Atrial Fibrillation and Systolic Heart Failure: The Role of Myocardial Fibrosis and Catheter Ablation

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Abstract

Atrial fibrillation and systolic dysfunction are both emerging epidemics in the developed world and both frequently co-exist. Each condition, both individually and in combination, are associated with significantly worsened morbidity and mortality. Both share pathophysiological mechanisms and may promote the progression of each other. Traditional pharmacological therapies for AF have limited efficacy, which is also the case in patients with concurrent systolic dysfunction. Catheter ablation has emerged as an effective treatment for AF with superior outcomes compared to pharmacological rhythm control, the current standard of care. An increasing body of evidence has shown that catheter ablation is feasible and effective in patients with systolic dysfunction. Nonetheless, identifying those patients with systolic impairment likely obtain the greatest benefit from catheter ablation remains a evolving challenge. Additionally, the electrophysiological and structural changes associated with the co-morbid AF and systolic dysfunction is yet to be fully elucidated.

The central aim of this thesis is to comprehensively evaluate the role of catheter ablation as a treatment for systolic dysfunction. Following a comprehensive review of the relevant existing literature in this area in Chapter 1, Chapters 2, 3 and 4, of this thesis seek to clinically evaluate the effectiveness of catheter ablation in selected patients with systolic impairment and AF, with a particular focus on utilising advanced imaging techniques such as cardiac magnetic resonance imaging (CMR), as a tool to optimise patient selection, and evaluate treatment outcomes. Secondly in Chapters 5 to 8, this thesis seeks to characterise the electrophysiological and structural characteristics of patients with AF in the setting of systolic impairment and additionally to highlight the limitations and challenges of catheter ablation in persistent AF, with a focus on pulmonary vein electrical activity and the role of intra-procedural adenosine.
Preface

This body of work was performed in clinical collaboration with a number of intuitions including:

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

All manuscripts and publications emanating from this research were undertaken with the candidate as the principal author. Responsibilities for all projects included: concept design, ethics approval, recruitment, clinical and logistical co-ordination of patient investigations, performance of clinical treatments (under appropriate supervision where required), clinical follow up of study participants, data collection and collation, statistical analysis, manuscript drafting and the performance of oral or poster presentations where required. Official primary and secondary 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 the requirements for co-authorship specified in the respective journals. Chapters 2 and 4 required critical input from the second listed co-authors who were afforded co-principle status in accepted or submitted manuscripts. However, those authors had no role in drafting the manuscript (excluding critical revision) and those works do not form components of any other submitted body of work.

Financial support for this PhD was provided by:

1. National Heath and Medical Research Council and National Heart Foundation Co-funded Postgraduate Scholarship (APP1076118) – 2014-2017
2. Baker Heart and Diabetes Institute Bright Sparks Top-up Scholarship – 2014-2017
A full list of publications and abstract presentations emanating from this body of work is provided in the section: “Peer reviewed publications arising from this thesis” below.
General Introduction

Atrial fibrillation and systolic heart failure are emerging epidemics in developed countries. This body of work consists of a series of original clinical research studies seeking to explore the interplay between both conditions, particularly the therapeutic role of catheter ablation and the impact of both conditions upon atrial and ventricular remodelling, with a focus upon myocardial fibrosis utilising electro-anatomical mapping and cardiac MRI assessments.

Chapter 1 is a comprehensive review of the relevant literature with a focus upon electrical and structural remodelling processes, especially in the unique setting of concurrent heart failure. Additionally, the current clinical literature on the role of catheter ablation in systolic dysfunction is also reviewed, with a focus upon historical and recent randomised controlled trials. The relevant literature regarding specific aspects of catheter ablation, which are also explored in thesis, particularly as roles of pulmonary vein cycle length in persistent AF and intra-procedural adenosine are also explored.

Chapter 2 is a multi-centre international retrospective analysis of patients with systolic dysfunction undergoing catheter ablation for AF. Both long-term procedural success (AF recurrence and burden), improvements in symptoms and heart function were assessed, with a particular focus upon the impact of known heart disease, such as myocardial infarction upon clinical outcomes. This international study, incorporating the data from two Australian and one UK centre, found that the absence of known heart disease predicted a greater improvement in symptoms, heart function, freedom from AF and overall mortality. This study highlighted the importance of known heart disease in predicting adverse outcomes following catheter ablation.

Chapter 3 is a multi-centre prospective randomised controlled clinical trial (the CAMERA-MRI study) comparing catheter ablation with ongoing medical rate control in patients with persistent atrial fibrillation and idiopathic, or otherwise unexplained cardiomyopathy. At the time of submission, this was the largest published randomised controlled trial of catheter ablation versus medical rate control in heart failure in the
world. This study randomised 68 patients to either catheter ablation or ongoing medical rate control, with the primary endpoint of ejection fraction improvement at 6 months as determined by cardiac MRI. A key secondary endpoint was to evaluate the impact of MRI detected ventricular fibrosis (late gadolinium enhancement) upon ejection fraction improvement. In addition to demonstrating a clearly greater improvement in ejection fraction in those undergoing catheter ablation (+18.3% vs +4.4%, p<0.0001) and 58% compared to 9% normalising ejection fraction (p<0.001), those patients without evidence of fibrosis on cardiac MRI demonstrated substantially greater improvements in ejection fraction (+10.7% (3.2, 18.3%), p=0.0069) post ablation. These novel findings highlight the benefits of catheter ablation in selected patients with systolic failure, and identify cardiac MRI as a useful novel tool to identify those patients likely to achieve the best results. Furthermore, this is the first study to draw the important distinction between ‘tachycardia mediated cardiomyopathy’ and ‘arrhythmia-medicated cardiomyopathy’ by demonstrating that AF can still mediate substantial reductions in systolic function even in the setting of well controlled ventricular rates.

Chapter 4 is a related study evaluating the change in diffuse fibrosis as measured by T1 mapping in those patients (n=36) from the CAMERA-MRI study who underwent assessment for diffuse fibrosis at baseline and follow-up (18 in each treatment arm). This study is the first to describe a reduction in diffuse fibrosis in concert with an improvement in heart function following the restoration of sinus rhythm with catheter ablation, with a -124ms (p=0.0176) relative reduction in myocardial T1 times in the catheter ablation group which had improved ejection fraction an average of 12.5%. Indeed, this is the first study to describe a reduction in diffuse fibrosis following any cardiac intervention and the first to do so utilising a non-intervention control arm. These findings may have important implications for the longevity of recovery of LV function in these patients, and highlight the importance of timely treatment.

Chapter 5 is a prospective study comparing the extent of atrial remodelling in patients with persistent atrial fibrillation with and without systolic dysfunction. Forty patients with persistent AF (20 with and without systolic impairment) underwent detailed bi-atrial electro-anatomical mapping and pulmonary vein cycle length measurement to accurately characterise the atrial substrate. The aim was to determine the contribution
of systolic dysfunction over and above that of AF itself to atrial remodelling. This study was the first to report that systolic impairment is associated with more advanced remodelling as evidence by reduced tissue voltage, increased scarring and increased electrogram complexity. These findings help to shed light on the clinical outcomes associated with ablation in heart failure and may help guide ablation strategies in this patient population.

The systemic nature of atrial remodelling in the setting of persistent atrial fibrillation is often underappreciated. Research has often focused upon remodelling processes occurring in the left atrium, with many studies inferring left atrial remodelling by evaluating changes occurring in the more accessible right atrium. However, a direct comparing the remodelling between the left and right atria in the atrial fibrillation has not been previously performed. Chapter 6 is a prospective study in which 40 patients with persistent AF underwent detailed bi-atrial electro-anatomical mapping (as described in Chapter 5), comparing tissue voltage, electrogram characteristics and conduction velocity between the atria. This novel study found that both atria correlated well with regards to electrophysiological markers of atrial substrate. These findings emphasise the bi-atrial nature of remodelling associated with persistent AF and add validity to previous and contemporary right atrial substrate studies.

