wave front directionality was symmetrical during $SR_{baseline}$ (cranial to caudal direction) but showed marked asymmetry propagating from spline A to D on the endocardial surface and from spline D to A on the epicardial surface during $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$. Conduction slowing (isochronal crowding) can also be seen on the endocardial surface post over-drive suppression. In Patient 14 (*Row 3*), activation exits at A1 on endocardial and epicardial surfaces but shifts caudally only on the epicardium to exit at A4. Wave front directionality was symmetrical during $SR_{baseline}$ (cranial to caudal) but differed markedly between the endocardial (spline A to D) and epicardial (caudal to cranial) post overdrive suppression. $SR_{baseline}$: SR at baseline, $SR_{post\text{-}pace\ 600}$: SR post overdrive pacing at 600ms, $SR_{post\text{-}pace\ 400}$: SR post overdrive pacing at 400ms.

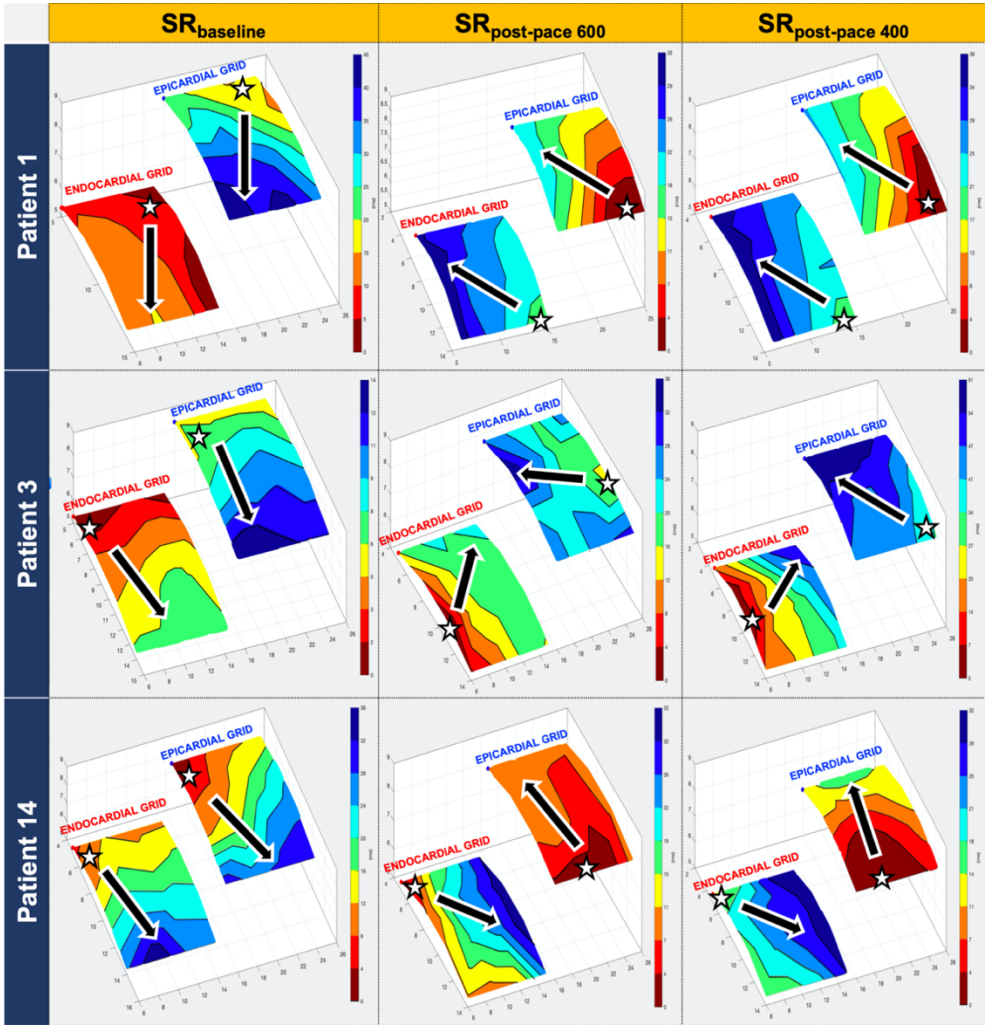


Figure 3: Simultaneous endocardial-epicardial mapping of human sinus node. Distribution of sinus node exits in the cranial (brown), mid (green) and caudal (violet) segments on endocardial and epicardial grids during $SR_{baseline}$, $SR_{post\text{-}pace\ 600}$ and $SR_{post\text{-}pace\ 400}$ are shown. A tendency for activations to shift from cranial to caudal segments is observed with overdrive suppression of the sinus node. The size of the markers reflects the number of exits recorded at that site. $SR_{baseline}$: SR at baseline, $SR_{post\text{-}pace\ 600}$: SR post overdrive pacing at 600ms, $SR_{post\text{-}pace\ 400}$: SR post overdrive pacing at 400ms.

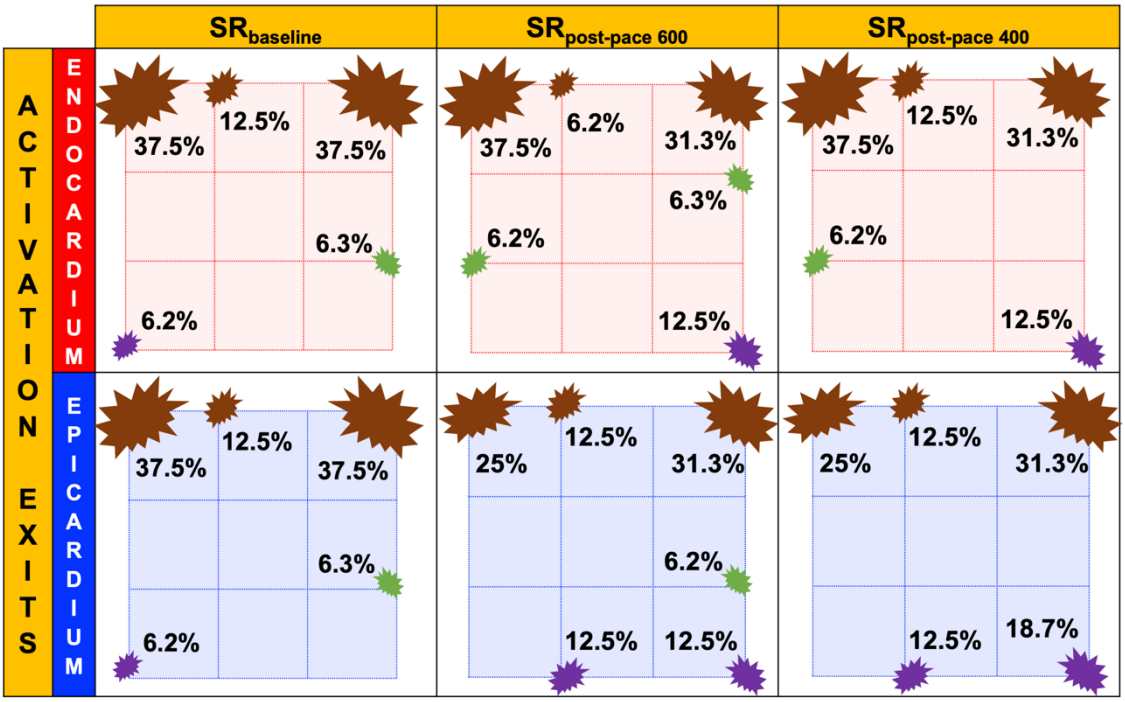


Figure 4: Simultaneous endocardial-epicardial phase mapping of sinus activation at baseline in Patient 3: (A) Atrial unipolar electrograms with instantaneous phase and activation peaks at each electrode of the endocardial (red) and epicardial (blue) HD grid catheters. (B) Histogram of the proportion of synchronous and dissociated activations based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface. (C) and (D) Propagation and isochronal maps showing symmetric endocardial-epicardial wave front propagation with the wave front entry at A1 electrode and following a diagonal trajectory exits at D4 electrode on both the endocardial and epicardial grid catheters. Supplementary video 1 shows dynamic phase maps with wave front propagation symmetry of this activation.

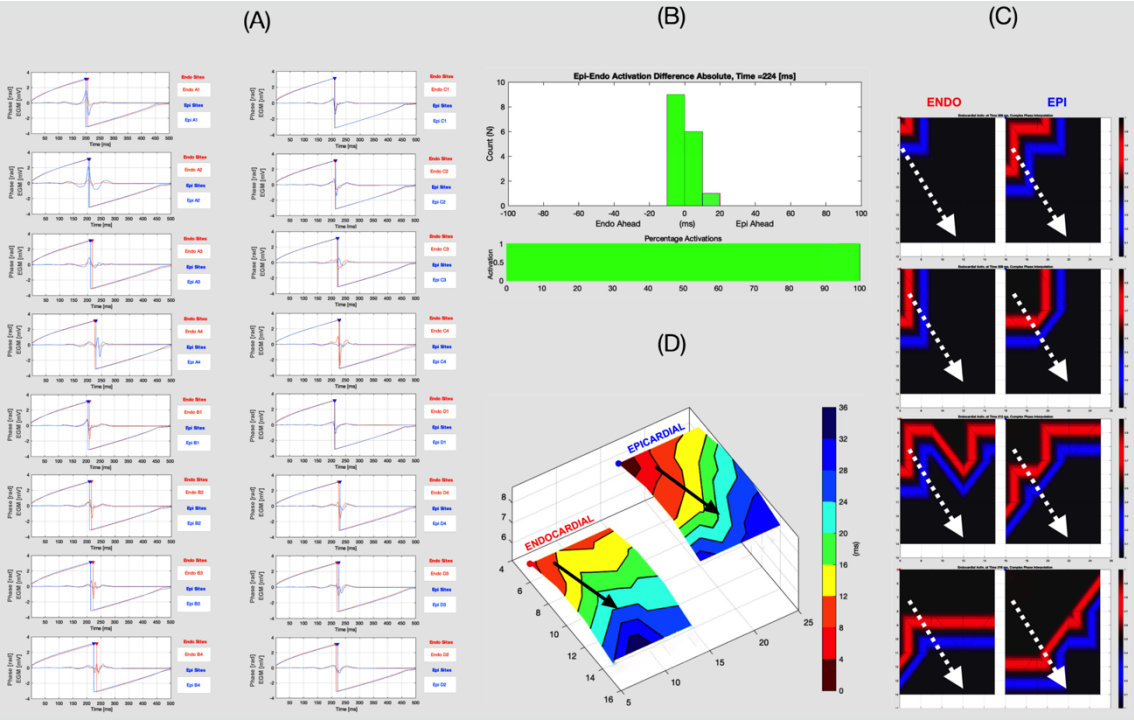


Figure 5: Simultaneous endocardial-epicardial phase mapping of sinus activation post overdrive pacing at 600ms (SRpost-pace 600) in Patient 3: (A) Atrial unipolar electrograms with instantaneous phase and activation peaks at each electrode of the endocardial (red) and epicardial (blue) HD grid catheters. (B) Histogram of the proportion of synchronous and dissociated activations based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface. (C) and (D) Propagation and isochronal maps showing caudal exit shift and asymmetric endocardial-epicardial wave front propagation (Endocardial: spline A to D; Epicardial: spline D to A). Supplementary video 2 shows dynamic phase maps with wave front propagation symmetry of this activation.

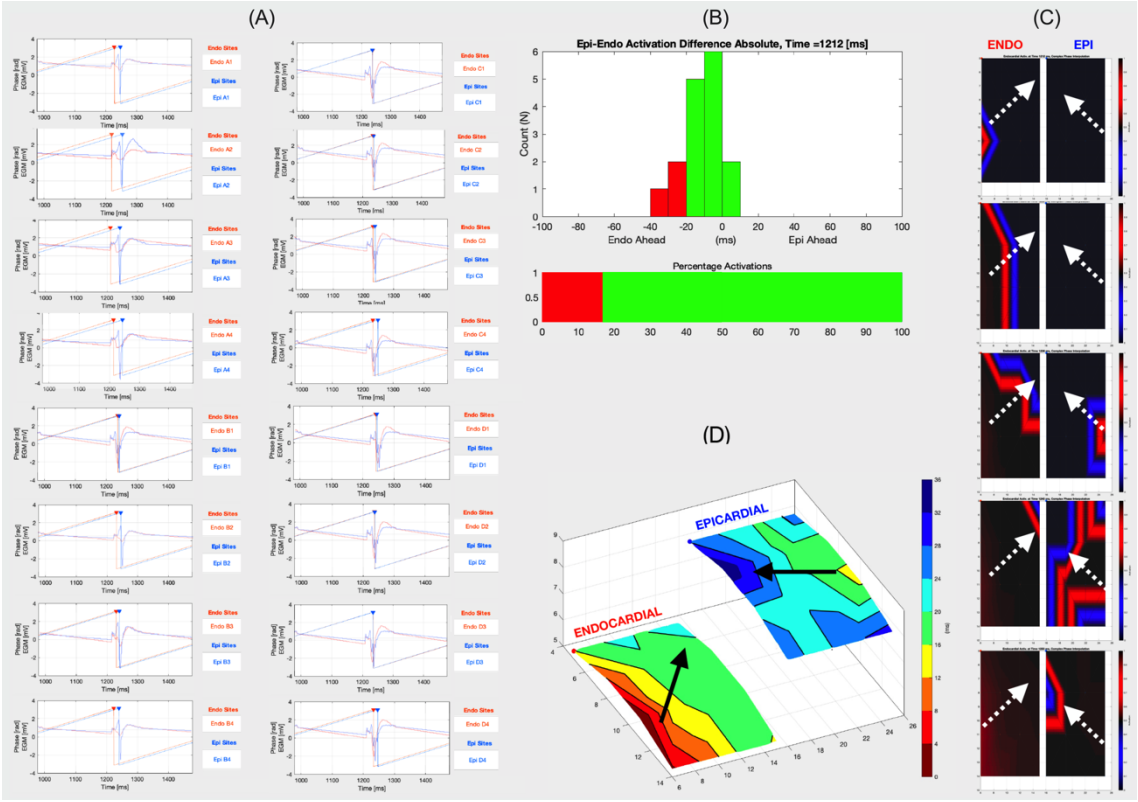


Figure 6: Simultaneous endocardial-epicardial phase mapping of sinus activation post overdrive pacing at 400ms (SRpost-pace 400) in Patient 3: (A) Atrial unipolar electrograms with instantaneous phase and activation peaks at each electrode of the endocardial (red) and epicardial (blue) HD grid catheters. (B) Histogram of the proportion of synchronous and dissociated activations based on comparisons between signal phase at each electrode of the endocardial surface to phase timing on the opposing epicardial surface. (C) and (D) Propagation and isochronal maps showing caudal exit shift and asymmetric endocardial-epicardial wave front propagation (Endocardial: spline A to D; Epicardial: D4 to A1). Supplementary video 3 shows dynamic phase maps with wave front propagation symmetry of this activation.