The contribution of PV electrical activity to the substrate of persistent AF is uncertain. Given that pulmonary vein isolation (PVI) remains the corner stone of AF ablation, even in persistent phenotypes, this clinical question is paramount in being able to predict those patients with persistent AF likely to have a successful outcomes with a PVI based ablation approach. Chapter 7 is another prospective multi-centre observational study seeking to evaluate the impact of pulmonary vein electrical activity upon long-term outcomes of patients with persistent AF. Over 3 years, 123 patients were enrolled and followed for an average of 24 months (minimum 12 months) post catheter ablation. For each patient, the PV activity was measured at the time of ablation and then characterised in detail offline. This negative study, in which PV electrical activity was not predictive of long-term procedural success, for the first time clarified this clinical question in a systematic and prospective fashion.
Chapter 8 describes another prospective trial characterising the role of adenosine in catheter ablation. Adenosine is utilised in AF ablation to unmask dormant pulmonary vein conduction following acute isolation with the aim of achieving more durable pulmonary vein isolation by identifying veins requiring further consolidation ablation. Adenosine is purported as an adjunctive measure to improve the outcomes of AF ablation. Nonetheless, recent large multicentre trials have yielded conflicting results. Importantly, the optimal dose for identifying dormant conduction has not been clarified. This prospective dose finding study of 50 consecutive patients undergoing catheter ablation performed a detailed assessment of the electrophysiological and haemodynamic effects of adenosine at a range of doses. Importantly, this study highlighted the importance of achieving AV block to unmask dormant conduction, and identified the important role of body habitus in the ability to achieve this. These findings may in part explain the discrepancies in previous randomised trials.
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 the Department of Cardiology, The Alfred Hospital and Baker Heart & Diabetes Institute (Melbourne, Australia), The Department of Cardiology, Royal Melbourne Hospital (Parkville, Australia) and the Department of Medicine, The University of Melbourne (Parkville, Australia) for the express purpose of this thesis and no part thereof has previously been presented for the award of a degree at this or any other university.

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

[Signature]

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18th December 2017
Peer-Reviewed Publications Arising From This Thesis

Highlights
At the time of submission, this body of work has encompassed seven accepted peer reviewed publications, with a further two currently under review. In addition there have been 28 first author local and international conference presentations including 18 oral and 10 poster presentations. Two projects (Chapters 3 and 8) were selected as finalists in the 2017 CSANZ Ralph Reader Young Investigator Award and 2016 APHRS Young Investigator Award respectively. Chapters 2 and 3 were also reported in 20 separate media outlets (including The Age, Herald Sun and Seven News), a focus piece by the National Heart Foundation, whilst Chapter 3 is also the subject of an editorial piece in the Journal of the American College of Cardiology, and was selected as the CME/MOC journal article for October 2017.

Chapter 1
Published manuscripts
- Prabhu S et al Atrial Structure and Function and its Implications for Current and Emerging Treatments for Atrial Fibrillation. Progress in Cardiovascular Diseases 2015, 58(2), 152-167
- Prabhu S et al Atrial Fibrillation and Heart Failure: Cause or Effect? Heart Lung and Circulation, 2017, 26, 967-974

Chapter 2
Published manuscript

Accepted abstracts
• Mini-oral presentation Cardiac Society of Australia and New Zealand (CSANZ) 2015 Annual Scientific Sessions (Melbourne, Australia)


  o Late breaking abstract presentation 2015 Asia Pacific Heart Rhythm Society (APHRS) Annual Scientific Sessions (Melbourne, Australia).


  o Oral abstract 2015 Heart Rhythm Society (HRS) Scientific Sessions (Boston, USA)

Media attention

• Physician’s Briefing “January 2016 Briefing – Cardiology” (1st February 2016)

• Physician’s Briefing “January 2016 Briefing – Geriatrics” (1st February 2016)

• MedicalXpress “Cardiomyopathy aetiology impacts catheter ablation outcomes” (11th January 2016)

• MPR “Long Term Catheter Ablation Outcomes Effected by Cardiomyopathy Aetiology” (11th January 2016)

• Altmetric attention score =35 (21st October 2017) - 96th percentile.

Chapter 3

Published manuscript


• **CME/MOC selection:** Selected for Continuing Medical Education / Maintenance of Certification article for October 2017. *Journal of the American College of Cardiology (October 2017).*

• Awarded 2014 Top Ranked Health Professional Scholar (National Heart Foundation, Australia)

**Accepted abstracts**

• Prabhu *et al* Catheter Ablation Versus Medical Rate Control in Heart Failure—an MRI Guided Multicentre Randomised Controlled Trial—the CAMERA-MRI Trial. *Heart Lung and Circulation* 2017, 26(2), S45
  
  o Oral abstract presentation. **Finalist 2017 CSANZ Annual Scientific Sessions Ralph Reader Young Investigator Award** (Perth, Australia)

• Prabhu *et al* Catheter Ablation Versus Medical Rate Control in Heart Failure—an MRI Guided Multicentre Randomised Controlled Trial—the CAMERA-MRI Trial. *Journal of Arrhythmia* 2017 Abstract Book
  
  o Oral abstract presentation 2017 APHRS Scientific Sessions (Yokohama, Japan)

**Media attention**

• Fairfax media* “Breakthrough vein-burning surgery gets hearts beating true” (29th August 2017)
  
  o Also reported in Channel Seven Nightly News (29th August 2017)

• Herald Sun “Total Repair of the Heart - Day procedure better at fixing atrial fibrillation” (29th August 2017)

• Cardiovascular Business “Ablation reverses left ventricular systolic dysfunction in patients with persistent atrial fibrillation” (1st September 2017)

• American College of Cardiology News “CASTLE-AF: Catheter ablation vs conventional therapy for patients with atrial fibrillation and LV dysfunction” (27th August 2017).

• Practice Updates “2017 Top Stories in Cardiology: Atrial Fibrillation and Systolic Dysfunction” (6th November 2017) – Written by Douglas P Zipes

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Chapter 4

Accepted Manuscript

- Regression of Diffuse Ventricular Fibrosis following restoration of sinus rhythm with catheter ablation in Patients with Atrial Fibrillation and Systolic Dysfunction: a Sub-Study of the CAMERA MRI Trial. Accepted JACC – Clinical Electrophysiology (March 2018)

Accepted Abstract

- Prabhu et al Regression of Diffuse Ventricular Fibrosis following restoration of sinus rhythm with catheter ablation in Patients with Atrial Fibrillation and Systolic Dysfunction: a Sub-Study of the CAMERA MRI Trial.
  - Oral abstract presentation 2018 Heart Rhythm Society Annual Scientific Sessions (Boston, USA)
  - Oral abstract presentation 2017 APHR Scientific Sessions (Yokohama, Japan)
- Prabhu et al Reverse ventricular remodeling following AF ablation in patients with persistent and systolic dysfunction - A prospective randomised study Journal of Arrhythmia, 2016, 32 Supplement, J14
  - Oral abstract presentation 2016 APHRS Scientific Sessions (Seoul, Republic of Korea)
- Prabhu et al Ventricular fibrosis improves following AF ablation in patients with persistent AF and heart failure Heart Rhythm 2017, 14(5), S129.
  - Poster presentation 2016 HRS Scientific Sessions (Chicago, USA)
• Prabhu et al Ventricular fibrosis improves following AF ablation in patients with persistent AF and heart failure Heart Lung and Circulation 2017, 26(2), S155.
  o Oral abstract presentation 2017 CSANZ Annual Scientific Sessions (Perth, Australia)
  o Oral abstract presentation 2017 Melbourne Health Research Week (August 2017)

Chapter 5

Accepted Manuscript
• Prabhu et al Bi-atrial Electrical and Structural Atrial Changes in Heart Failure: Electro-anatomic Mapping in Persistent Atrial Fibrillation in Humans (Accepted Journal of the American College of Cardiology: Clinical Electrophysiology 29th August 2017)
• Winner 2017 JACC Clinical Electrophysiology Young Author Achievement Award – American College of Cardiology (Awarded 10th March 2018).

Accepted Abstract
• Prabhu et al Systolic heart failure is associated with more advanced bi-atrial substrate independent of AF duration in persistent AF Heart Rhythm 2017, 14(5), S171
  o Poster presentation 2017 HRS Scientific Sessions (Chicago, USA)
  o Mini-oral abstract presentation 2016 APHRS Scientific Sessions (Seoul, Republic of Korea)
  o Poster presentation 2016 APHRS Scientific Sessions (Seoul, Republic of Korea)
• Prabhu et al Electrophysiologic remodelling of the atria and pulmonary veins in co-morbid persistent atrial fibrillation and systolic heart failure *Journal of Arrhythmia* 2017 Abstract book
  o Oral abstract presentation 2017 APHRS Scientific Sessions (Yokohama, Japan)

  o Mini-oral abstract presentation 2016 CSANZ Annual Scientific Sessions (Adelaide, Australia)

  o Mini-oral abstract presentation 2016 CSANZ Annual Scientific Sessions (Adelaide, Australia)

• Prabhu et al Systolic heart failure is associated with more advanced bi-atrial substrate independent of AF duration in persistent AF *Heart Lung and Circulation* 2017, 26(2), S148-9.
  o Oral abstract presentation 2017 CSANZ Annual Scientific Sessions (Perth, Australia)

• Prabhu et al Systolic Heart Failure is Associated with More Advanced Bi-atrial Substrate Independent of Atrial Fibrillation Duration in Persistent Atrial Fibrillation
  o Poster presentation 2017 *Melbourne Health Research Week*.