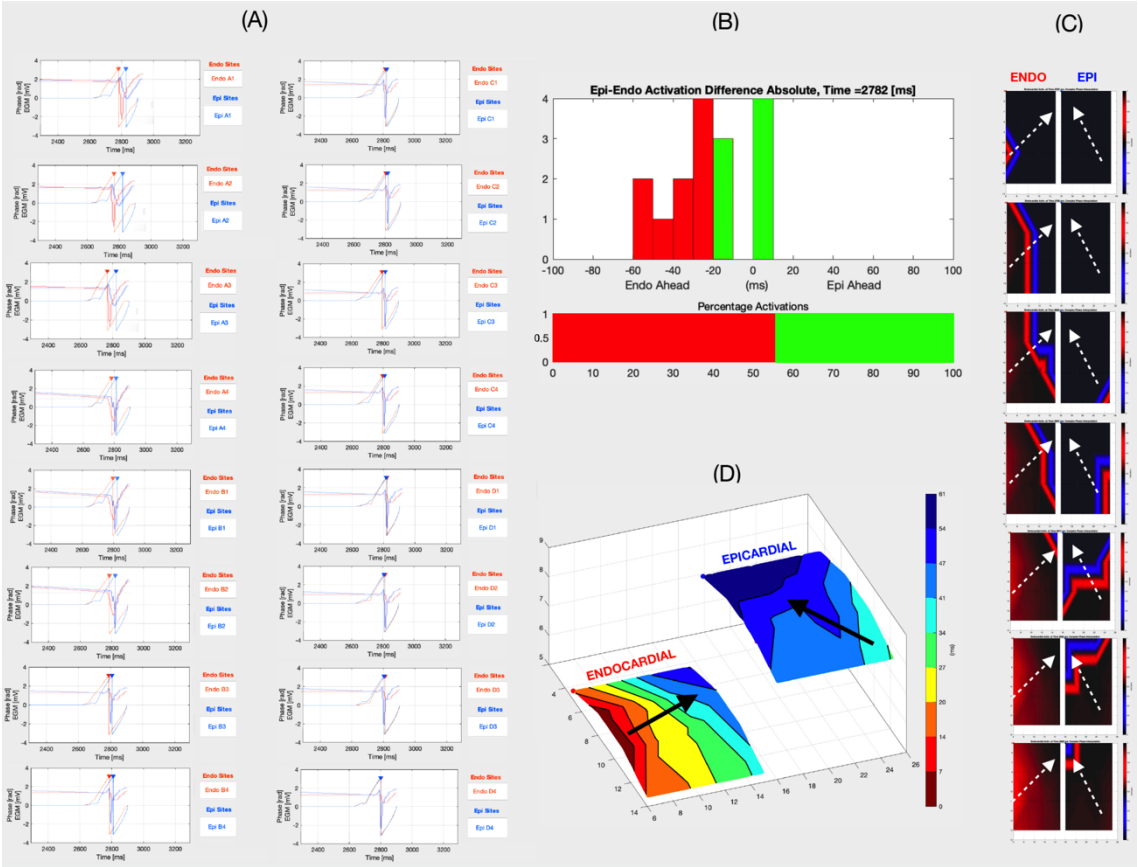
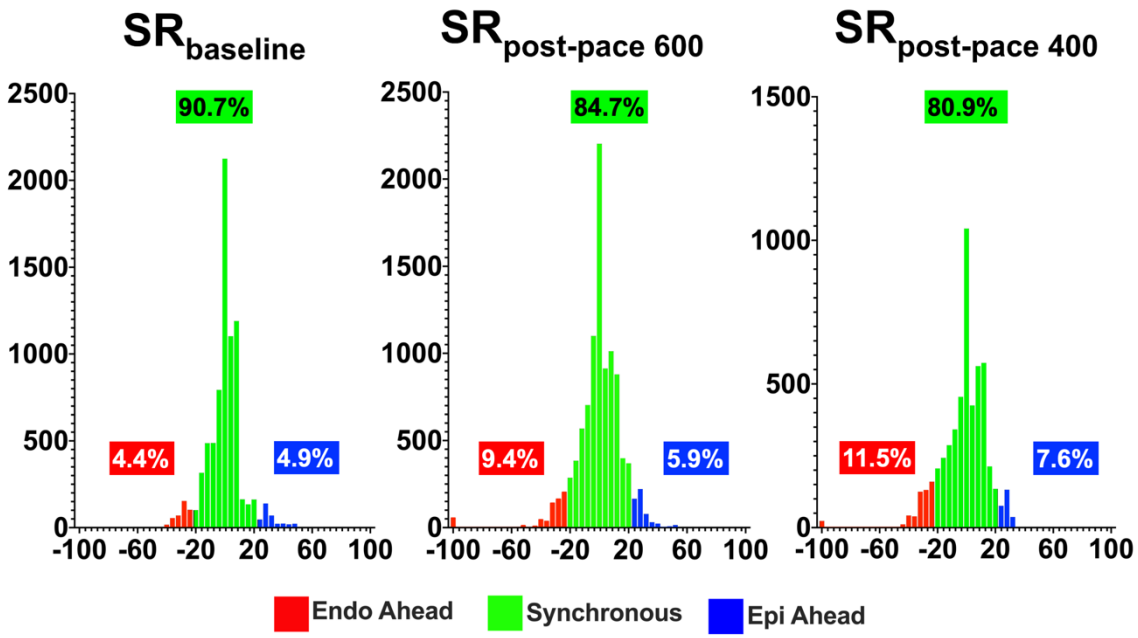


Figure 7: Endo-Epi phase dispersion during SRbaseline, SRpost-pace 600 and SRpost-pace 400. Frequency histograms show the prevalence of synchronous activations to decrease during overdrive suppression than at baseline. Of the dissociated activations, a larger proportion of activations were earlier on the endo- than epicardium with overdrive suppression but no preference for either side was observed during $SR_{baseline}$. $SR_{baseline}$: SR at baseline, $SR_{post\text{-}pace\ 600}$: SR post overdrive pacing at 600ms, $SR_{post\text{-}pace\ 400}$: SR post overdrive pacing at 400ms



SUPPLEMENTARY MATERIAL

Figure I: Intra-op photograph of simultaneous endocardial-epicardial mapping of the human sinus node using two Advisor HD Grid catheters (★endocardial, ★ epicardial). Mapping was performed with the grid catheters positioned over the supero-lateral wall of the RA covering the sulcus terminalis at and below the SVC-RA junction. Ao, aorta; RAA, right atrial appendage; SVC, superior vena cava; RA, right atrium.

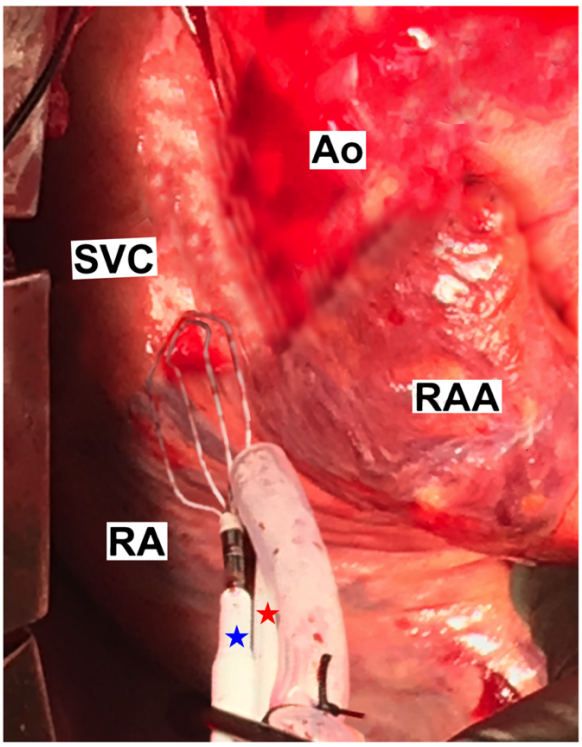
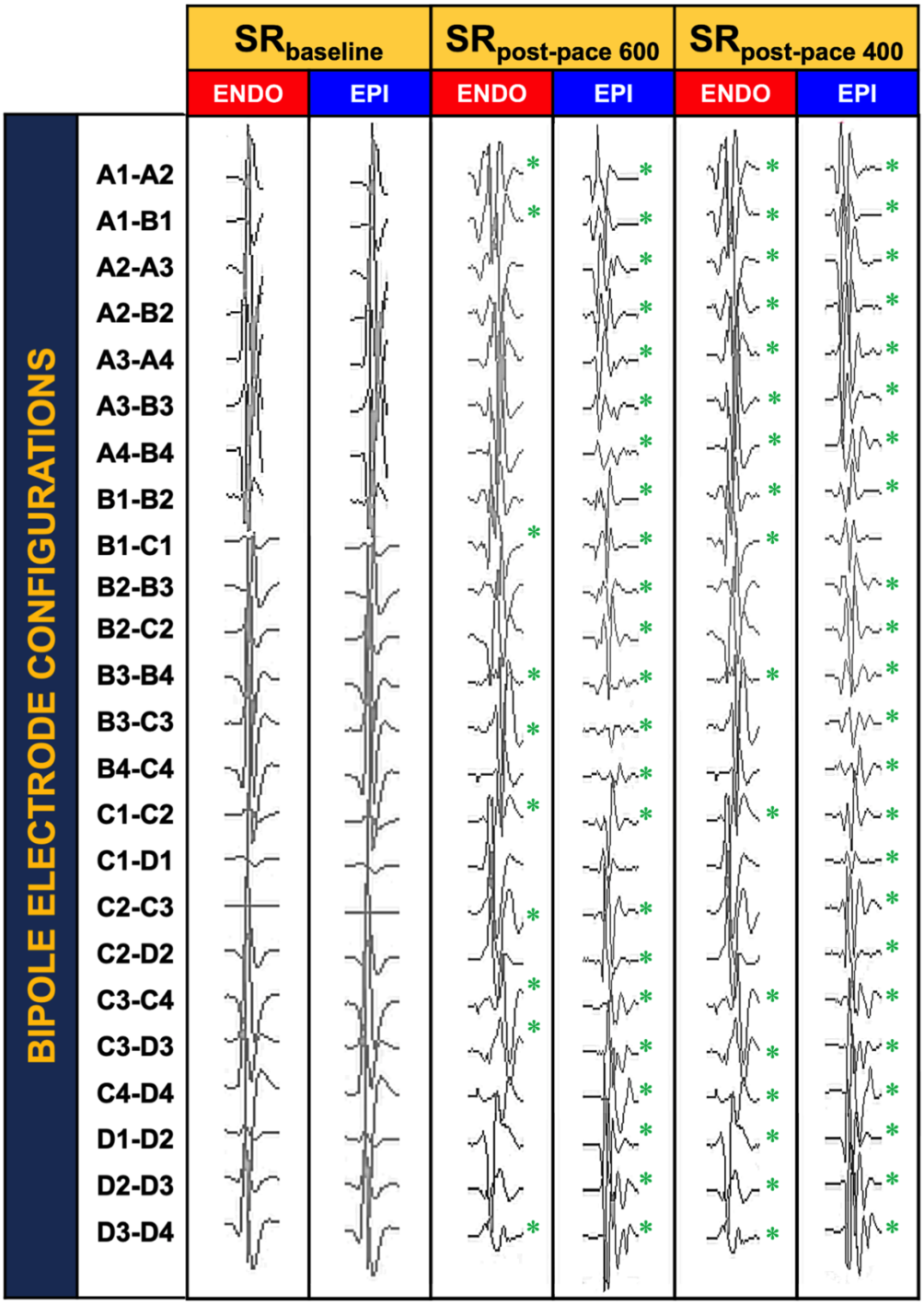


Figure II: Summary of wave front directionality on simultaneous endocardial-epicardial mapping of sinus node region during SR at baseline ($SR_{baseline}$) and post overdrive pacing at 600ms ($SR_{post\text{-}pace\ 600}$) and 400ms ($SR_{post\text{-}pace\ 400}$)

PATIENT	$SR_{baseline}$		$SR_{post\ pace\ 600}$		$SR_{post\ pace\ 400}$	
	ENDOCARDIAL	EPICARDIAL	ENDOCARDIAL	EPICARDIAL	ENDOCARDIAL	EPICARDIAL
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						

Figure III: Example of sinus node activation showing increased bipole electrogram fractionation (green asterisks) post overdrive pacing at 600ms ($SR_{post\text{-}pace\ 600}$) and 400ms ($SR_{post\text{-}pace\ 400}$) compared to sinus rhythm at baseline ($SR_{baseline}$).



VIDEO I: Simultaneous endocardial-epicardial phase mapping of sinus activation at baseline ($SR_{baseline}$) in Patient 3: Dynamic phase maps showing symmetric wavefront propagation on endocardial and epicardial surfaces (arrow line) with synchronous activation.

VIDEO II: Simultaneous endocardial-epicardial phase mapping of sinus activation post overdrive pacing at 600ms ($SR_{post\text{-}pace\ 600}$) in Patient 3: Dynamic phase maps showing caudal exit shift (❋) and asymmetric wavefront propagation (arrow lines) between endocardial (spline A to D) and epicardial (spline D to A) surfaces and dissociated activation.

VIDEO III: Simultaneous endocardial-epicardial phase mapping of sinus activation post overdrive pacing at 400ms ($SR_{post\text{-}pace\ 400}$) in Patient 3: Dynamic phase maps showing exit shifts (❋) and asymmetric wavefront propagation (arrow lines) between endocardial (spline A to D) and epicardial (spline D to A) surfaces and dissociated activation.

VIDEO IV: Dynamic endo-epicardial phase maps of the sinus node region showing impact of overdrive suppression and recovery to baseline in Patient 14: *Panel A* shows unicentric activation and symmetrical endo-epi wave front propagation during $SR_{baseline}$. *Panel B* shows dynamic phase maps of the last 4 beats of pacing drive train @ 400ms followed by $SR_{post\text{-}pace\ 400}$ during when multi-centric breakthroughs and asymmetric wave front propagation is seen between endo and epicardial surfaces for 9 beats after which sinus node activation recovers to that of baseline. $SR_{baseline,}$ SR at baseline; $SR_{post\text{-}pace\ 400}$, SR post overdrive suppression @ 400ms; cSNRT, Corrected sinus node recovery time; ms,

milliseconds. (Video playback speed set faster to show the complete sequence of dynamic shifts and recovery post overdrive pacing)

CHAPTER – 7

PAUCITY OF DRIVER DOMAINS IN PERSISTENT ATRIAL FIBRILLATION: INSIGHTS FROM REGIONAL HIGH-DENSITY DOUBLE PENTARAY MAPPING OF THE HUMAN LEFT ATRIUM

INTRODUCTION

The mechanisms that sustain persistent AF is a topic of ongoing debate. With advances in computational mapping techniques there is emerging data to suggest that AF is maintained by organized functional re-entry or focal sources rather than random excitation of the atrial tissue. Previously, computational panoramic left atrial (LA) mapping with basket catheters[114,398] and surrogates like dominant frequency[91,96], complex fractionated atrial electrograms[117,495] and AF cycle length[496,497] have been used to identify substrate/drivers with variable success. More recently, AF propagation maps based on direct contact mapping using the 64-electrode basket catheter (without phase transformation) with a dedicated software (CARTOFINDER; Biosense Webster Inc, Diamond Bar, CA) was shown to reliably and reproducibly identify repetitive activation patterns[126,127,129,498]. It has also been reported that electrical isolation of the left atrial appendage (LAA) improves outcomes of AF ablation[378,384] raising the possibility of drivers in LAA that sustain AF. However, there are also concerns for thromboembolic risks following electrical isolation of LAA[386,387].

To date, all mapping studies have either utilized low density wide coverage (Basket catheters) or high density but very localized mapping. To improve the coverage of high density mapping we have taken the novel approach of simultaneous mapping with two PentaRay catheters. We sought to characterize driver domains in the LA and LAA with regional high-density mapping with double PentaRay catheters using CARTOFINDER in patients with persistent AF. We also sought to determine the relationship between short AFCL 'driver' sites (<140ms)[497] with their actual AF activation patterns using CARTOFINDER.

METHODOLOGY

Study population

Patients undergoing catheter ablation for persistent AF were enrolled. Persistent AF was defined as episodes sustained longer than 7 days, or longer than 48 h and <7 days but requiring chemical or electrical cardioversion. Exclusion criteria were previous AF ablation, amiodarone use within the last nine months or patients with absolute contraindication for remaining on systemic anticoagulation post procedure. This study complies with the Declaration of Helsinki and was approved by the Melbourne Health Research and Ethics Committee.

Electrophysiology and Mapping protocol

Antiarrhythmic medications were withheld at least 5 half-lives prior to procedure. Anticoagulation was managed according to operator preference. All procedures were performed under general anaesthesia with periprocedural transesophageal

echocardiography to exclude LA thrombus. Double transseptal access was performed using a BRK needle via two 8.5F SL1 sheaths (St Jude Medical, St Paul, MN) and heparin was administered for a target activated clotting time 350 seconds. Two PentaRay NAV catheters (Biosense Webster, 2-6-2mm inter-electrode spacing) with constant irrigation were inserted into the LA through these sheaths for AF mapping. Bipolar intracardiac electrograms and 12-lead electrocardiography were recorded on a digital amplifier system (EP Med Systems, Chicago, Illinois), filtered from 30 to 500 Hz and measured with digital calipers at 200 mm/s sweep speed.

The mapping catheters were deployed perpendicularly to the endocardial surface so that the five splines of each PentaRay were spread out and AF recordings were acquired simultaneously from both these mapping catheters. Recordings were acquired from multiple sites in a sequential fashion including posterior wall, roof and anterior wall of LA, LAA and also within a pulmonary vein (PV) as shown in fluoroscopy images in Figure 1. After sequential mapping of the LA, RF ablation was performed with a lesion set determined as per operator discretion. Ablation was not guided by the CARTOFINDER analysis.

CARTOFINDER analysis

Multiple 30-seconds AF recordings of unipolar signals were obtained simultaneously from both PentaRay catheters at each site by referencing to Wilson's Central Terminal and filtering between 0.05 and 500 Hz. Analysis of these AF recordings were performed offline by CARTOFINDER. Details of CARTOFINDER have been described before[498]. In brief, CARTOFINDER subtracts far-field ventricular signals. For each unipolar signal, two bipolar

signals are created by pairing the electrode with the two neighbouring electrodes. A window is then applied to the unipolar signals that range from earliest onset to the latest offset of the two bipolar electrograms. The maximum slope of the unipolar atrial signals within the bipolar electrogram window are then annotated, while areas outside this window are excluded. The local activation time (LAT) was determined based on the annotation of atrial signals. Dynamic 3D activation maps were generated based on the LAT.

All recordings were reviewed off-line with dedicated software allowing automated annotation of the local activation time of the fibrillatory EGMs (CARTOFINDER; Biosense Webster Inc). Off-line analysis consisted of the following two parts: (a) identification and characterization of drivers as rotational or focal activity and (b) Assessment of manual driver identification on CARTOFINDER activation maps and agreement between investigators.

AF Cycle Length

Mean AFCL (mAFCL) was manually measured by averaging 100 consecutive cycles using atrial activations from coronary sinus catheter. Mean regional AFCL and LAA AFCL (mLAA-AFCL) were measured from atrial activation recordings on the PentaRay catheters while positioned in the various regions of the LA and LAA. Percentage of activations with CL <140ms was calculated by the ratio of the area of CL <140ms over the total area on the CL histogram for each map per region as shown in Figure 2. CL measurements were performed offline by two independent blinded cardiologists with good interobserver agreement (K = 0.84).

Definitions

Activations were classified as rotational or focal. Activations with ≥ 2 revolutions were defined as rotational. Focal sources were defined as ≥3 consecutive activations earliest at the mapped site with centrifugal spread of activation. For the LAA, based on previous studies, focal drivers were defined as consistent premature atrial contractions (>3 consecutive) with the earliest activation in the LAA or AF originating from the LAA. AFCL drivers were defined as sites with AFCL <140ms based on previous studies[497].

Statistical Analysis

Statistical analyses were performed using MINITAB (version 18, Minitab Inc., State College, Pennsylvania, USA). Continuous variables are displayed as mean ± SD or median (IQR). Categorical variables are presented as a number and percentage. The student-t-test, or its non-parametric equivalent, Mann-Whitney U test when appropriate was used for comparison of continuous variables. Fisher's exact test was used for the comparison of nominal variables. Kappa statistic was used to examine interobserver agreement. A p-value of <0.05 was considered significant.

RESULTS

We included fifteen patients (11 men; 59.4±9.6 years) with persistent AF (Mean AF duration: 4.0±3.4 years) undergoing catheter ablation. Participant characteristics are presented in Tables 1. Majority of the patients were hypertensives and nearly 50% had treated obstructive sleep apnea with enlarged LA size in 93.7% patients.

CARTOFINDER analysis

A total 229 CARTOFINDER maps (138 LA walls, 46 superior PV's, 45 in LAA) were available for analysis with an average of 7.6±0.7 min of AF mapped per patient. The average procedure duration was 190.7±25.7min and mean fluoroscopy time of 12.8±3 min. Mapping characteristics are presented in Table 2.

Left Atrium and Pulmonary Veins

Only 3/15 (20%) patients (5.6% of total maps) were noted to have a driver in the LA and PV as per the study definition. The 3 patients had a total of 46 maps out of which only 13 maps demonstrated the presence of a driver (28.2%). A total of 5 drivers were identified in the 3 patients (1.6 ± 0.4 drivers per patient, 1 driver in 1 patient, and 2 drivers in 2 patients). In each of these 3 patients the potential driver was seen in 58±12.3% of maps. Of the 5 potential drivers, most demonstrated focal activity (n = 28; 70%) with a mean of 3.4±0.7 repetitive activations and the remainder was of rotational activations.

Among the focal activations the commonest site was the posterior wall (n=16, 57.2%; 3.5±0.9 repetitions) followed by roof (n=7, 25%; 3.2±0.4 repetitions) and anterior wall (n=5, 17.8%; 3 repetitions). The number of electrodes displaying earliest activation was similar across the posterior wall, roof and anterior wall (1.93±0.9 vs 2.8±1.5 vs 2±0.7, p=0.37). No focal activations were observed from the PV maps. Figure 3 show examples of focal activations on the posterior wall, roof and anterior wall of the LA.

Rotational activations were seen only in 2/15 patients of whom one had them in the posterior wall (n=8, 2.3±0.4 revolutions) and the other around the left superior PV (n=4, 2 revolutions). Figure 4 and 5 show examples of rotational activations in the posterior wall and the base of left superior PV respectively. The rotational activations were unstable recurring only 0.8±0.8 times per 30-seconds map.

Of the remainder of CARTOFINDER maps from LA and PV's (n=138), no discernible rotational or focal activity was observed. These maps showed a predominance of disorganised activations and occasional linear wavefront that circulated in a random trajectory. Several random ill-sustained focal activations (78.8% single activations; 21.2%, 2 consecutive activities) were observed but none qualified to be a driver.

Left Atrial Appendage

In 2/15 (13.3%) patients (17.7% of LAA maps), 67 focal activations were observed from the LAA. In these 2 patients, all the 8 LAA maps showed focal activations with a mean 5.9±2.2 repetitions. Focal activations were more spatially conserved in the LAA (number of electrodes with earliest activation, LAA vs LA: 1.7±0.7 vs 2.2±1.1, p=0.032) occurring exclusively on the anterior wall of LAA distally. The LAA was passively activated in the remainder of patients (13/15, 86.7%). Figure 6 shows an example of focal activation with associated unipolar ECG's arising from the anterior wall of LAA. As observed in the LA, several isolated early activations were seen to arise from the LAA, but none satisfied the definition of a driver. No rotational activations were observed in the LAA in any of the patients.

AF Cycle Length and Driver Sites

The mAFCL was 239.6±18.9ms. Mean regional and LAA AFCL are listed in Table 3.

In contrast to 5.6% CARTOFINDER LA maps showing potential AF drivers, short AFCL (<140ms) was identified in 26.2% (95% CI, 21.1 - 31.3%) of maps with common sites being in the posterior wall (31.4%) followed by roof (29.2%), anterior wall (11.2%) and PV's (8%). Even among patients with drivers, there was no difference in CL between maps with potential drivers and those without (176±21.2ms vs 190±18ms, p=0.34). Rotational activations were observed to have shorter CL than focal activity (157.5±17.7 vs 186.4±17.2ms, p=0.02) with no regional preference. Overall, mLAA-AFCL was significantly shorter than mAFCL (194±14.7 vs 239.6±18.9ms, p=0.008) but in majority of these LAA maps (82.2%), activation was passive.

DISCUSSION

Regional high-density double PentaRay CARTOFINDER mapping of the LA and LAA in persistent AF showed the following main findings:

1) Paucity of rotational and focal drivers despite regional high-density mapping and lack of temporal stability even among infrequently observed drivers.
2) AF cycle length is a poor surrogate of drivers in persistent AF.

CARTOFINDER was developed as a novel technology that had the advantage of automated annotation to identify localised sources based on wavelet analysis of high

quality unipolar electrograms. Following the initial validation study by Daoud et al[125] several studies on CARTOFINDER panoramic atrial mapping[126-129] have shown evidence for reliable identification of localised sources which have been targeted during catheter ablation with good clinical outcomes in PeAF. However, the basket catheters used for panoramic LA mapping are often limited by poor coverage of the atrial walls[464] which leave extensive areas of the endocardium unexplored.

To increase mapping resolution, Calvo et al used a single PentaRay and performed CARTOFINDER mapping of long-standing PeAF in 13 patients and identified rotational activations. These sites fluctuated yet remained spatially stable over time and, when ablated, the impact on local and remote tissue was consistent with elimination of mechanistic drivers. The authors found stable sites of rotational activity (defined as >3 cycles) in both right and left atria, stabilized in attractor regions over time. Clinical outcomes were excellent for patients with long-standing persistent AF, with 70% in sinus rhythm at 12 months[320]. More recently, Takahashi et al extended CARTOFINDER mapping to determine the mechanistic role of LAA in 70 PeAF patients. Using a single PentaRay catheter and the automated proprietary FINDER-Focal and FINDER-Rotational algorithms they reported a high burden of focal activity in the LAA (91%) and a minority of rotational activations thereby concluding that LAA focal activity was an important driver in PeAF[131].

Contrast to these reports, in our study, despite widening the area of high-density mapping by using double PentaRay technique we could not identify stable sustained drivers in the LA. More importantly, only a minority of LAA maps (<20%) showed focal activations. Although using a single PentaRay catheter in the earlier studies that reported

frequent drivers provided increased mapping resolution when compared to the basket catheters, the spatial resolution was limited by the smaller area of mapped endocardium. Consequently, there arises a tendency for overestimation of focal activity as activation times of the unmapped neighbouring cardiac tissue is unavailable to determine the true characteristic of identified drivers. Another limitation in studies assessing LAA trigger is the lack of universal definition for focal activity. We used a strict definition of ≥3 consecutive earliest activation with centrifugal spread but previous studies have used ≥2 consecutive earliest activations[127] and a even further lenient definition of 10 premature activations per minute[499] which often overestimates driver domains.

Previously, it was reported based on computational modelling that short AFCL could be used as surrogate for identifying drivers/substrate[497]. We compared these short AFCL driver sites to their corresponding activation maps and determined no correlation to localised sources. Indeed, focal activations had a longer cycle length than rotational drivers suggesting organisation of AF at the sites of focal activity.