### Chapter 6

*Accepted manuscript*

• Prabhu et al A comparison of the electrophysiologic and electroanatomic characteristics between the right and left atrium in persistent atrial fibrillation: Is the right atrium a window into the left? *Journal of Cardiovascular Electrophysiology* 2017, 28(10), 1109-16.

*Accepted abstracts*
• Prabhu et al A comparison of the electrophysiologic and electroanatomic characteristics between the right and left atrium in persistent atrial fibrillation: Is the right atrium a window into the left? Journal of Arrhythmia Abstract 2017
  o Oral abstract presentation 2017 APHRS Scientific Sessions (Yokohama, Japan)
  o Poster presentation 2016 APHRS Scientific Sessions (Seoul, Republic of Korea)
• Prabhu et al A comparison of the electrophysiologic and electroanatomic characteristics between the right and left atrium in persistent atrial fibrillation: Is the right atrium a window into the left? Heart Lung and Circulation 2017, 26(2), S176.
  o Oral abstract presentation 2017 CSANZ Annual Scientific Sessions (Perth, Australia)
• Prabhu et al Bi-Atrial Electroanatomic Mapping in Persistent AF: Does the Right Atrium Represent the Left? Heart Lung and Circulation 2016, 25(2), S139.
  o Poster presentation 2016 CSANZ Annual Scientific Sessions (Adelaide, Australia)
• Prabhu et al. A comparison of the electrophysiologic and electroanatomic characteristics between the right and left atrium in persistent atrial fibrillation: Is the right atrium a window into the left? 2017 Melbourne Health Research Week.
  o Poster presentation, Royal Melbourne Hospital, Melbourne, Australia.

Chapter 7
Submitted manuscript
• Prabhu et al Pulmonary vein activity does not predict long-term outcome of catheter ablation for persistent atrial fibrillation – A multi-centre prospective study. Accepted Heart Rhythm February 26th 2018.
Accepted abstracts

  - Oral abstract presentation 2017 APHRS Scientific Sessions (Yokohama, Japan)
- Prabhu et al. Rapid pulmonary vein firing does not predict AF ablation outcome in persistent AF *Heart Lung and Circulation* 2017, 26(2), S189.
  - Mini-oral presentation 2017 CSANZ Annual Scientific Sessions (Perth, Australia).
  - Poster presentation, Royal Melbourne Hospital, Melbourne, Australia.

Chapter 8

Accepted manuscript


Accepted abstracts

  - Poster presentation 2016 HRS Scientific Sessions (San Francisco, USA)
- Prabhu et al. Determining the Optimal Dose of Adenosine for Unmasking Dormant Pulmonary Vein Conduction Following Atrial Fibrillation Ablation:
Electrophysiological and Hemodynamic Assessment. *Journal of Arrhythmia* 2016, 32 Supplement, J43
  - Oral abstract presentation – 2016 APHRS Scientific Sessions, 1st Runner Up Young Investigator Award (Seoul, Republic of Korea)
    - Oral abstract presentation 2017 CSANZ Annual Scientific Sessions (Perth, Australia)

**Media attention**

- Bionity.com “Determining the Optimal Dose of Adenosine for Unmasking Dormant Pulmonary Vein Conduction Following Atrial Fibrillation Ablation: Electrophysiological and Hemodynamic Assessment” (19th October 2017)
- Altmetric score = 7 (as of 22nd October 2017)

**Chapter 9**

**Accepted editorial**

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This PhD has only been possible through the incredible support of many individuals whom I wish to make special mention.

Firstly, I wish to thank Professor Peter Kistler, my primary supervisor. In addition to taking a chance on a young trainee with no previous electrophysiology experience, he has provided the perfect balance of rigorous attention to detail and pragmatism that has made completing this ambitious project even remotely possible. Furthermore his approachability for advice and counsel, even beyond the field of electrophysiology, and often out of hours, has been extraordinary. Equally, I wish to thank Professor Jonathan Kalman, whose world-class collaborative research program has been the bedrock for this work and was a privilege to be a part of. His advice, particularly at key cross-roads in many of the projects was critical, and not infrequently, expertly condensed into the time taken to walk from the Royal Melbourne cardiology conference room to his nearby consulting rooms! In addition, both Peter and Jon have simultaneously provided me with comprehensive training in clinical electrophysiology, and catheter ablation. They will both forever be the ‘voices in my head’ for my practicing career.

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For Loui, Jasmine and Tristan.
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CHAPTER 1: Literature Review

1 Atrial Fibrillation and Heart Failure

1.1 Epidemiology of atrial fibrillation
Atrial fibrillation (AF) is one of the few cardiovascular conditions increasing in incidence across the world. It is the most common sustained cardiac arrhythmia and confers a considerable health, social and economic burden worldwide. The prevalence of AF in Australia in those older than 55yrs is 5.4%, projecting to 6.4% by 2034 equating to more than 600,000 Australians. Similarly, the health burden from heart failure continues to increase. It affects roughly 2% of the population, a three fold higher incidence in the elderly.

1.2 Epidemiology of atrial fibrillation and heart failure
AF and heart failure frequently coexist as there are physiologic mechanisms common to both. 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%. AF was present in 21% of a “real world” population of 3,513 heart failure patients. Age, the presence of NHYA class greater than II and a non-ischaemic aetiology of HF were strong predictors for co-existence of AF. It should be noted that the term ‘heart failure’ may refer to either systolic dysfunction, (also termed heart failure with reduced ejection fraction (HFrEF)), or heart failure with preserved ejection fraction (HFpEF), previously termed diastolic dysfunction. In this thesis, the term ‘heart failure’ will refer to systolic dysfunction (HFrEF) only, unless otherwise specified.

1.3 Mortality of concurrent atrial fibrillation and heart failure
Importantly, the co-existence of both conditions confers increased mortality and morbidity. In the Framingham cohort, Wang et al examined and characterised the temporal relationship between both atrial fibrillation and heart failure and its impact on mortality. In patients who developed both conditions (n=382), 38% had AF preceding the heart failure, 41% had heart failure preceding the development of AF.
and the remainder (21%) having both conditions co-diagnosed together. Regardless of the temporal relationship, the co-presence of both conditions conferred an increased mortality between 1.5 and 3.7 time higher than the baseline population. Roy et al performed a randomised clinical trial of pharmacological rhythm or rate control strategies in 1,376 patients with heart failure and atrial fibrillation, and evaluated cardiovascular mortality. Whilst cardiovascular mortality did not differ significantly between the groups, the overall mortality was high 32% after an average of 3 years of follow up. Aleksova et al examined the impact of AF on mortality specifically in patients with idiopathic cardiomyopathy and found that the development of AF during the first 3 years of follow up, but not its presence at baseline, predicted worse survival (HR=3.7 (2.1-6.5), p<0.001). These results suggest that mortality data in a general heart failure population may not directly extrapolate to the specific idiopathic cardiomyopathy population. Additionally, recent mortality data in all patients with non-ischaemic cardiomyopathy in large clinical trials has emphasised a much lower incidence of sudden cardiac death (6.2%) and overall mortality of 22.5%. Addison evaluated the long term outcome of patients with predominately non-ischaemic cardiomyopathy undergoing catheter ablation for AF, an overall mortality rate of 13% was noted. The potential for a significant number of these patients to improve their ejection fraction following catheter ablation may have contributed to the lower mortality rate. Nonetheless, the increased mortality associated with concurrent heart failure and atrial fibrillation is apparent in many large studies.

1.4 Economic impact of atrial fibrillation and heart failure
Individually, AF and heart failure present significant economic burdens for health system systems in developed countries. Patel et al examined the economic impact of AF in the United States from 2000-2010. Hospitalizations due to AF increased by 23% from 2000-2010. Additionally the cost of admission also rose by 24% over the same period (p<0.001). Other studies have shown similar results. In addition, worldwide, healthcare costs attributable to heart failure continue to exert enormous pressure of national health budgets. In 2012, total pooled worldwide expenditure on heart failure exceeded $100 billion US. In Australia, total health care costs attributable to AF in 2008-2009 were approximately $874 million. Of that, $216 million (25%) was attributable to thromboembolic complications of AF (namely...
stroke) and an equivalent amount of $223 million (26%) attributable to heart failure complicating atrial fibrillation. This accounted for 13% of all heart failure related costs\(^1\). Thus, the economic burden of AF is considerable, with a significant proportion of this attributable to concurrent heart failure.