The role of LAA in PeAF continues to remain controversial. In keeping with our observation, a previous large observational series consisting of 7,129 patients undergoing AF ablation found LAA triggers in only 21 patients (0.3%) and only three patients demonstrated triggers exclusively from the LAA[382]. However, empirical LAA ablation as part of the extensive ablation strategy in the BELIEF study[384] showed that after 1.3 procedures, the rate of success at the 24-month follow-up was 76% when the LAA was isolated and 56% when the LAA was not isolated. The concerns associated with adopting LAA ablation are twofold. First, on the basis of the data from the BELIEF trial[384],

achieving complete LAA electrical isolation is technically challenging, requires prolonged ablation even in experienced operators and is associated with a high chance of reconnection. Second, emerging data have implicated a substantial thrombus risk in the isolated appendage and patients undergoing LAA ablation will generally also require LAA occlusion[386,387]. To date, LAA ablation has not been widely adopted and further studies are required to test its role in maintaining AF.

Limitations

We acknowledge the small sample size in our study. Only one PV and specific regions of the LA (roof, posterior wall and anterior walls) were mapped to assess for drivers limiting our ability to establish any sustained drivers from unmapped LA walls or PV's. Finally, although a small number of focal activations were observed in our cohort, determining their mechanism was not possible as the earliest activation observed could represent endocardial break-out of intramural re-entry or epicardial activations from a remote site.

CONCLUSION

In patients with persistent AF, regional high-density double PentaRay mapping of LA and LAA showed infrequent drivers. AFCL is a poor surrogate to identify driver sites. Further studies are required to clarify the mechanistic roles of reported drivers particularly from LAA before empirical ablation is undertaken due to significant safety concerns.

TABLES AND FIGURES

Table 1: Baseline characteristics

Age in years, mean±SD	59.4±9.6
Gender, n (%)	
Males	11 (73.3)
Females	4 (26.7)
AF duration in years, mean±SD	4.0±3.4
Diabetes mellitus, n (%)	2 (13.3)
Hypertension, n (%)	9 (60)
Cerebrovascular accident, n (%)	1 (6.7)
Coronary artery disease, n (%)	1 (6.7)
Sleep Apnea, n (%)	7 (46.7)
Medications, n (%)	
Sotalol	8 (53.3)
Flecainide	1 (6.7)
Beta-Blockers	4 (26.7)
Calcium Channel Blockers	1 (6.7)
Digoxin	3 (20)
Systemic Anticoagulation, n (%)	
NOAC	14 (93.3)
Warfarin	1 (6.7)
LA Volume in ml/m^2 BSA, n (%)	
<30	1 (6.7)
30-40	5 (33.3)
40-50	6 (40)
>50	3 (30)
LV ejection fraction > 55%, n (%)	12 (70)

Table 2: Mapping characteristics

CARTOFINDER (30s) maps, n	229
Posterior wall	53
Roof	43
Anterior wall	42
Left Atrial Appendage	45
Pulmonary vein	46
LSPV	33
RSPV	13
CARTOFINDER maps per patient, mean±SD	15.2±1.8
Duration of AF mapped in minutes, mean±SD	7.6±0.7
Fluoroscopy in minutes, mean±SD	12.8±3.1
Procedural duration in minutes, mean±SD	190.7±25.7

Table 3: Regional AF cycle length

Regions	AF Cycle Length (ms)
Posterior wall	166±18.7
Roof	172±14.1
Anterior wall	201±21.1
LSPV	181±15.5
RSPV	196±14.1
LAA	194±14.7

Figure 1: Fluoroscopy images (RAO) of regional high-density double PentaRay (*) CARTOFINDER mapping of left atrium. (A) Posterior wall (B) Roof (C) Anterior wall (D) Left atrial appendage and (E) Right superior pulmonary vein. TOE, transesophageal echocardiography probe; H, quadripolar catheter in the His position; CS, deflectable decapolar catheter in coronary sinus; Eso, esophageal temperature probe.

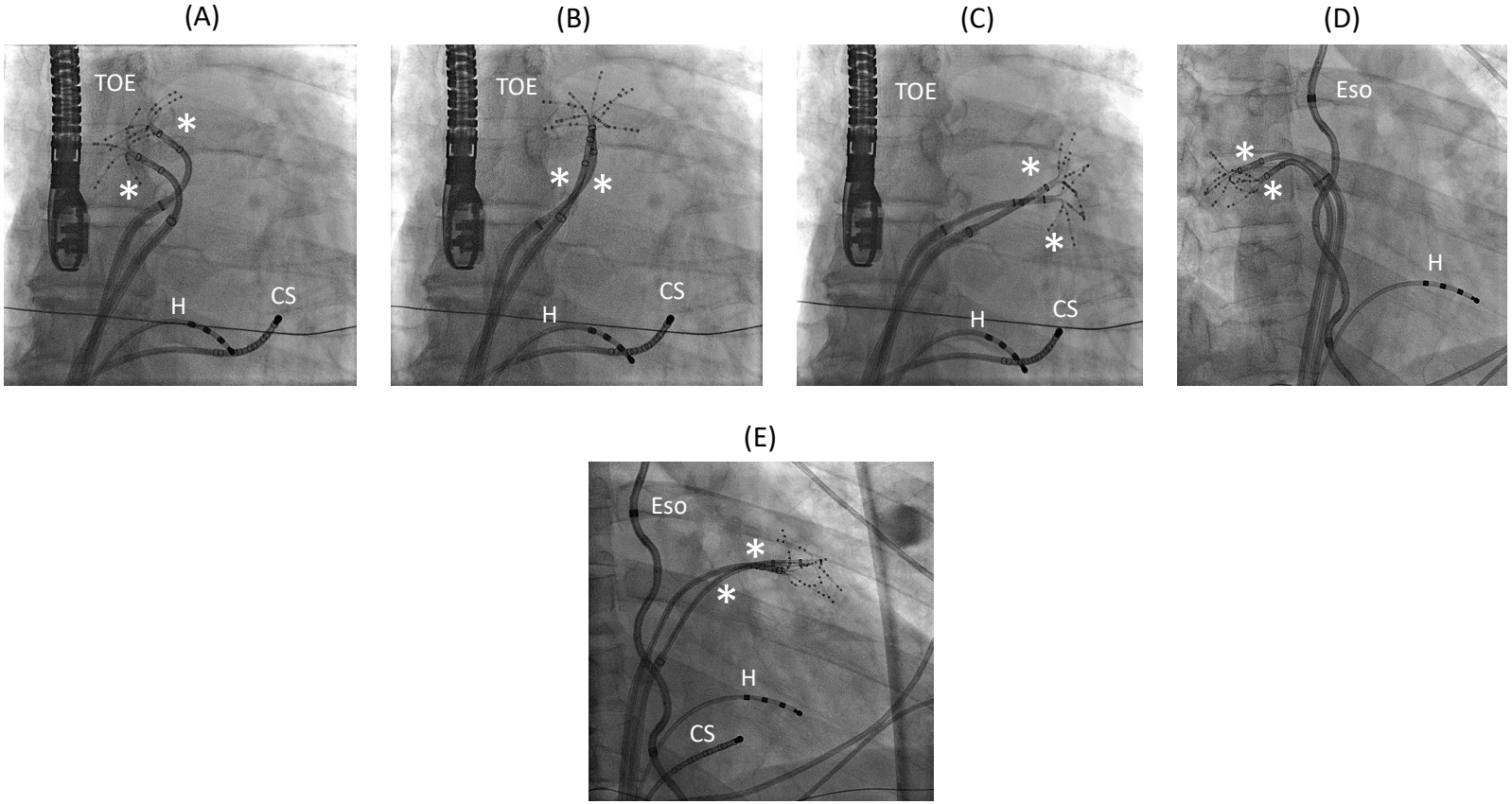


Figure 2: Determining the proportion of short AF cycle lengths from histograms. Percentage of activations with CL <140ms was calculated by the ratio of the area of CL <140ms over the total area on the CL histogram for each map per region as shown in this CL histogram of a single 30-second posterior wall with 35.3% of activations with CL<140ms.

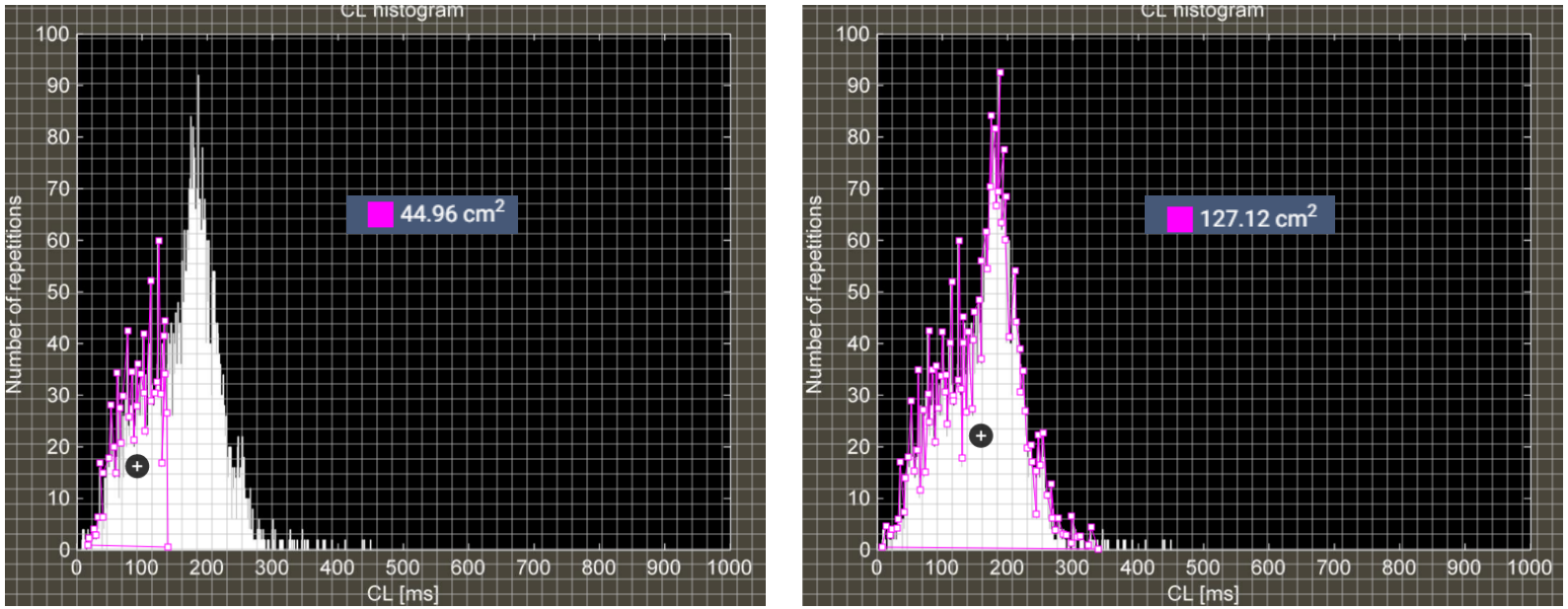


Figure 3: Example of focal activations on regional high-density double PentaRay CARTOFINDER mapping of the left atrium.

* denotes focal activation with centrifugal spread on (A) posterior wall, (B) roof and (C) anterior wall with associated unipolar EGM.

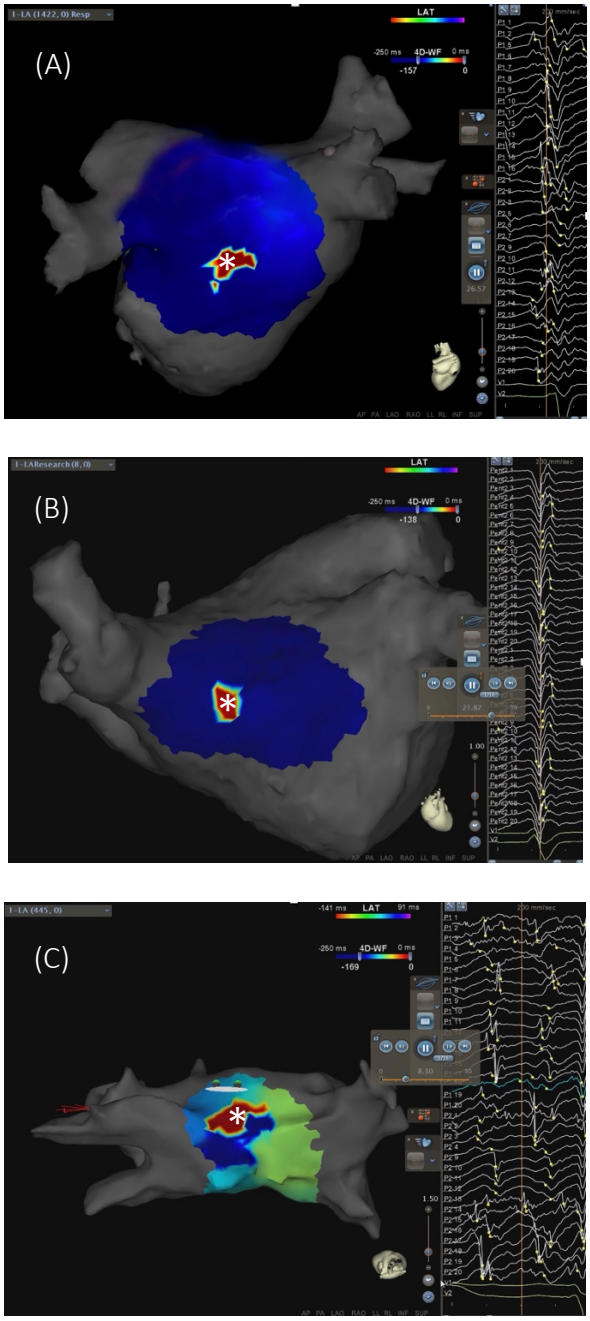


Figure 4: Example of counterclockwise rotational activation (white arrow) on the posterior wall of left atrium.