2 Cardiac Remodelling in Atrial Fibrillation and Heart Failure

A key determinant of the severity of the AF phenotype, is the extent to which changes in atrial and ventricular tissues both influence and are influenced by the AF. The left atrium is a complex entity displaying a considerable degree of physiological, electrical and anatomical plasticity in disease states. Remodelling refers to electrical and structural alterations to the atrial tissue leading to impairment of normal atrial function. Many disease processes lead to atrial remodelling including, hypertension, valvular disease and cardiomyopathy, however remodelling in the setting of AF is of particular interest as its occurrence appears to directly impact disease progression and the effectiveness of treatments.

2.1 Atrial remodelling processes

Electrical remodelling encompasses the electrophysiological changes promoting AF development and maintenance. These occur via changes in: ion channel function, intracellular calcium handling, cardiac autonomic activity and intercellular electrical conduction. Structural remodelling refers to alteration in the atrial tissue composition (primarily by fibrosis) generally heralding irreversible microscopic (and often macroscopic) changes and a more severe disease phenotype. Both processes are intimately related and with several overlapping disease pathways. The inter-relationship of remodelling processes are summarised in Figures

2.1.1 Electrical remodelling

The mechanisms of electrical remodelling in AF are multifaceted. Fundamentally, electrical remodelling facilitates all three of the universally acknowledged arrhythmia mechanisms, namely focal ectopic activity, triggered activity and re-entry\(^1\). Focal activity arises when alteration in diastolic ion current activity promoting depolarisation is enhanced resulting in premature depolarisation. Early or delayed
after-depolatisations (EADs or DADs) result from abnormalities of calcium handing which promote prolonged action potential duration (APD) and facilitate EADs from recovery of inactivated calcium channels. Re-entry is facilitated by processes which shorten atrial effective refractory period (ERP), reduce APD and slow conduction velocity\textsuperscript{16}. In this regard with respect to re-entry, both electrical and structural remodelling play a role. Alteration in the electrical properties of atrial tissue in response to sustained rapid atrial rates, also known as atrial tachycardia remodelling, has been well described in both animal\textsuperscript{17} and human models\textsuperscript{18}, in which repetitive atrial depolarisations result in shortening of the effective atrial refactoriness (ERP) and atrial action potential duration (APD) (in sinus rhythm)\textsuperscript{19}. In addition, slowed atrial conduction velocity and loss or ERP rate adaptation also play a significant role. These changes increase the period of potential excitability (excitable gap) of atrial myocytes facilitating their ability to maintain re-entry an important prerequisite for sustaining AF\textsuperscript{20}.

2.1.1.1 The normal action potential
In order to appreciate the mechanism of action of pharmacological agents on electrical remodelling in AF, it is crucial to appreciate the ionic mechanisms associated with the normal atrial myocyte action potential. The resting membrane potential of the atrial myocardium ranges from -85 to -65 mV, noticeably lower than the ventricle as activity of the inward rectifying potassium current (I\textsubscript{K1})\textsuperscript{21}. Notably, the atrial depolarisation is triangular in shape as opposed the classic ‘spike and dome’ appearance of the ventricular depolarisation, and has a slower upstroke velocity. Rapid Initial rapid depolarisation following stimulation to threshold is driven by sodium influx via voltage dependant ion channels (I\textsubscript{Na}) with subsequent plateau phase driven by the L-type Ca current (I\textsubscript{CaL}) which triggers stored calcium release from the sarcoplasmic reticulum via Ryanodine receptors (known as Ca induced Ca release) which facilitates myocyte contraction and simultaneously inactivates I\textsubscript{CaL}. Calcium is subsequently taken back up into the sarcoplasmic reticulum via sarcoplasmic reticulum Ca\textsuperscript{2+} ATPase (SERCA2a) with excess diastolic calcium handled by the Na/Ca changer which extrudes 1 Ca ion for taking in 3 Na ions, generating a net inward positive current. Homeostasis is maintained in part by Na/KT ATP ase pump which extrudes 3 Na ions for taking in 2 K ions. In-vitro experiments have suggested
the magnitude of the ICaL current is significantly higher in the atrium compared to
the ventricle. Repolarisation is driven primarily by a collection outwardly directed
potassium currents. IK1 currently dictates the atrial resting membrane potential. Its
comparatively sparse distribution in the atrial in part explains the relative
depolarisation of the atrial myocardium relative to the ventricle, and the slower late
phase of repolarisation. Initial transient repolarisation occurs via the Ito current which
although more abundant in the atria, contributes to the action potential a similar
magnitude to that in the ventricle, largely as a result of action potential morphology.
The bulk of mid to late repolarisation occurs via delayed rectifier potassium currents
of which the ultra-rapid delayed rectified current (IKur) is the most dominant with
variably minor contributions from the rapid and slow potassium currents (IKr and IKs
respectively). Other ion channels such as the achetycholine dependant IKAch channel
(thought to shorten APD, in the setting of vagal stimulation), ATP sensitive potassium
current, IKATP may modulate sinus node activity in varying physiological states22
and ‘funny’ potassium channels (IF) modulates, with predominately diastolic and
hyperpolarisation activated activity, modulate pacemaker (also known as phase 4)
activity23.

2.1.1.2 Electrical remodelling
Firstly, alteration in ionic currents (such as ICaL and IK1) responsible for maintaining
the plateau phase of the myocyte action potential, leads to reduced APD20. Secondly,
neutrally mediated mechanisms, in the form of vagal stimulation, also play a role in
altering acetylcholine dependant potassium channels (IKACh) which become
constitutively active in the setting AF, shortening repolarisation and decreasing
APD20 (see below). Thirdly, alterations in intracellular calcium handling have an
increasingly recognised role in electrical remodelling. Fourthly, neutrally mediated
mechanisms play as key role. Lastly, the role of inter-cellular electrical coupling and
conduction velocity in electrical remodelling is increasingly being appreciated. Figure
1 details these processes schematically

2.1.1.3 Ionic remodelling
In vitro analysis has facilitated detailed study of ionic changes associated with atrial
fibrillation and provided potential hypotheses for mechanism of action and in some
instances the identification of potential therapeutic targets. Analysis of isolated human atrial myocytes demonstrated that a 70% reduction $I_{Ca,L}$ and $I_{to}$ density, largely in response to increased intracellular calcium at rapid rates, promotes reduced APD and reduced rate response of atrial repolarisation. The inward rectifier $I_{K1}$ current and $I_{Ach}$ both display increased activity in atrial fibrillation at hyperpolarising potentials. These changes increase the overall excitability of atrial myocytes, promoting conditions favouring repetitive and rapid depolarisations, facilitating atrial fibrillation$^{21, 24}$. Changes also occur at a transcription level with the expression of $I_{Ca,L}$ and $I_{K1}$ likely secondary to reduced mRNA pore forming activity. Similarly regulation of normal physiological protein function is altered with $I_{Ach}$ becoming constitutently active and increasing the resting membrane potential and increasing excitability.

2.1.1.4 Calcium handling alterations in atrial fibrillation

Molecular alterations associated with intracellular calcium handling have an increasingly recognised role in AF development and maintenance, although the majority of this understanding has been extrapolated from in-vitro and animal models. A complex interplay between various processes occur, and whilst the mechanisms may be the subject of continued investigation, the primary changes can be summarised as causing increased intracellular Ca2+ instability and increased spontaneous sarcoplasmic reticular release of stored intracellular calcium via reduced $I_{Ca,L}$ activity and via RyR2 and SERCA2a altered function$^{25}$. This results in an increased propensity to triggered activity from EADs and DADs$^{21}$, abnormal electric-mechanical coupling$^{26}$ and in ultra-structural changes and inflammatory cell and fibroblast modulation – providing an important mechanistic link between electrical and structural remodelling in AF$^{25}$.

2.1.1.5 Neural mediated electrical remodelling

Autonomic cardiac inputs are well described and originate both centrally (extrinsic) and locally (intrinsic), contain both cholinergic and adrenergic inputs and have been recently expertly reviewed by Chen et al$^{27}$. Extrinsic inputs arise from the medulla (vagal nerve) or the paravertebral ganglia (superior cervical, middle cervical and cervicothoracic or stellate ganglion). Broadly, parasympathetic and sympathetic inputs are mediated via the vagal nerve and stellate ganglion respectively, although
considerable overlap exists. Intrinsic parasympathetic and sympathetic neural inputs are heavily co-localised with up to 30% having dual adrenocholanergic properties – making selective targeting of autonomic activity by localised ablation difficult. By far most intrinsic nerve complexes are located in the atria, often congregating in known arrhythmogenic ‘hot spots’ such as the pulmonary vein / left atrial junction and have been heavily implicated in arrhythmogenesis. The mechanisms in which autonomic inputs promote atrial arrhythmia have been well explored. β-adrenergic stimulation results in a protein kinase A mediated cascade of phosphorylation of a range of intracellular proteins involved in calcium handling, including RyR, SERCA2a and ICaL – promoting conditions favourable for delayed after depolarisations. By far most intrinsic nerve complexes are located in the atria, often congregating in known arrhythmogenic ‘hot spots’ such as the pulmonary vein / left atrial junction and have been heavily implicated in arrhythmogenesis. The mechanisms in which autonomic inputs promote atrial arrhythmia have been well explored. β-adrenergic stimulation results in a protein kinase A mediated cascade of phosphorylation of a range of intracellular proteins involved in calcium handling, including RyR, SERCA2a and ICaL – promoting conditions favourable for delayed after depolarisations. Direct effects upon IK1 and If channels increase focal firing, whilst modulation of APD via enhanced ICaL (adrenergic) or IK Ach (cholinergic) can promote phase 2 and phase 3 early after depolarisations. The net effect is the promotion of conditions favourable to rapid firing and focal activity. In addition, β stimulation, via calcium activation of calmodulin and calcinuerin, also activates transcription processes implicated in driving ultra-structural changes involved in structural remodelling. Lastly, the effect of IK Ach activity on APD abbreviation is though to occur with significant regional variation, promoting conditions favourable for functional re-entry and pro-arrhythmia.

2.1.1.6 Electrical remodelling and conduction velocity
The large INa current, which provides the source of electrical propagation, is generally unaffected by electrical remodelling. However, the intercellular transmission of conduction relies on the efficient, low resistant electrical coupling, which occurs via gap junctions namely connexin 40 and 43 (the most prevalent in atrial tissue). These gap junction are located predominately in the intercalated discs which promote longitudinal conduction over transverse conduction. Thus atrial conduction is anisotropic rather than uniform. The effects of AF on conduction velocity in atrial fibrillation represent a combination of electrical and structural remodelling. Electrical remodelling has been implicated in processes resulting in slowed and heterogeneous conduction promoting conditions favourable for re-entry. In particular, myocardial ischaemia results in reduced opening of gap junctions, promoting slowed conduction and may be a key mechanism of arrhythmogeneisis in ischaemia. The relationship
between connexin expression and conduction velocity is not linear and still the subject of ongoing investigation. However, recently a murine model with a loss of function mutations in connexin 40, adapted from mutations described in humans with AF, had demonstrated a preponderance to sustained AF with demonstrable slowed conduction in the setting of normal expression, mirroring the human phenotype31. This suggests that functional impairment rather than expression may be important factor in electrical remodelling of gap junctions in humans. In contrast, the expression of connexin 43 may be more directly implicated in human AF based on recent histological studies in patients with chronic valvular AF, compared to patients with sinus rhythm31. In addition to gap junction function, disruption of normal myofilament architecture by structural remodelling processes also promotes slowed conduction.

2.1.1.7 Implications of electrical remodelling

Despite these demonstrated changes, the ability of atrial tissue sustain AF increases despite plateauing of these parameters in the setting of increased tachycardia burden. Furthermore, the complete reversibility of these electrical changes after cessation of tachycardia stimulus, usually over the course of a few days and independent of the duration of preceding tachycardia stimulation, highlights the role of other structural remodelling (often termed the second factor) in maintaining AF32. Kirchhof et al explored this aspect of electrical remodelling in the clinical setting in the Flec-SL trial33. This study prospectively randomised patients with persistent AF post successful DCR reversion to no therapy, 4 weeks (short term) of flecanide therapy or 6 months (long term) of flecanide. The rational was that flecanide, like other antiarrhythmics, primarily modulates electrical remodelling by increasing APD. Given these electrical changes have demonstrated relatively rapid (over days) reversal post reversion to sinus rhythm independent of preceding AF duration, antiarrhythmic therapy beyond and initial 4 week period was hypothesized to have little impact upon prevention of recurrence. In fact, whilst both treatment groups were superior to no therapy, long-term therapy had significantly less recurrence highlighting the likely role of factors other than electrical remodelling in AF.
2.1.2 Structural remodelling

Structural remodelling refers alterations in the tissue architecture of the left atrium at both a cellular and macroscopic level. Whilst electrical remodelling as outlined above may be an important precursor to structural remodelling processes, the reversibility of electrical remodelling distinguishes it from structural remodelling. In contrast, the reversibility of structural remodelling is less clear, and its relationship to control of arrhythmia may be indeed be a disease specific phenomenon.

2.1.2.1 Atrial fibrosis

Atrial fibrosis the is hallmark of structural remodelling and is increasingly recognised as a crucial component of the AF substrate. Whilst the association of atrial fibrosis and AF (particularly more established forms of AF) is well established, a divergence of opinion exists regarding the direct causal relationship between AF and atrial fibrosis\(^{34}\). Atrial fibrosis promotes the development of AF by causing alterations to the electrical properties, such as heterogenous conduction slowing\(^{35}\), and creating a substrate capable of sustaining re-entry and more likely to develop and sustain AF\(^{36-38}\). This is suggested in humans where single episodes of documented AF demonstrate early atrial fibrotic changes\(^{39}\). Other studies suggest AF itself can precipitate atrial fibrosis as demonstrated by rapid atrial pacing canine models\(^{40}\), and the presence of atrial fibrosis at autopsy in patients with structural heart disease yet no AF\(^{41}\). These discrepancies in findings complicate our understanding of structural remodelling and its implications for AF management. In addition, the relationship (causal or otherwise) of fibrosis quantity, type and distribution to various AF phenotypes remains unclear\(^{40}\). The physiological processes involved in structural remodelling and the formation of atrial fibrosis are summarised in Figure 2.

2.1.2.1.1 Renin angiotensin aldosterone system (RAAS) and atrial fibrosis

Murine models with overexpression of angiotensin converting enzyme (ACE) and increased levels of angiotensin II (Ang II) demonstrate areas of focal atrial fibrosis, atrial dilatation, myocyte apoptosis and hypertrophy and slowed conduction. Ang II mediate these profibrotic changes via several mechanisms. Firstly, activation of mitogen activated protein (MAP) kinases mediate downstream alteration of gap junction proteins facilitating conduction abnormalities promoting arrhythmia\(^{42}\).
Secondly, Ang II up regulates matrix metalloproteinase 9 (MMP9), a key regulator of collagen turnover, which promotes collagen deposition. Thirdly, Ang II is involved in the activation of myeloperoxidases (MPOs), which are instrumental in the development of reactive oxygen species and free radicals – promoting cell injury and fibrosis in murine models. Lastly, Ang II is also directly implicated electrical remodelling promoting increased density if calcium channels through a variety of intracellular signalling pathways. The promising effects of renin-angiotensin system (RAAS) blockade in in vitro and animal models of fibrosis have not directly translated to compelling clinical use solely for the treatment of atrial fibrillation. Rapidly paced canine models have shown attenuation in atrial fibrosis and reduction in LA area in response to ACE inhibition, with reversal of electrical remodelling and reduced AF inducability. A meta-analysis of 14 randomised trials including over 90,000 patients investigated the role of RAAS inhibition in preventing new onset atrial fibrillation. Ang II receptor blockade demonstrated a significant benefit (RR=0.78, p=0.009) although no benefit was evident for ACE inhibitor or aldosterone antagonist therapy. The benefit was most notable in those with heart failure suggesting that in part the benefit may be the result of favourable ventricular remodelling rather than a true anti-fibrotic effect. The LIFE study evaluated outcomes in patients with hypertension treated with losartan or atenolol and found reduced incidence (RR=0.67, p<0.001) of new-onset AF despite equivalent in patient in the losartan arm although again ventricular reverse remodelling may have played a role. The ANTIPAF, and J-RHYTHM trials evaluated the potential for olmesartan and candesartan respectively to reduce on AF burden in patients with no structural heart disease and found no significant benefit in atrial remodelling or AF reduction.

Aldosterone antagonists such as spironolactone and eplerenone are alternative approaches to RAAS inhibition by counteracting the activity of Ang II in producing aldosterone, which has wide ranging pro-fibrotic and pro-remodelling properties, including an effect on intracellular calcium handling. Aldosterone levels are known to be increased in humans with AF, which reduces in sinus rhythm. The beneficial effects of spironolactone and eplerenone on atrial fibrosis, electrical remodelling and have been demonstrated in animal models of tachycardia induced remodelling. In the EMPHASIS-HF study looking the role of eplerenone in patients with mild (NYHA II) heart failure, randomisation to eplerenone was associated with reduced...
incidence of new onset AF (2.7% vs 4.5%, HR=0.58, p=0.034)\(^5\). A non-randomised study evaluating the effects of eplerenone in 106 patients long standing persistent AF (continuous AF duration for greater than 1 year) undergoing AF ablation and found that eplerenone use (55 patients) significantly improved freedom from AF in long term follow-up\(^5\). We await the outcome of further clinical studies to further understand the role of routine aldosterone antagonist use in the AF patient population.