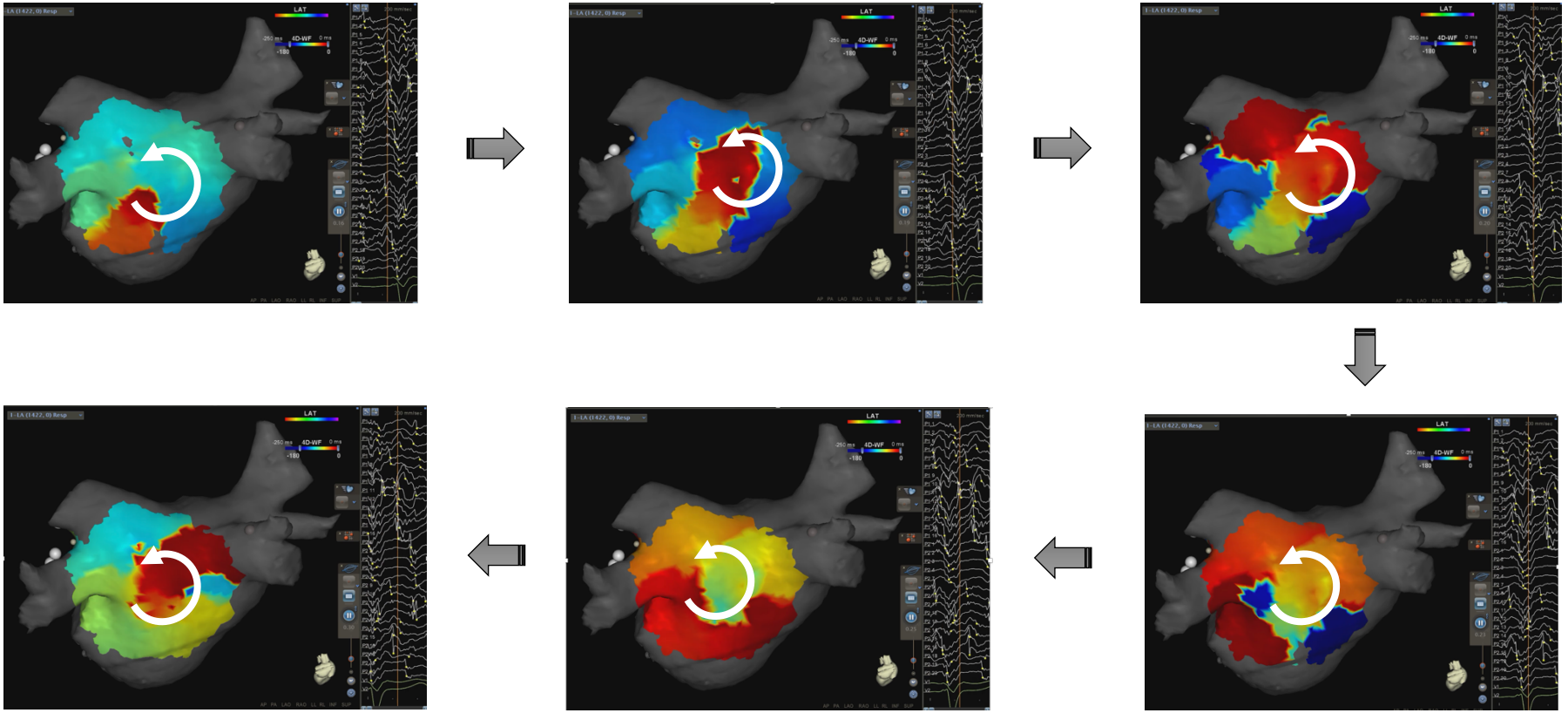


Figure 5: Example of counterclockwise rotational activation (white arrow) around the left superior pulmonary vein

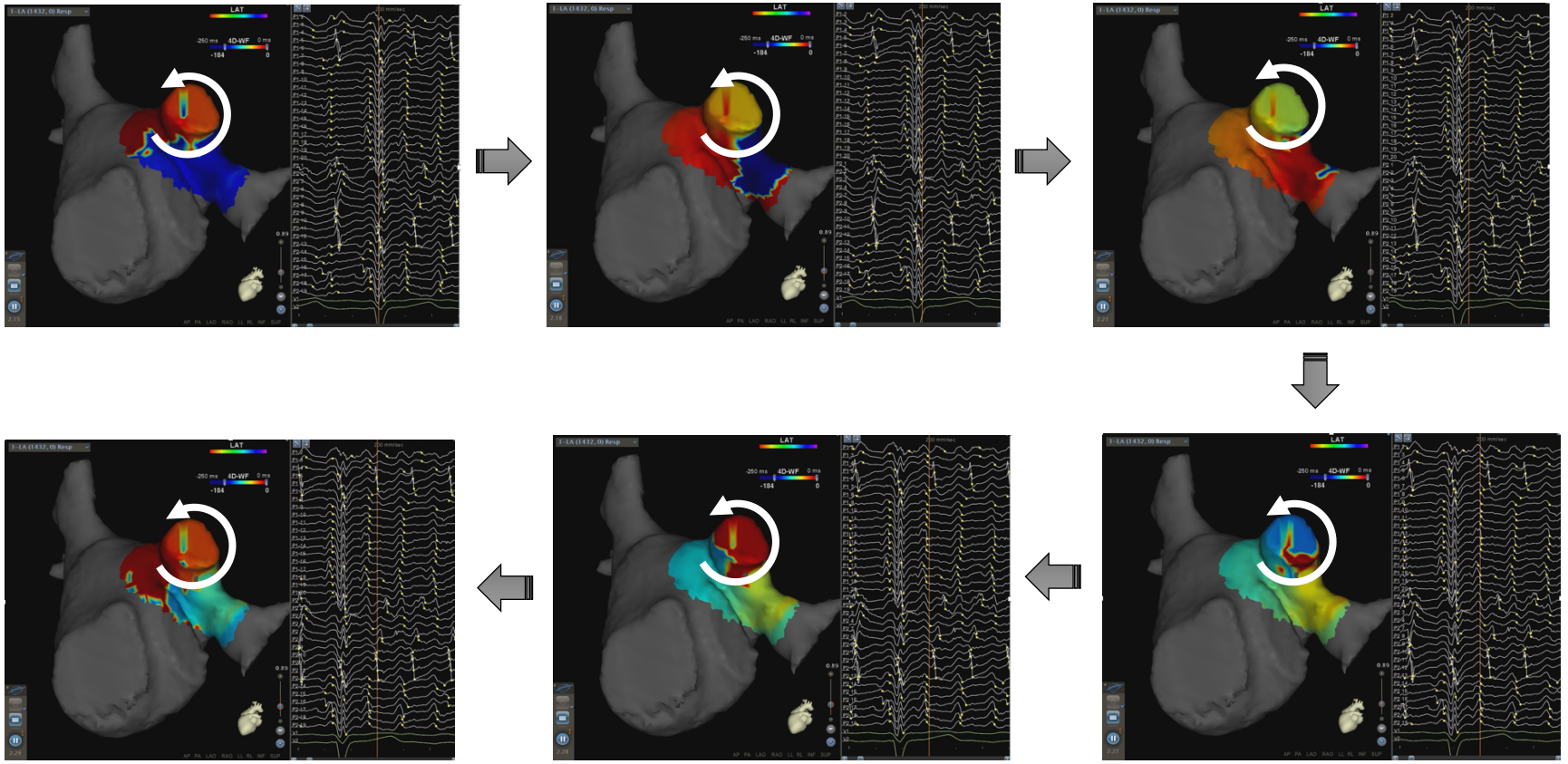
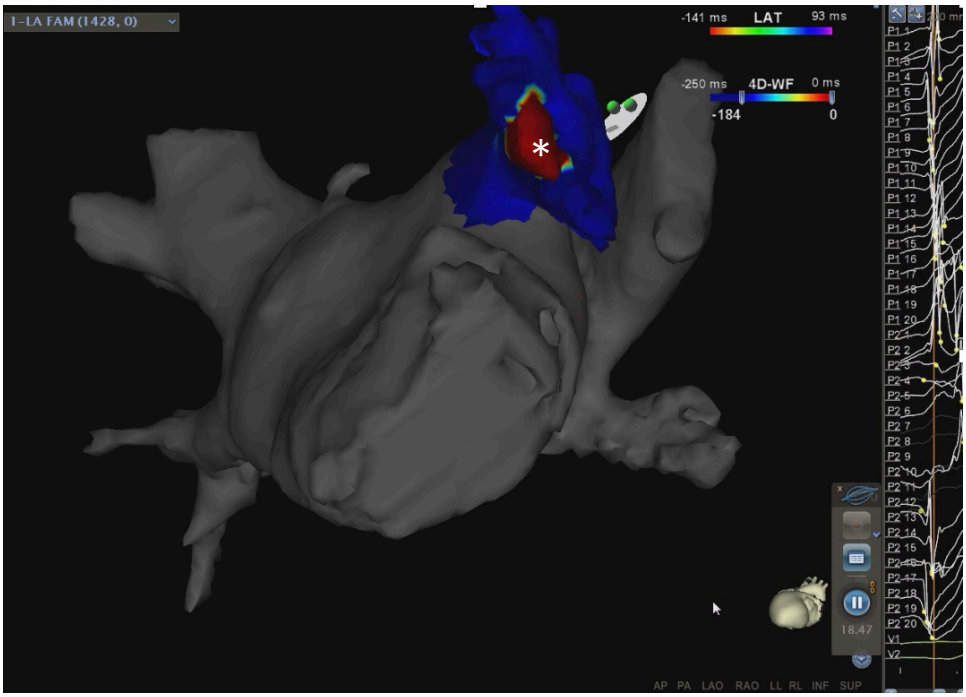


Figure 6: Example of a focal activation (asterisk) in the anterior wall of left atrial appendage



CHAPTER – 8

RANDOMISED EVALUATION OF THE IMPACT OF CATHETER ABLATION ON PSYCHOLOGICAL DISTRESS IN ATRIAL FIBRILLATION: RATIONALE AND DESIGN OF THE REMEDIAL-PD STUDY

INTRODUCTION

Atrial fibrillation (AF) is a serious public health problem with increasing prevalence world-wide[1]. In addition to increased risk of stroke[2], heart failure[3] and mortality[4], patients with AF have substantially impaired quality of life (QOL)[5,6]. Psychological co-morbidities such as anxiety, depression and specific personality traits are important determinants of the impact of AF on severity of decline in QOL[47]. Indeed, a recent report has suggested that nearly a third of AF patients referred for tertiary evaluation suffer from severe psychological distress with up to 20% reporting suicidal ideation[46].

The primary goal in managing AF patients is to improve symptoms and catheter ablation (CA) is a well-established treatment strategy to achieve this[268]. CA has also been demonstrated to improve psychological distress in a recent observational study[46]. However, to date, there are no randomised controlled trials to assess the differential effect of curative catheter ablation versus medical therapy (AAD) on measures of psychological distress in atrial fibrillation.

In the current randomised controlled study, we aim to compare the direct effects of CA versus AAD on psychological distress in a consecutive cohort of paroxysmal or persistent AF patients referred for CA.

HYPOTHESES

We hypothesise that:

- Successful management of AF with CA will result in a greater improvement in markers of psychological distress compared to ongoing medical management.

Secondary hypotheses include:

- There will be a high prevalence of psychological distress and suicidal ideation in a consecutive cohort of AF patients referred for management and consideration of catheter ablation.
- Level of psychological distress relates to personality type
- Level of psychological distress correlates positively with AF burden and inversely with medical therapy.

METHODOLOGY

Study Design

REMEDIAL is an investigator-initiated, prospective, multicenter, randomized clinical trial. Patients will be recruited from two tertiary hospitals in Australia. Ethics committee approval has been sought and obtained at each participating institution. This study is

conducted in full conformity with the 1964 declaration of Helsinki and all subsequent revisions as well as in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines). The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000062224) on 17th January, 2018 before the enrolment of the first patient and the study protocol is available online at the ANZCTR website (www.anzctr.org.au).

Study Population

A total of 100 patients with AF referred to the arrhythmia centre at The Royal Melbourne Hospital and The Alfred Hospital in Victoria, Australia for further management will be enrolled.

Eligible participants are required to have paroxysmal or persistent AF (defined as per 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[500]) that warranted CA as judged by the managing electrophysiologist. Patients being treated for severe depression will be excluded. Full eligibility criteria are listed in Table 1. All participants provided written informed consent to participate in the study.

Randomisation

Participants will undergo sequential randomisation on a 1:1 basis between medical management and catheter ablation. Concealment of allocation will be achieved by using sequentially numbered, opaque sealed envelopes (SNOSE) scheme. Patients undergoing CA could not be blinded to treatment allocation. Investigators following up participants and engaging in assessing psychological distress and reporting echocardiography will be

blinded to treatment allocation. Investigators reporting imaging were not involved in the performance of ablation procedures or clinical management.

Study Procedures

Eligible patients will be screened for exclusion criteria and after consent will be randomised to either CA or medical management. An overview of the schedule of testing over the 12-month study period is provided in Figure 1.

Evaluations include:

Detailed assessments for evaluation of psychological distress,

QoL assessment via SF 36, the University of Toronto AF severity scale and the Canadian Cardiovascular Society Severity in AF Scale.

Transthoracic echocardiography with LA strain imaging for analysis of atrial reservoir function.

AF burden assessment. This will be determined either from pre-existing implanted devices (pacemaker, defibrillator or resynchronisation therapy) or implanted loop recorder (Reveal LINQ; Medtronic Inc, Minneapolis, MN, USA) in consenting participants or through Kardia device using the AliveCor mobile phone application.

Assessments will commence at baseline and will be repeated at 3, 6, 9 and 12 months by qualified interviewers (with the exception of the echocardiogram which will be repeated at 6 and 12 months). After completion of the study, patients randomised to the medical

management arm will be eligible to undergo CA on the basis of symptom severity. Patients who missed follow-up appointments will be contacted by either telephone or email until contact was made. For patients who did not attend in person, questionnaires will be mailed to follow up with phone calls to ensure compliance. Rhythm data for these patients will be derived from remote monitoring or in-clinic interrogation of implanted device at a later date. A summary of the study workflow is shown in Figure 1.

Psychological Testing

Participants will be assessed for anxiety and depression, personality type and quality of life using validated self-report questionnaires.

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) questionnaire has been validated as a useful tool for initial diagnosis and to track progression (or resolution) of psychological symptoms. It is one of the National Institute for Health and Care Excellence (NICE) recommended tools for diagnosis of depression and anxiety[501]. The questionnaire comprises seven questions for anxiety and seven questions for depression and is designed to evaluate symptoms of anxiety and depression in medical populations, with minimal influence from somatic symptoms that may falsely elevate the scores. Cut-off scores are available for quantification, for example a score of 8 or more for anxiety has a specificity of 0.78 and a sensitivity of 0.9, and for depression a specificity of 0.79 and a sensitivity of 0.83[502]. In our study we will define significant psychological distress based on HADS score ≥ 8.