2.1.2.1.2 Transforming Growth Factor-β1 (TGF-β1)

TGF-β1 is primarily a down stream mediator Ang II activity and promoted fibrotic remodelling by stimulating collagen production, although other mediators such as MMP-2, MMP-9, plasmin and other oxygen reactive species have also been known to promote TGF-β1 release. Its act predominately via the Smad signalling pathway and is a potent mediator of a multitude of inflammatory, pro-fibrotic and remodelling processes on multiple organs. In the heart it promotes myocyte hypertrophy and extra cellular matrix deposition –being able to mediate these processes at very low intracellular levels\(^5\). In cardiac remodelling, the atrial specificity of its activity is quite marked. A transgenic murine model overexpressing TGF-β1 demonstrated atrial specific fibrosis and increased propensity to AF\(^38, 56\). The downstream activity of TGF-β1 in RAAS mechanisms of atrial remodelling may explain part of the clinical benefits demonstrated with RAAS modulating agents as discussed above\(^5\)

2.1.2.1.3 Platelet derived growth factor (PDGF)

PDGF has recently been described as an important mediator of structural remodelling. PDGF has a role of functions and was initially of interest due to its role in uncontrolled angiogenesis in neoplastic diseases. However, it also an important mitogen for mesenchymal cells (such as fibroblasts and smooth muscle cells) implicating it in processes involved in structural atrial remodelling\(^5\). In-vitro analysis also demonstrated a role in electrical remodelling by reducing the density of ICaL. In both models, the fibrotic and electrical remodelling effects were reversed in the presence of a blocking monoclonal antibody\(^5\). Whilst biological agents capable of selectively targeting isoforms of PDGF exist for use in varying neoplastic conditions, to date their potential clinical role in AF treatment has not been explored.
2.1.2.4 Peroxisome proliferator-activated receptor (PPAR-γ)

Recently the role of the PPAR-γ activation in atrial fibrosis had been appreciated as an important downregulator of several pro-inflammatory and pro-fibrotic pathways (including IL-1, IL-6, inducible nitric oxide synthase (iNOS), tumour necrosis factor alpha (TNF-α) and MMP-9), by inhibition of transcription factors which act via interaction with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in macrophages and neutrophils—down regulating its function. PPAR-γ activation is also involved in increasing the expression of molecules involved in anti-oxidant processes such as super oxide dismutase (SOD-2) and heat shock protein (hs70) as well as attenuating the activity of nicotinic dinucleotide phosphate (NADPH) oxidase—implicated in the generation of reactive oxygen species⁶⁰.

2.1.2.2 Inflammation and atrial fibrillation

Recently, the role of inflammation in AF has been increasingly appreciated and investigated. A multitude of markers of inflammation have been identified including IL-2, IL-6, IL-8, monocyte chemoattractant protein (MCP)-1, CRP and TNF-α and have been associated with pro-inflammatory activities of leukocytes.

2.1.2.2.1 Inflammation

It is likely that a significant bilateral causative relationship exists between AF and inflammation. Several animal and human studies have demonstrated that in that pro-inflammatory states are associated with AF. Goldstein et al found that AF was inducible in a sterile canine pericarditis model displaying atrial inflammation, this effect was attenuated with steroid treatment of the inflammation⁶¹. In the clinical setting, post-operative cardiac patients who developed AF were more likely to have elevated CRP levels⁶², although interestingly this finding was not demonstrable in women⁶². In large number longitudinal cohort studies of healthy middle aged women, the presence elevated inflammatory mediators (CRP, intercellular adhesion molecule (ICAM)-1 and fibrinogen) independently predicted the incidence of AF over the 14 year follow-up period⁶³. Marcus et al demonstrated a reduction in pre-procedural IL-6 and CRP levels post atrial flutter ablation suggesting that the arrhythmia was driving
2.1.2.2 Receptor for Advanced Glycation End Products (RAGE)

The RAGE axis mediates a complex array of pro-oxidation and pro-inflammatory pathways in the hyperglycaemic environment when advanced glycation end products (AGEs) accumulate and stimulate RAGE receptors. The inflammatory processes stimulated by RAGE activation can generate further AGEs and promote appositive feedback mechanisms. These mechanisms have been implicated in the pathogenesis of AF by promoting atrial fibrosis by the generation of IL-6 and TNF-α, in addition to increasing the production of connective tissue growth factor (CTGF), TGF-β1 and up-regulating MMP activity. Furthermore, AGE/RAGE interaction leads to activation of the pleiotropic transcription factor NF-κB which may mediate cell apoptosis - a process inhibited by N-acetylcysteine (NAC).

2.1.2.3 Oxidative Stress

Oxidative stress is an important pathway implicated in both structural and electrical remodelling in AF. Oxidative stress refers to the generation of reactive oxygen species (ROS), which mediate a multitude of downstream inflammatory processes. In AF, there is increased activity in the enzymes implicated in ROS generation in the myocyte nicotinamide adenine dinucleotide phosphate oxidase (NOX), mitochondrial xanthine oxidase (mitochondrial), and uncoupled endothelial nitric oxide synthase. Downstream effects are complex and incompletely understood however are known to affect calcium ion channels, Ca2+ /calmodulin-dependent protein kinase (CAMK)II (involved in Ca reuptake and cytosolic homeostasis) and TGF-β1/Smad pathway (and thus interacting with RAAS pathways). Antioxidant treatments have been postulated to play a role in AF treatments. Statins have a well described anti-oxidant mechanism and their role in AF has been discussed above. Poly unsaturated fatty acid (PUFA) such as Omega 3 fatty acids had initially shown some promise in the prevention of post operative AF however subsequent larger trials have failed to demonstrate a benefit in this or other populations with established AF. Other potential therapies targeting this pathway are being investigated. These
include NyK 1001 – a known inducer of hsp70, which is implicated in the scavenging of ROS and ISIS-CRPR_\chi_ is a novel inhibitor of CRP currently in phase II trials. Other investigational drugs whose mechanisms remain unknown are also in phase II development and the clinical community awaits their progress to the clinical evaluation phase. They have been expertly reviewed by Maan et al and Woods et al.

2.1.2.3 Atrial stretch

Atrial stretch and dilation is an adaptive process by the left atrium to haemodynamic stressors such as atrial fibrillation, hypertension, valvular disease, LV dysfunction or other structural lesions which may induce elevated cardiac filling pressure. In any case, the physical processes, which contribute to atrial stretch trigger a constellation of remodelling mechanisms, leading to structural and electrical remodelling of the left atrium. Firstly, atrial dilatation is an obvious consequence of atrial stretch due to increase wall tension. However, animal models suggest that the degree and rapidity atrial dilatation is related more to the presence of LV dysfunction or rapid ventricular rates rather than rapid atrial pacing alone. Alterations in calcium handling appear to be the primary consequence of atrial stretch with a demonstrated effect on ICaL. The pro-remodelling effects of dysfunctional calcium handling, including electrical remodelling, have been described above. Secondly, myocyte hypertrophy occurs in response to atrial stretch largely driven by RAAS mediators, as localised stretch increases the production of local angiotensin converting enzyme (ACE) and can facilitate activity of Ang II type 1 receptor (AT1) in the absence of Ang II. In stretch remodelling associated with LV remodelling, systemic activation of RAAS is likely to also play a role. Thirdly, stretch can induce atrial fibrosis possibly mediated by plasma endothelin 1 (ET-1), which is known to upregulate MMP2 activity, promoting collagen deposition. Lastly, atrial stretch can induce remodelling by activation of pro-inflammatory pathways and by facilitating oxidative stress, both of which can promote fibrosis as described previously.