Depression will also be quantified using the Centre for Epidemiological Studies-Depression (CES-D) which is a 20-item measure of how often over the past week symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely are experienced. Response options range from 0 to 3 for each item (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the time, 3 = Most or Almost All the Time). Scores range from 0 to 60, with high scores indicating greater depressive symptoms. The CES-D also provides cut-off scores (≥ 16 points) that aid in identifying individuals at risk for clinical depression, with good sensitivity and specificity and high internal consistency[503].

Screening participants for self-harm will be undertaken using the Beck Depression Inventory (BDI-II), a 21-item self-report rating inventory that measures characteristic attitudes and symptoms of depression[504]. The BDI demonstrates high internal consistency, with Cronbach's alpha coefficients of 0.86 and 0.81 for psychiatric and non-psychiatric populations respectively[505]. Cut-offs used in our study will be based on the following guidelines that have been suggested to interpret the BDI-II[506]: Minimal range 0–13; Mild depression 14–19; Moderate depression 20– 28; Severe depression 29 – 63.

Type D Personality and Chronic Anxiety State

The DS-14 is an accepted and widely used diagnostic instrument for the assessment of the type-D pattern, which has been established as a predictor of adverse clinical events and cardiac prognosis in patients with heart disease[507]. The Type D personality denotes a high degree of negative affectivity and social inhibition in the underlying personality. The DS-14 is a 14-item questionnaire, with each item scored between 0 and 4. Cronbach's

alpha co-efficient of internal consistency is between 0.86 and 0.88[508]. Subjects will be classified as Type D personality if they demonstrate both negative affectivity ≥10 and social inhibition ≥ 10[507].

The Cohen Perceived Stress Scale (PSS) measures the degree to which life situations are appraised as stressful. Each item is scored on a 5-point Likert scale from 0 to 4, with higher total scores indicating greater perceived stress. The Cronbach alpha co-efficient of internal consistency is 0.85 and test-retest reliability 0.85[509]. Scores ranging from 0-13 would be considered low stress, 14-26 as moderate stress and 27-40 would be considered high perceived stress[510].

Quality of Life Assessment

Quality of life will be assessed using the SF-36 generic quality of life instrument, the University of Toronto AF severity scale and the Canadian Cardiovascular Society Severity in AF Scale.

The SF-36 questionnaire consists of 36 items that assess eight health domains: physical functioning, role limitations because of physical problems, bodily pain, general health perception, vitality, social functioning, role limitations because of emotional problems and mental health. In addition to these eight subscales, physical component summary (PCS) and mental component summary (MCS) scores are also generated, which are normalised to an overall population mean of 50±10 (± SD)[511]. For all subscales, higher scores represent better functioning and QoL. The mental component summary provides

only a general measure of the overall mental health and cannot differentiate the constructs of depression and anxiety.

The University of Toronto AF Severity scale measures global well-being in addition to total AF and current AF status and has the advantage of capturing QoL changes over time. Individual symptoms attributable to AF are scored on a five-point Likert scale, such that the total AFSS severity score ranges from 0 to 35, with higher scores indicating increased AFSS[512]. Similarly, the Canadian Cardiovascular Society Severity in AF scale determines symptom-rhythm correlation, its effect on patient daily function, and QoL. It has been viewed as achieving a balance of simplicity, precision, and comprehensiveness in assessing QoL[513].

Trans-Thoracic Echocardiography

Patients will undergo echocardiograms at baseline to ensure no structural heart disease exclusion criteria are present (significant valvular heart disease, prior infarct with myocardial scar and EF<40%; Hypertrophic cardiomyopathy, ASD or ASD repair/closure). LA strain and volumetric analyses will be performed at baseline and during 6-month and 12 months follow up time points to monitor LA reservoir function in all participants of both treatment arms.

AF Burden Assessment

Quantification of AF burden will be determined through the AliveCor mobile phone application (app). Patients will be asked to transmit twice-daily 30s ECG tracings regardless of their symptoms; and if symptomatic, additional tracings at symptom onset

and termination will be requested. Patients who did not adhere to ECG monitoring will undergo adjunctive 7-day Holter monitoring. The investigators will review all ECGs, including all mobile app tracings, stored electrograms from implantable devices, and Holter recordings. All ECGs logged as "possible atrial fibrillation" by the computerized algorithm or those suspected to represent AF on initial review will be reviewed by two cardiologists who are unaware of the group assignments. The end point would be met if both cardiologists concurred that the tracing represented AF. Burden will be calculated as the percentage of days during the study period when AF was detected and confirmed[514].

Medical Management

Patients randomized to ongoing medical therapy will have their anti-arrhythmic drugs maximised in an effort to maintain SR. Among patients on rate control therapy, medications will be titrated to achieve a resting rate <80 beats/min and/or an average 24-hr ventricular rate <100 beats/min in accordance with current guidelines[515]. Changes in medication regimens and dose alterations will be recorded during each follow-up visit.

CA procedure

Catheter ablation will be performed within 1 month of randomization. Oral anticoagulation will be discontinued 24h before the procedure with the exception of vitamin K antagonists or dabigatran, which will not be interrupted. Antiarrhythmic medication will be discontinued 5 half-lives pre-procedure with the exception of amiodarone. All procedures will be performed under general anaesthesia with the assistance of a 3-D mapping system. After exclusion of intracardiac thrombus,

transesophageal echocardiographic-guided double transseptal punctures will be performed. Unfractionated heparin will be administered to achieve an activated clotting time 300-350s with 10,000 units of heparin administered prior to the first transeptal puncture. Mapping of the left atrium and pulmonary veins will be performed with a 20-pole circular mapping catheter and ablation with a 3.5-mm irrigated-tipped catheter following direct current cardioversion (DCCV) to restore sinus rhythm (SR) (power range: 25 W [posteriorly] to 30 W; contact force range: 10 to 40 g anteriorly and 10 to 25 g posteriorly). In patients with paroxysmal AF, the index procedure consists of wide antral pulmonary vein isolation. In patients with persistent AF the procedure also consists of wide antral circumferential pulmonary vein isolation incorporating much of the posterior left atrial myocardium. In persistent AF patients, additional roof and inferior lines to isolate the remaining posterior LA will be performed as per the physician's discretion. In general, antiarrhythmic medications will be continued for 3-months after the procedure and then weaned and discontinued at the managing physician's discretion. Repeat procedure will be permitted for symptomatic recurrence occurring beyond 3 months' post-index procedure.

Study Endpoints

The primary endpoint of the study is difference in psychological distress assessed by the HADS scale between the two arms during 12 months of follow-up.

Secondary endpoints will include between group comparative assessment of:

1) Depression as measured by the Centre for Epidemiological Studies-Depression (CES-D)

2) Depression and risk of self-harm as measured by the Beck Depression Inventory (BDI-II)
3) QoL outcome using (i) the SF 36, (ii) The University of Toronto AF Severity scale. (iii) The Canadian Cardiovascular Society Severity in AF scale
4) AF burden which will be calculated as a percentage of days with documented AF episodes.
5) Measures of reverse structural remodelling (LA volume and LA strain)
6) Arrhythmia related hospitalisations or hospital presentations
7) Complications
8) Medication usage

Additional secondary endpoints for each group will include a correlation between:

1) AF burden and psychological outcomes
2) Personality type and psychological distress in each group.

Statistical Analysis

Categorical variables will be reported as count and percentages, while continuous variables as mean and SD. All modelling will be based on an intention-to-treat model. Modelling of continuous outcomes at each endpoint will use a general linear model with explanatory variables including site, treatment arm and baseline measurement. However, a more comprehensive analysis of continuous outcomes will be based on a mixed linear model and will include participant as the random factor and treatment, site and time as fixed factors and the baseline measurements as a covariate. Mean treatment differences between groups at each follow-up period will be estimated from this model.

95% confidence intervals (CI) will be reported for this difference of means to quantify the precision of the estimates. A p-value <0.05 will be considered statistically significant.

Sample size calculation

Based on our previous study on psychological distress in patients with AF[46], the average HADS score (score range 0-21) was approximately 11 (in the abnormal range) in this cohort. A meaningful clinical effect of CA would be to reduce the mean HADS score to the normal range – the upper limit of which is 7. This corresponds to a mean difference of 4 points. Using this mean difference, and assuming a standard deviation of 5.5, in order for the study to reach a power of 80% with type 1 error of 5%, a minimum of 31 patients will be required in each arm.

Sample size calculations were also considered for secondary outcome parameters based on background data as shown (Table 2a). Table 2b shows the sample size calculated for each of the additional outcomes considered using power of 80% and type I error rate of 5%. In cases where the standard deviations differ between arms, the higher value was used for the sample size calculation.

Using the above data and allowing for a 10% drop out rate, 100 participants will be recruited for the REMEDIAL study.

DISCUSSION

The REMEDIAL study is a randomised controlled trial that will compare the impact of CA versus AAD's on psychological distress in a cohort of symptomatic paroxysmal or persistent AF patients referred for arrhythmia management to two tertiary care hospitals. The study will also correlate AF burden to symptoms and psychological distress and assess improvement of LA reservoir function with treatment strategies.

Mental Health and AF

Patients with AF have a high prevalence of depression and anxiety. In a study by Thrall et al[45] 38% of AF patients met the criteria for depression according to the BDI and in comparison to hypertensive controls, anxiety levels were more common in AF patients (37.4 vs 33.3, p=0.02). High burden of psychological distress (35%) was also observed in the study by Walters et al[46] among 78 symptomatic AF patients and strikingly 20% reported suicidal ideation. Both Type-D personality and personality marked by vulnerability to stress were independent predictors of distress.

Personality style and symptom severity

Several other aspects of personality style have also been associated with the subjective experience of AF. Ong et al[516] showed that anxiety sensitivity (assessed by the Anxiety Sensitivity Index (ASI), a 16-item measure that assesses the fear of anxiety sensations and the extent to which anxiety sensations are believed to cause embarrassment, illness, and loss of control) was associated with poorer QoL assessed by SF-36, greater symptom severity (AFSS), and higher psychological distress (assessed by HADS). On the other hand, optimism correlated with better mental QoL (MCS, SF-36) and lower distress. Elevated

perception of symptoms also impacted upon QoL. In a study by Lane et al[517], illness identity (as assessed by the Illness Perception Questionnaire), inversely correlated with the physical health slope over 12-months.

Psychological factors and AF symptom severity

It is now well-established that psychological factors also influence AF symptomatology. Gehi et al[47] observed that psychological comorbidities including depression, anxiety, and somatization are associated with worse general health status and AF attributed symptom severity and that greater severity of depression and anxiety symptoms were associated with more frequent visits to seek medical attention for AF. Sears et al[518] showed that higher levels of reported negative emotions were more strongly associated with a greater number of reported AF symptoms. Depression and anxiety were thought to be more important than number of AF episodes in predicting AF symptom severity. In a specific population with paroxysmal AF and an implantable cardioverter defibrillator with atrial tachyarrhythmia therapies in situ, Camm et al[519] reported the number of device-counted and treated AF episodes to be one factor associated with symptom severity, and also found psychological distress to be a more powerful predictor of AF symptoms than any device-recorded objective measure of AF burden.

Robust evidence on the impact of CA on psychological distress is lacking but observational studies have supported its beneficial effects. In a study with 166 symptomatic PAF patients, Sang et al[520] showed that among those who underwent CA (n=82), 26.8% reported a significant reduction in symptoms of depression and 21.4% had a significant reduction in symptoms of anxiety at the 12-month follow-up while no difference was

observed in patients treated with AAD's alone (n=84). They postulated that the improvement may have been attributable to the beneficial effects of sinus rhythm on physical capability allowing patients to regain a positive affective disposition. In addition, freedom from side effects of AAD's and anticoagulation was also considered a major factor in improved QoL. More recently, similar observations were also made by Walters et al[46] where compared to medical management, 20/78 symptomatic AF patients who underwent CA showed significant reductions in psychological distress (HADS, 13.9±1.8 to 4.3±1.8; P<0.05) and prevalence of suicidal ideation (30–5%; P=0.02).

With the ability to assess general mental well-being, data from studies using the SF-36 tool have also provided indirect evidence for the positive impact of CA. In a 2015 meta-analysis of 12-RCT's (n=1707) by Siontis et al[283], CA demonstrated early improvement in SF-36 scores when compared to medical therapy. However, this effect was not maintained beyond 9-months of follow-up. Most recently, the CAPTAF trial[284], showed a sustained improvement in QoL determined by SF-36 that persisted at 12-months for those treated with CA compared with the medical treatment arm. Although reassuring, drawing definitive conclusions based on these results are challenging as the SF-36 does not provide a detailed assessment of depression-, anxiety-, or PTSD-related diagnoses as it cannot differentiate specific psychological conditions.

In the current study, both SF-36 and psychological disease-specific tools will be utilised to assess the impact of CA on psychological distress in AF.

CURRENT STATUS

Enrolment for the REMEDIAL study commenced in June 2018 and 100 participants have been recruited by March 2020. At the time of submission of this manuscript, 54 have completed 12 months follow up. Final results of the study are expected by June 2021.

SIGNIFICANCE OF THE REMEDIAL STUDY

A high prevalence of psychological distress in AF patients has been previously demonstrated. This study will provide further insights into the clinical spectrum and predictors of psychological distress in patients with AF. More importantly, we will able to assess the response and improvement of this distress with appropriate and timely management. We will specifically evaluate the response in patients with psychological distress to either medical management or catheter ablation. Psychological distress response has been shown to be critical to determining clinical outcomes and general well-being across a range of medical conditions[521,522] and preliminary data suggests this is true of AF[46].

CONCLUSION

The randomised controlled REMEDIAL study will assess the direct effects of CA on psychological distress compared with medical management. The results will strengthen the rationale for using broad endpoints focussed on the patient's overall health in defining successful outcomes and help in implementing a patient-centred treatment strategy.

TABLES AND FIGURES

Table 1: REMEDIAL Inclusion/Exclusion criteria

Inclusion	Exclusion
1) Documented symptomatic AF over the preceding 6 months have: a. Paroxysmal episodes lasting ≥ 1 hour in duration: (that terminate spontaneously within 7 days or cardioversion is performed within 48 hours of AF onset) or b. Persistent AF episode: (sustained for ≥ 7 days: 2) Warrant active therapy beyond simple ongoing observation. 3) Be eligible for CA and ≥ 2 sequential rhythm control and/or ≥ 2 rate control drugs 4) Have the capacity to understand and sign an informed consent form. 5) Age ≥18 and ≤80 years.	1) Severe valvular heart disease 2) Prior myocardial infarction and LVEF<40% 3) Hypertrophic cardiomyopathy 4) ASD or ASD repair/closure 5) Patients treated for suicidal ideation 6) Patients being treated for severe depression, anxiety or mood disorders 7) Pregnancy 8) Reversible causes of AF including thyroid disorders acute alcohol intoxication, recent major surgery procedures, or trauma. 9) Prior LA catheter ablation with the intention of treating AF 10) Prior surgical interventions for AF such as the Maze procedure 11) Contraindication to appropriate anti-coagulation 12) Medical conditions limiting expected survival to <1 year 13) Unable to give informed consent.

AF, atrial fibrillation; ASD, atrial septal defect; CA, catheter ablation; LA, left atrium; LVEF, left ventricular ejection fraction.

Table 2a: Background data for additional outcomes considered in sample size calculations

Outcome measure	Untreated		Treated		Scale range	SD (either)
	Mean	SD	Mean	SD		
AFSS[46]	9.7	1.0	2.2	1.8	0-35	
BDI [523]	17	9.7	5.4	3	0-63	
STAI (State) [524]	48.9		42.2		20-80	9.6
STAI (Trait) [525]	37.4		33.3		20-80	11

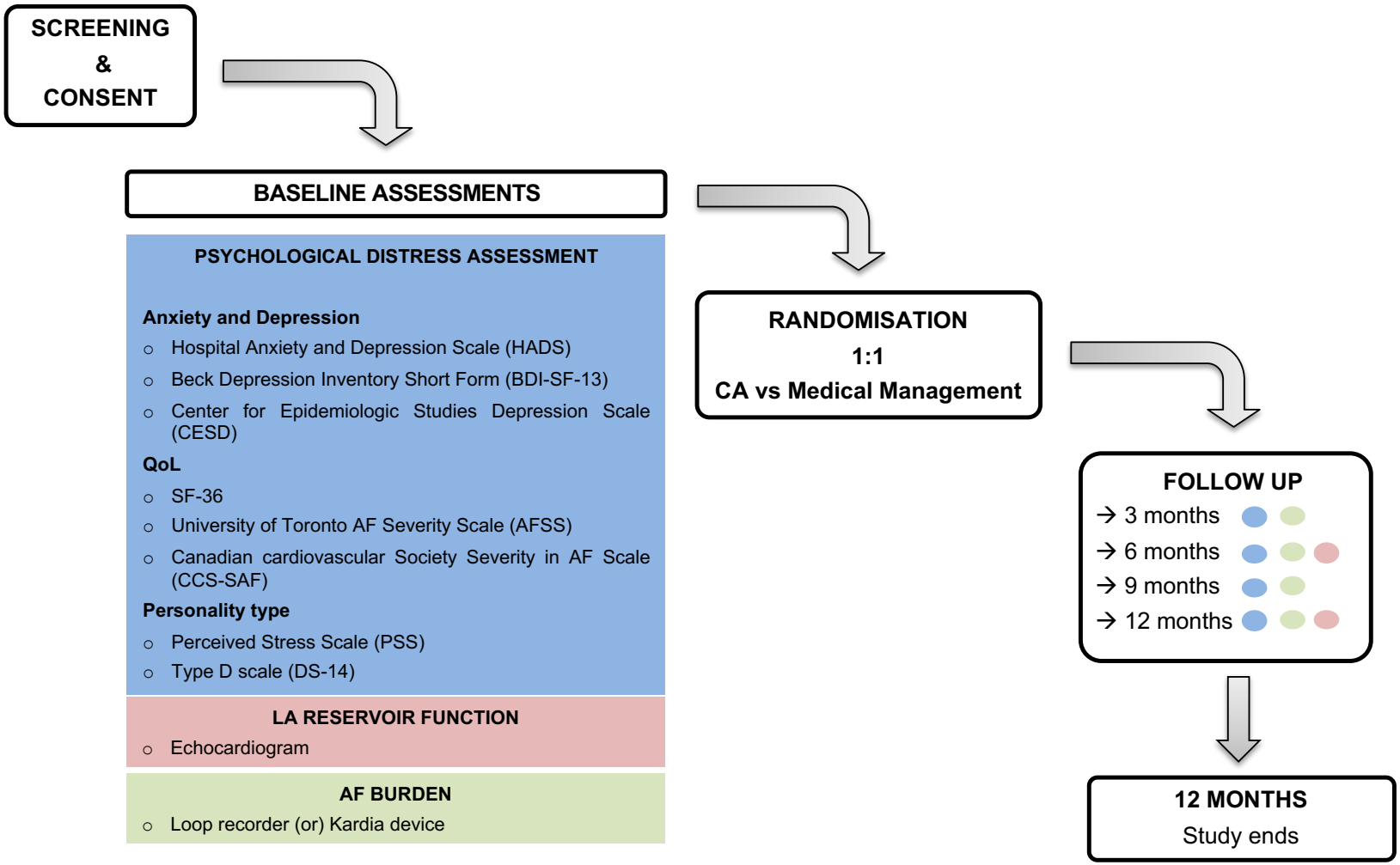
AFSS, Atrial Fibrillation Symptom Severity Scale; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory.

Table 2b: Sample size calculated for each of the additional outcomes

Outcome measure	Untreated (means)	Treated (means)	SD assumed in each arm	Sample size in each arm
AFSS	10	3	8.75	26
BDI II	20	10	7.5	10
STAI (State)	49	42	9	26
STAI (Trait)	38	32	10	44

AFSS, Atrial Fibrillation Symptom Severity Scale; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory.

Figure 1: REMEDIAL-PD Workflow



CHAPTER – 9

RANDOMISED EVALUATION OF THE IMPACT OF CATHETER ABLATION VERSUS MEDICAL THERAPY ON NEUROCOGNITIVE FUNCTION IN ATRIAL FIBRILLATION: RATIONALE AND DESIGN OF THE REMEDIAL-CF STUDY

INTRODUCTION

Atrial fibrillation (AF) is the commonest arrythmia encountered in clinical practice with increasing prevalence in ageing population [315]. Besides its associated risk for stroke [2], heart failure [3] and mortality [4], AF has been independently linked to memory impairment, cognitive decline, and general dementia in patients without pre-existing disease [300,526]. Furthermore, a recent meta-analysis of eight prospective studies, has also shown that AF independently increases the risk of incident dementia [301].

The primary goal in managing AF patients is to improve symptoms and catheter ablation (CA) is a well-established treatment strategy to achieve this [268]. Despite its well established safety profile when performed in large volume centres by experienced operators [527], there exists some concern with regard to the incidence of silent cerebral embolisms post CA [40,42] which could potentially contribute post-operative cognitive decline [43]. With AF also being a risk factor for development of cognitive dysfunction, it remains unclear where the balance of cognitive risk lies with respect to AF management.

In the current randomised controlled study, we aim to compare the direct effects of CA to AAD on neurocognitive function in a consecutive cohort of paroxysmal or persistent AF patients referred for CA.

HYPOTHESES

We hypothesise that successful management of AF with CA will result in a significantly greater improvement in markers of neurocognitive function compared to ongoing AAD.

METHODOLOGY

Study Design

REMEDIAL is an investigator-initiated, prospective, multicentre, randomized clinical trial. Patients will be recruited from two tertiary hospitals in Australia to evaluate the study hypotheses. Ethics committee approval has been sought and obtained at each participating institution. This study is conducted in full conformity with the 1964 declaration of Helsinki and all subsequent revisions as well as in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines). The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000062224) on 17th January, 2018 before the enrolment of the first patient and the study protocol is available online at the ANZCTR website (www.anzctr.org.au).

Study Population

A total of 100 patients with AF referred to the arrhythmia centre at Royal Melbourne Hospital and Alfred Hospital in Victoria, Australia for further management will be enrolled.

Eligible subjects were required to have paroxysmal or persistent AF (defined as per 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation [500]) that warranted CA as judged by the electrophysiologist caring for the patient's AF. Patients being treated for pre-existing neurological condition will be excluded. Full eligibility criteria are listed in Table 1. All participants provided written informed consent to partake in the study.

Randomisation

Participants will undergo sequential randomisation on a 1:1 basis between medical management and catheter ablation. Concealment of allocation will be achieved by using sequentially numbered, opaque sealed envelopes (SNOSE) scheme. Patients undergoing CA could not be blinded to treatment allocation. Investigators following up participants and administering neurocognitive testing will be blinded to treatment allocation but could not be blinded to cardiac rhythm or the presence of implantable loop recorders (ILRs).

Study Procedures

Eligible patients would be screened for exclusion and after consent would be randomised to either CA or medical management. At baseline participants would undergo detailed assessments for neurocognitive function with eight different tests as discussed later. Burden of AF will be determined either from pre-existing implanted devices (pacemaker, defibrillator or resynchronisation therapy) or implanted loop recorder (Reveal LINQ; Medtronic Inc, Minneapolis, MN, USA) in consenting participants or through Kardia device using the AliveCor mobile phone application. Clinical review will be repeated at 3, 6, 9 and 12 months and all assessments will be repeated during each of the follow-up visits. After completion of the study, patients in the medical management arm could undergo CA at physician discretion. A summary of the study workflow is shown in Figure 1.

Neurocognitive Testing

Eight validated neurocognitive tests [528] will be administered by trained interviewers and the results will be based on the number of correct answers or the time taken to complete the test. These tests include:

- The Consortium to Establish a Registry for Alzheimer's Disease Auditory Verbal Learning Test (CERAD): This test assesses the memory domain and requires the participant to listen to a list of 10 words read to them by the examiner and then to immediately recall as many of those words as possible. This procedure is repeated three times with the same word list, with the order of word presentation

changed on each occasion. After a 10-min delay filled with other cognitive tasks, patients must recall as many words from the word list as possible. The number of words recalled at this point is measured.

- The Digit–Symbol Substitution Test from the Wechsler Adult Intelligence Scale-Revised: This requires participants to reproduce on paper, within 90s, as many coded symbols as possible in blank boxes beneath randomly generated digits, according to a coding scheme for pairing digits with symbols. The number of boxes completed in 90s is counted, and errors are deducted from this. Memory and processing functions are assessed using this test.

- The Trail Making Tests (Parts A and B): These tests are designed to evaluate executive functioning. In Part A the participants connect numbered circles in sequence as quickly as possible. Part B requires participants to connect a series of circles that contain a sequence of numbers and letters in the correct but alternating order (i.e., numeric and alphabetical). The number of seconds required to complete these tasks is measured.

- The Controlled Oral Word Association Test (COWAT): Participants are presented with a letter and are asked to spontaneously generate as many words as possible for the given letter within 60s. This task is repeated for three separate letters to check for verbal fluency. This test provides an overall assessment of frontal and temporal lobe functions.

- The Semantic Fluency test requires the participant to name as many words as possible from a predefined category (e.g., animals, clothing, first names) within 60s. The number of words correctly named provides a measurement of verbal fluency, semantic memory as part of temporal and frontal lobe functions.

- The Grooved Pegboard Test (Dominant and Non-Dominant Hand): This test requires participants to place 25 keyed pegs in an array of holes with randomly oriented slots using their dominant hand first and then the test is repeated with the non-dominant hand. The number of seconds required to complete the task with the dominant and non-dominant hands are measured.

Quality of Life Assessment

Quality of life will be assessed using the SF-36 generic quality of life instrument. This questionnaire consists of 36 items that assess eight health domains: physical functioning, role limitations because of physical problems, bodily pain, general health perception, vitality, social functioning, role limitations because of emotional problems and mental health. In addition to these eight subscales, physical component summary (PCS) and mental component summary (MCS) scores are also generated, which are normalised to an overall population mean of 50±10 [511]. For all subscales, higher scores represent better functioning and QoL.

AF Burden Assessment

Quantification of AF burden will be determined either through cardiac rhythm management devices (pacemaker or implantable loop recorder) or through the AliveCor mobile phone application (app). Patients will be asked to transmit twice-daily 30s ECG tracings regardless of their symptoms; and if symptomatic, additional tracings at symptom onset and termination will be requested. Patients who did not adhere to ECG monitoring will undergo adjunctive 7-day Holter monitoring. For patients with implanted devices, remote monitoring will be available further to in-clinic interrogation for quantifying burden.

Medical Management

Patients randomized to ongoing medical therapy will have medications titrated to achieve a resting rate <80 beats/min and/or an average 24-h ventricular rate <100 beats/min in accordance with current guidelines [515].

CA procedure

Catheter ablation will be performed within 1 month of randomization. Oral anticoagulation will be discontinued 24h before the procedure with the exception of vitamin K antagonists or dabigatran, which will not be interrupted. Antiarrhythmic medication will be discontinued 5 half-lives pre-procedure with the exception of amiodarone. All procedures will be performed under general anaesthesia with the assistance of a 3-D mapping system. After exclusion of intracardiac thrombus, transesophageal echocardiographic-guided double transseptal punctures will be

performed. Unfractionated heparin will be administered to achieve an activated clotting time >350s. Mapping of the left atrium and pulmonary veins will be performed with a 20-pole circular mapping catheter and ablation with a 3.5-mm irrigated-tipped catheter following direct current cardioversion (DCCV) to restore sinus rhythm (SR) (power range: 25 W [posteriorly] to 30 W; contact force range: 10 to 40 g anteriorly and 10 to 25 g posteriorly). Pulmonary vein isolation will be achieved with wide antral circumferential ablation with additional roof and inferior lines performed as per the physician's discretion. In general, antiarrhythmic medications would be continued if present or commenced after early recurrence. Repeat procedure would be permitted for symptomatic recurrence occurring beyond 3 months' post-index procedure.

Study Endpoints

The primary end point is change in neurocognitive function assessed by eight neuropsychological tests between the two arms during 12 months of follow-up. Secondary endpoints include assessment of 1) quality of life and 2) symptom burden of AF.