Given the multitude of overlapping processes contributing to atrial electrical and structural remodelling, Sanders and co-workers sought to investigate the contribution of atrial stretch to these processes electrophysiologically evaluating the left atrial substrate in the dilated atria in 21 patients prior to, immediately after and 6 months
following percutaneous balloon mitral commissurotomy for severe mitral stenosis. They identified progressive improvements in P wave duration, conduction velocity, global voltage and atrial ERP (at 6 months), suggesting that after the contribution of atrial stretch to atrial remodelling, significant reverse remodelling was possible. In contrast to atrial fibrosis and electrical remodelling, left atrial dimensions and function can readily and non-invasively assessed. As such the predictive potential of LA dimension. LA diameter, a traditional albeit rather crude measurement of LA size has been shown to correlate with AF recurrence in large population cohort studies. In a post hoc analysis of the AFFIRM trial, LA diameters > 4.1cm predicted recurrence in cohort of patients with mixed treatment strategies (rate and rhythm control). A similar analysis looking specifically at the population undergoing electrical cardioversion suggested LA diameter > 4.5cm was predictive of requiring > 2 cardioversion attempts, however the sensitivity and specificity of this measure was poor suggesting the clinical utility of this measurement was low. Left atrial volume index (LAVI) – essentially a measure of left atrial volume corrected for body habitus – has also been shown LAVI values < 30mL/m² correlate with increased AF recurrence post cardioversion. Older studies had suggested that in setting of amiodarone therapy, LA dimensions may not significantly predict AF outcomes, however, firstly, these studies may have self selected patients prone to recurrence, and secondly, assessments of LA dimensions at that stage (with primarily M-mode echocardiography) were likely crude at best. Apart from predicting AF, LA diameter had been independently associated with ischaemic stroke in women, and increased all cause mortality in all patients including those without AF, although whether this represents an independent risk factor or merely non-diagnosed subclinical atrial fibrillation remains unclear.

2.1.2.3.1 Ablation therapy
Being one of the few pre-procedural non-invasive indicators of AF ablation, there has been much interest in the predictive potential of pre-procedural LA dimensions on outcomes post ablation. Lee et al found that LAVI (<43mL/m²) predicted recurrence of AF following atrial flutter ablation. Given the increasingly recognised co-existence of atrial flutter and AF and often eventual need to treat both conditions (with each requiring a markedly different ablative approach), the investigators argued that LAVI may help in predicting that population – potentially allowing an empirical
AF ablation which has been associated with improved outcomes\(^8^6\). However, the sensitivity and specificity of LAVI in this regard was only modest (69\% and 70\%)\(^8^4\).

With regards to AF ablation outcomes, several studies have shown a predictive value of LA size on outcomes post catheter ablation. A detailed description of the predictive potential of pre-procedural LA imaging in predicting outcomes post AF ablation are described elsewhere in this series, however a few relevant studies warrant mention here. A meta-analysis of 22 studies and 3750 patients found that LA diameter as measured by echocardiography predicted single procedure success in a predominately paroxysmal patient population\(^8^7\). Von Bary et al evaluated the predictive potential of LA dimensions as measured by other non-invasive imaging techniques such as CT and MRI, which are often necessary pre-procedure as images are incorporated into 3D mapping systems utilised during ablation. These modalities offer a detailed 3D assessment of atrial volume and reasonable correlation with each other, although echocardiography may underestimate LA volume\(^8^8\). That study found that in purely paroxysmal AF, LA volume did not necessarily predict recurrence post AF ablation, although it did predict progression to persistent AF in those patients who did develop recurrence\(^8^9\). Amin et al evaluated the correlation between CT derived LA volume and the outcomes in patients with persistent AF undergoing AF ablation. Patients with persistent AF had larger LA volumes at baseline, and LA volume was predictive of recurrence at 12 months but this did not reach statistical significance\(^9^0\).

The strong overlap between atrial size and the concurrent presence of other remodelling processes, to degree may explain this finding. Furthermore, the ‘multiple wavelet’ hypothesis of AF mechanisms (which is not universally accepted) suggests that a critical mass of atrial tissue is required to sustain AF. Atrial dilatation makes this more likely by increasing the endocardial surface area, promoting multiple wavelets in the setting of appropriate AF triggers\(^9^1\). Further prospective randomised studies need to be performed to elicit the true predictive potential of LA dimensions in setting of AF ablation.

2.2 Invasive substrate analysis in AF

Invasive substrate analysis is an established technique for the characterisation of structural remodelling occurring in atrial tissue, and has been performed in efforts to characterise atrial remodelling in a number of disease states including aging,
hypertension, valvular heart disease and heart failure. Typically, electrophysiological parameters such as tissue voltage, complex electrograms and conduction velocity are indicative of structural changes of the atrial myocardium due to adverse remodelling secondary to the presence of pathological atrial fibrosis. The following sections outline the validation of invasive electroanatomical mapping parameters for the characterisation of atrial substrate from adverse atrial remodelling.

2.2.1 Tissue Voltage

Several studies have demonstrated a correlation between low tissue voltage and adverse atrial remodelling. Oakes et al performed electro-anatomical mapping and cardiac MRI assessment of 81 patients undergoing catheter ablation for AF. They found that the percentage of atrial LGE correlated with the percentage of low voltage points as measured by electro-anatomical mapping\(^92\). Another study by Marcus et al examined the atrial substrate in 22 patients undergoing catheter ablation for AF or atrial tachycardia. They found a significant correlation between atrial size (associated with adverse atrial remodelling) as measured on pre-procedural CT scan and atrial tissue voltage such that every millilitre reduction in LA volume resulted in a 0.02mV increase in bipolar tissue voltage (p=0.0015).

2.2.2 Conduction velocity

The presence of atrial fibrosis results in reduced conduction velocity promoting regional conduction heterogeneity and the creating the substrate for re-entry. Fukumoto et al calculated the local conduction velocity at various left atrial location in 22 patients undergoing AF ablation who also underwent assessment for atrial fibrosis with cardiac MRI. In that study, local conduction velocity correlated directly with unit image intensity (ie the presence of atrial late gadolinium enhancement) with a reduction in conduction velocity of 0.2m/s for every unit increase in image intensity ratio (p<0.001). Importantly, conduction velocity can only be determined by invasive assessments performed in sinus rhythm or atrial pacing.
2.2.3 Complex electrogram activity

Complex electrograms are thought to be indicative of underlying remodelled atrial tissue, indicative of atrial fibrosis and AF substrate. It is important to differentiate the analysis of atrial electrical activity during atrial activity and during sinus rhythm. Complex fractionated electrical activity (CFAE) typically refers to continuous electrical activity present during atrial fibrillation with mechanistic importance to the perpetuation of AF\textsuperscript{93}, though to represent either focal or rotational drivers of atrial fibrillation. However, the utility of measurements during AF is far from certain. Teh et al explored the electrograms characteristics of electrograms in 12 patients in both AF and during paced rhythm. They found poor correlation between complex fractionated electrograms measured in and areas of low voltage, fractionation and slow conduction velocity as measured during paced rhythm\textsuperscript{94}. Miyamoto et al similarly demonstrated complex fractioned signals measured in 20 patients during AF represented healthy tissue in patients with likely PV triggered AF (ie terminating with PVI), but correlated with areas of low voltage in patients with more persistent forms of AF (ie without termination during PVI), when measured in sinus rhythm\textsuperscript{95}. Perhaps in part for this reason, a large international multi-centre randomised trial evaluating ablation strategies in patients with persistent AF did not show a benefit of targeting complex fractionated electrograms (as assessed in AF), over PVI alone.

2.2.4 Previous studies performing invasive substrate analysis in AF

Several studies have utilised invasive substrate analysis by determining the electrophysiological parameters outlines above. These have included analysis both in the setting of AF\textsuperscript{96-97} and in known associated disease states. For example, Teh et al analysed the atrial substrate in 31 patients with AF compared to 15 aged matched controls to determine the impact itself upon atrial substrate formation\textsuperscript{96}. Similarly, Sanders et al examined the atrial substrate in 21 patients with heart failure and 21 patients with no known history of AF, to determined the impact of heart failure upon atrial substrate\textsuperscript{98}. Other studies utilised these parameters in assessment of other disease states including aging\textsuperscript{99}, hypertension\textsuperscript{100-101} and valvular heart disease\textsuperscript{78}.
2.3 Remodelling in the setting of heart failure

AF and HF are associated with physiological conditions that contribute to the initiation and maintenance of the other. AF precipitates LV dysfunction via (1) the loss of atrial contraction, (2) the precipitating irregular ventricular rhythm and (3) rapid ventricular rates. Conversely, HF precipitates AF by contributing to atrial remodelling due to (1) increased filling pressures, (2) alterations in calcium handling and (3) alterations to the electrical properties of the atrial tissue. As such a circuitous ‘cause and effect’ or chicken and egg relationship underpins the complex interaction between these two conditions (Figure 3).

2.3.1 Atrial fibrillation induced heart failure

The mechanisms behind HF precipitated by AF have been explored in both animal models and extrapolated from clinical experience.