Statistical Analysis

Categorical variables will be reported as count and percentages, while continuous variables as mean and standard deviations (SD). Continuous outcomes at each endpoint will be analysed using a 2-sample t-test. However, a more comprehensive analysis of continuous outcomes, including additional explanatory variables will be based on a mixed linear model with the participant as the random factor and treatment, site and time as

fixed factors. 95% confidence intervals (CI) will be reported. A p-value <0.05 will be considered significant. All analyses will be based on an intention-to-treat model. Mean treatment differences between groups at baseline and at each follow-up period will be estimated from this model.

Sample size calculation

Based on a previous study on neurocognitive function in patients with AF [529], CA is likely to improve psychomotor speed and attention span (Trail Making Tests A and B) by 10%. Using this valid clinical effect to detect minimum absolute difference and in order for the study to reach a power of 80% with type 1 error of 5%, a minimum of 42 patients will have to be enrolled in each arm. Allowing for a 10% drop out rate, a total of 100 participants will be recruited for the REMEDIAL study.

DISCUSSION

The REMEDIAL study is a randomised controlled trial that will compare the impact of CA on neurocognitive function to AAD's in a cohort of symptomatic paroxysmal or persistent AF patients referred for CA to two tertiary care hospitals.

Neurocognition and AF

There is strong evidence from many prospective registries and studies that AF is associated with cognitive impairment, cognitive decline, and dementia[299,530-532]. Furthermore, in a meta-analysis of 21 studies with 89,907 participants AF was

significantly associated with a higher risk of cognitive impairment independent of a history of stroke (RR: 1.34). The risk of dementia was also significantly increased (RR: 1.38). Both silent cerebral infarcts[533] and smaller microinfarcts (beyond the resolution of conventional neuroimaging)[534] are linked to this cognitive impairment.

Despite the complexities associated with AF ablation, large registries have consistently shown that CA can be safely performed in high volume centres by experienced operators[527,535] with acceptable risk of stroke or TIA (0.5-1.0%)[536] as endocardial damage caused by ablation may trigger thrombus formation despite use of anticoagulation. However, AF ablation also carries a risk of silent cerebral embolic lesions (SCE). Lickfett et al[537] first reported this in a small group of patients in their study by performing MRI before and after ablation. In a larger cohort Gaita et al[41] showed an incidence of 14% SCE on MRI scans post ablation compared to baseline imaging pre procedure. In this study the ACT value maintained during the procedure strongly related to the incidence of SCE: 9% of patients with an ACT > 250 reported SCE following the procedure compared to 17% within those maintaining lower ACT values. Since these initial studies, numerous further studies have been undertaken. The reported incidence of SCI in these studies was variable and dependent both on the degree of intra-procedural anticoagulation and the type of ablation technology being used. Irrigated catheters and the cryoballoon have a lower incidence than solid electrode catheters[41]. When the procedural ACT is maintained consistently above 300, the incidence of SCI with irrigated catheters or cryoablation is approximately 5-10%. However, with the solid tip catheter event rates were between 30-40%. These latter catheters are no longer in use.

While these lesions have been described as “silent”, pathology studies have demonstrated that they correspond to areas of endothelial and glial cell proliferation[538] and therefore may be associated with cognitive dysfunction. Thus, although the lesions disappear over time with repeated MRI imaging, they nevertheless are associated with pathological change. We have previously evaluated the prevalence of cognitive impairment after RFA in a study of 150 patients [539]. 60 patients were undergoing ablation for paroxysmal AF, 30 for persistent AF, 30 for supraventricular tachycardia, and 30 matched AF patients awaiting RFA (the control group) all underwent eight neuropsychological tests at baseline and at 2 and 90 days after RFA. The prevalence of neurocognitive dysfunction at day 90 was 13, 20, 3, and 0 percent, respectively, indicating that AF ablation is associated with subtle neuro-cognitive decline.

To date there are no randomised studies of neurocognitive function comparing changes over time in AF ablation versus medically managed patients.

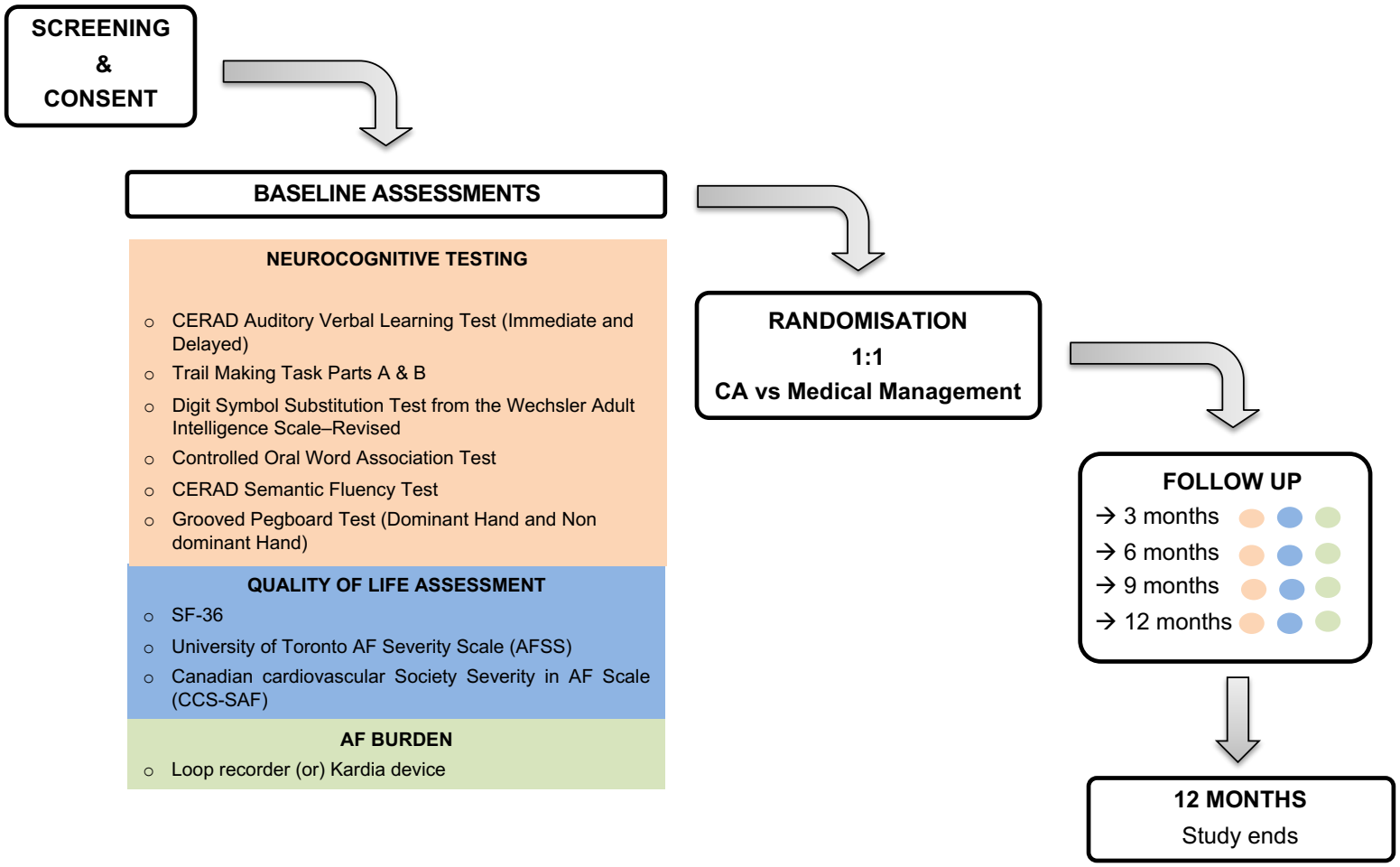
CURRENT STATUS

Enrolment for the REMEDIAL study commenced in June 2018 and 100 participants have been recruited by March 2020. At the time of submission of this manuscript, 54 have completed 12 months follow up. Final results of the study are expected by June 2021.

CONCLUSION

The randomised controlled REMEDIAL study will assess the direct effects of CA on psychological distress and neurocognitive function compared to medical management. The results will strengthen the rationale for using broad endpoints focussed on the patient's overall health in defining successful outcomes and help in implementing a patient-centered treatment strategy.

Figure 1: REMEDIAL-CF Workflow



CHAPTER – 10

CONCLUSION

Advancements in electrophysiological tools and mapping techniques over the last two decades have refined our understanding of AF arrhythmogenesis but the exact mechanism that sustains the arrhythmia remains a topic of ongoing debate. Both localised sources and endocardial-epicardial dissociation have emerged as novel mechanisms in recent years. From a therapeutic standpoint, localised sources, in the form of stable rotors and focal activations, have gained favour as these potential drivers could serve as targets for catheter ablation. But accurate identification of these drivers is challenging and their direct link in maintaining the arrhythmia remains controversial. Furthermore, ablation outcomes despite targeting these endocardial drivers remain suboptimal in non-paroxysmal AF which begs the possibility of an additional mechanism that cannot be targeted via endocardial approach alone.

In Chapter 2, we review the evidence for catheter ablation of AF, present the novel tools that have become available to improve ablation outcomes and present the data to support the role of lifestyle modification in improving treatment outcomes. Catheter ablation is certainly a safe and effective rhythm-control strategy for symptomatic AF patients and there is convincing evidence that show mortality reduction in patients with

comorbid AF and heart failure. It is now an accepted paradigm that both rhythm control and risk factor management are key to successful management of AF patients.

Chapter 3 is a meta-analysis assessing the impact of rotor ablation in AF. In both paroxysmal and non-paroxysmal AF patients, pooled estimates of outcomes after rotor ablation were widely variable between centres with significant heterogeneity in the published studies. Study characteristics alone could not substantiate for these heterogeneities and further evidence from randomized controlled trials on FIRM ablation are needed to confirm the efficacy of this before widespread adoption of this strategy.

Chapters 4 and 5 demonstrate the three-dimensional nature of atrial activation in humans with structural heart disease. In Chapter 4 we provide compelling evidence for functional nature of the three-dimensional atrial substrate. Using phase and activation mapping of endocardial and epicardial surfaces simultaneously, we showed functional dissociation with increased signal complexity and conduction slowing in the RA. These electrophysiological alterations underpin the fundamental mechanisms for developing arrhythmias in this cohort. Data presented in Chapter 5 represent analysis of simultaneous endocardial-epicardial phase mapping of prolonged persistent AF recordings in humans. Besides significant endocardial-epicardial dissociation and marked temporal heterogeneity, we demonstrated for the first time, discordant endo-epicardial wave front patterns with multiple unstable wave fronts transitioning from one pattern to another on both the endo- and epicardial surfaces in all patients. Furthermore, multiple unstable rotational activations and possible transmural migration of rotational

activations was observed. Such complex 3D-interactions provide insight into why endocardial mapping alone may not fully characterise the AF mechanism.

In Chapter 6 simultaneous endocardial–epicardial phase mapping of intact human sino-atrial node was performed to characterise preferential nature of conduction. Analysis showed predominant cranial exits with symmetrical activation sites on the endocardial and epicardial surfaces during sinus rhythm and caudal shift in the activation exits with marked asymmetry in endocardial–epicardial exit sites consistent with multicentricity and redundancy of sinoatrial conduction during over drive suppression. These findings demonstrate the complex and dynamic 3D nature of sinoatrial conduction in the intact human heart, confirming studies in isolated preparations.

Several mapping techniques have become available for identification of localised sources in persistent AF. To overcome the limitation of low-density wide coverage (Basket catheters) or high density but very localized mapping data, in Chapter 7 we present the results of our novel approach of simultaneous mapping with two PentaRay catheters to characterize driver domains in the LA and LAA using CARTOFINDER in patients with persistent AF. The results showed infrequent and unstable drivers in the LA. Notably, there was paucity of stable focal drivers from the LAA on regional high-density mapping which makes the case for the limited role of empirical LAA isolation in AF patients particularly given the unexplored long-term safety concerns. Further mechanistic studies are warranted to clarify if the observed benefit of LAA isolation in large scale studies is by some mechanism other than trigger elimination.

In the final chapters of the thesis, we present the rationale and methodology of the REMEDIAL-PD and REMEDIAL-CF studies. These randomised controlled trials assess the impact of catheter ablation on psychological distress and neurocognitive function respectively in patients with AF. Preliminary data from observational studies have suggested a significant burden of psychological distress in AF patients that improves with ablation. With neurocognitive function, there is data show benefits but also short-term concerns regarding procedure related cognitive decline. These studies have completed recruitment and results will clarify the direct effects of catheter ablation on psychological distress and neurocognitive function both of which will significantly impact quality of life and morbidity in AF patients.

CHAPTER - 11

FUTURE DIRECTIONS

The current thesis expands our understanding of the complexities involved in the pathogenesis of AF. The evidence for atrial endocardial-epicardial electrical discordance is compelling and adds a novel dimension to the mechanism of AF. In our experience, electrical dissociation between atrial myocardial layers was observed in the RA. Whether similar mechanisms exist in the LA, the chamber which harbours most of the known mechanisms of AF, is yet to be demonstrated as safety concerns preclude simultaneous endo-epi LA mapping in intact human heart with available tools. From the therapeutic standpoint, ablative therapy via epicardial and endocardial approaches have been shown to be safe and feasible with good medium term outcomes[540-542]. In this context, surrogates based on patient factors or imaging modalities that could be used to identify patients who may benefit from additive epicardial ablation is yet to be determined and is also worthy of investigation in future studies.

The current research also presents the limitations of some of the mapping techniques and our ability to identify localised sources as potential ablation targets. Data on prevalence of drivers is heterogenous and this is largely driven by variations in definitions and the mapping technique used. There is also a need for technological advancement that would allow real time phase mapping without the need for laborious offline analysis

and signal processing. Actual validation in experimental settings using optical mapping comparisons of the current wide range of methodologies has also not been performed and may refine our understanding and interpretation of 'drivers' identified by these mapping techniques.

Finally, the design of the REMEDIAL study highlights the need for expanding the indications for catheter ablation based on patients' well-being rather than focussing on cardiovascular end-points alone. Traditional parameters, such as survival, healing or regression of disease, are not always sufficient ways to evaluate different treatments. The correlation between physical health and wellbeing can be rather weak. Considering this, there is an increasing demand to find new criteria to evaluate risks and advantages with new treatments focusing on the patient's subjective view. This will help define priorities and arrange new care programs with limited waiting periods for these elective procedures.

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