2.3.1.1 Tachycardia

Rapid ventricular rates have a well-described deleterious impact upon LV systolic function in canine rapid pacing models\textsuperscript{102-103}. The physiological mechanisms implicated in precipitating LV impairment include haemodynamic stress, activation of neuro-hormonal systems, myocardial and cardiac exoskeleton remodelling and, if tachycardia continues, eventual induction of apoptosis, cell death and replacement fibrosis\textsuperscript{104}. Clinically, incessant or high burden rapid regular tachycardia’s such as those seen in focal atrial tachycardia (FAT) are often accompanied by LV systolic dysfunction which is reversed following the restoration of sinus rhythm by catheter ablation\textsuperscript{105}. Medi et al demonstrated that LV dysfunction was largely confined to those with incessant atrial tachycardia with slower ventricular rates speculating that symptoms may be more subtle and as such patients present later with heart failure rather than earlier with palpitations\textsuperscript{105}. This highlights that rapid rates alone do not explain the entirety of LV dysfunction precipitated by arrhythmia. Indeed, 60 patients (20%) with normal LV function had incessant or high burden tachycardia, at a higher average rate than those with reduced LV function\textsuperscript{105}. As such the term arrhythmia mediated cardiomyopathy is more appropriate than tachycardia-mediated cardiomyopathy.
2.3.1.2 Heart rate irregularity

Apart from rapid ventricular rates, the irregularity of ventricular rate itself can have adverse haemodynamic effects resulting in LV dysfunction. Nalto et al explored the impact of various pacing strategies upon cardiac output in a canine model with iatrogenic AV block. They found that in both AV sequential pacing and in underlying atrial fibrillation, irregular ventricular rhythm with the same average ventricular cycle length of 400ms, resulted in a significant 7-9% reduction in cardiac output\textsuperscript{106}. Similarly, Clark et al examined the haemodynamic impact of regular and irregular ventricular pacing following AVN ablation in 16 patients with high burden or chronic atrial fibrillation undergoing AV node ablation. At equivalent average ventricular cycle lengths (587ms), cardiac output was notably diminished in patients paced irregularly compared to regular ventricular pacing (4.4 vs 5.2 L/min, p<0.01). Right and left sided filling pressures, as determined by RA pressure and PCWP were also significantly elevated during irregular pacing\textsuperscript{107}.

2.3.1.3 Loss of atrial systolic function

Pacing studies have utilised iatrogenic A-V dysynchrony to quantify the contribution of atrial systolic function to cardiac output. Benchimol et al performed a haemodynamic analysis of 18 patients with complete heart block under varying strategies of AV sequential pacing and varying ventricular rates. They found that atrial systole significantly contributed to cardiac output at all ventricular rates, but most obviously at rates 50-80 bpm\textsuperscript{108}. Mukharji et al quantified atrial contribution to systolic function in 20 patients both with and without underlying LV systolic dysfunction. Atrial contribution to cardiac output was estimated at 20%, irrespective of the presence of underlying LV dysfunction\textsuperscript{109}.

2.3.1.4 Genetic factors

Nonetheless, the incomplete penetrance of atrial fibrillation phenotypes to precipitating LV dysfunction in all patients, highlights the likely role of other contributing factors in those patients susceptible to LV dysfunction. A myriad of genetic mutations implicated in non-ischaemic cardiomyopathy may play a role in determining susceptibility to LV dysfunction. These may include those encoding molecules involved in contractile function, cellular integrity and/or cytoskeletal
In the setting of atrial arrhythmia with rapid rates, those patients with a tachycardia-mediated cardiomyopathy had a higher frequency of the ACE gene polymorphism compared to both patients with tachycardia and normal LVEF, and healthy controls ($p<0.035$ and $p<0.009$ respectively). The genomic determinants of arrhythmia-mediated cardiomyopathy remain to be fully elucidated.

2.3.2 Occurrence of AF in pre-existing heart failure

2.3.2.1 Electrical and structural remodelling in heart failure
Systolic left ventricular dysfunction is associated with atrial structural and electrical changes which initiate and sustain AF. Sanders et al characterized the atrial electrophysiological properties in patients with heart failure ($n=21$) compared to age matched controls with no heart failure ($n=21$), in the absence of documented atrial fibrillation. Heart failure was associated with an increase in atrial ERP, regional conduction slowing, increased fractionation and increased areas of low voltage and scar. These features are hallmarks of atrial remodelling underlying even modest burdens of AF. This study clearly demonstrated the capacity of heart failure to precipitate a physiological environment favourable to AF.

2.3.2.2 Mechanisms of heart failure precipitating AF
The hallmark of LV dysfunction (both systolic and diastolic) is an elevated LV end diastolic pressure leading to increased left atrial (LA) filling pressures. Elevated atrial pressure increases atrial wall stress with consequent effects upon the renin angiotensin system, calcium handling, pro fibrotic and pro-inflammatory pathways to promote electrical and structural remodelling.

2.3.2.3 Neuro-hormonal activation
Left ventricular dysfunction is associated with the activation of several neuro-hormonal pathways implicated in atrial remodelling. The most important of which is activation of the renin angiotensin system, which in turn activates a myriad of pathways including: mitogen-activated protein kinase (MAPK), the Janus kinase (JAK)/signal transducers and activators of transcription (STAT), transforming growth factor-$eta$.
growth factor β1 (TGF-β1), angiotensin II activated platelet-derived growth factor A (PDGF-A), Rac1 and nuclear factor-kappa B (NF-κB). Additionally, angiotensin II can activate these signalling pathways both indirectly and directly via activation of angiotensin II type 1 (AT-1) receptors. This promotes myocyte hypertrophy, apoptosis, collagen deposition and interstitial remodelling, all which contribute to structural remodelling of the atria and the development of AF. To some extent, natriuretic peptides such as ANP and BNP exert a counter-regulatory effect, opposing the activity of angiotensin II and the overall progression of remodelling may depend upon the interplay of these opposing processes.

2.3.2.4 Abnormal calcium handling
In addition to neuro-hormonal pathways promoting atrial remodelling in the setting of heart failure, disordered calcium handling contributes to a propensity to AF. In an ovine model of heart failure, Clarke et al determined that a reduction in I_Ca,L in atrial myocytes resulted in increased intra-cellular calcium, predisposing to early and late after depolarisations, promoting the automatic atrial activity identified as triggers for AF. Ling et al demonstrated that irregular ventricular rhythms in the setting of heart failure, were associated with reduced expression of sarcoplasmic reticulum calcium channels, compared to patients with regular pacing, and in sinus rhythm.

2.3.2.5 Adrenergic stimulation
The autonomic nervous system plays an important role in heart failure. Chronically reduced cardiac output leads to sustained adrenergic overactivity and an increase in circulating noradrenaline, adrenaline and noradrenaline. In addition to significant derangements to ventricular adrenergic regulatory processes, increased adrenergic stimulation has been shown to increase the inducibility of AF in a dose dependant manner. The mechanisms in which autonomic inputs promote atrial arrhythmia have been well documented. β-adrenergic stimulation results in a protein kinase A mediated cascade of phosphorylation of a range of intracellular proteins involved in calcium handling, including RyR2, SERCA2a and I_Ca,L – promoting conditions favourable for delayed after depolarisations. Direct effects upon I_Kr and I_f channels increase focal firing, whilst modulation of APD via enhanced I_Ca,L (adrenergic) or I_KAch (cholinergic) can promote phase 2 and phase 3 early after depolarisations. The
net effect is the promotion of conditions favourable to rapid firing and focal activity. In addition, β stimulation, via calcium activation of calmodulin and calcinuerin, also activates transcription processes implicated in driving ultra-structural changes. Lastly, the effect of I_{K,ach} activity on APD abbreviation is though to occur with significant regional variation, promoting conditions favourable for functional re-entry and pro-arrhythmia. However, when AF and HF co-exist, patients may paradoxically develop a marked attenuation of sympathetic activity, impairing the ability to respond to acute haemodynamic stresses. Thus, a complex interplay between AF and HF characterise the adrenergic response.

2.3.2.6 Functional mitral regurgitation
Additionally, functional mitral regurgitation (FMR), which often accompanies ventricular remodelling it the setting of systolic heart failure, also contributes to the development of AF. In 894 patients with previous AMI and FMR, a dose dependant relationship between FMR severity and both the presence of AF and new onset AF was reported. AF itself may contribute to functional mitral regurgitation resulting in further atrial remodelling, over and above the contribution of LV dysfunction.

2.4 Predictors of LVEF recovery post catheter ablation
Inferences may be cautiously drawn from limited clinical trials exploring the use of catheter ablation to improve LV function for patients with co-existing AF and heart failure. Prospective randomised studies have generally included patients with a variety of aetiologies for heart failure and both paroxysmal and persistent AF. These are detailed further in the next section (section 3). The patients most likely to benefit from restoration of sinus rhythm with catheter ablation include (1) no alternate explanation for cardiomyopathy; (2) the absence of myocardial fibrosis; (3) patients co-diagnosed with AF and heart failure and (4) high AF burden.

2.4.1 Heart failure aetiology
Whilst the occurrence of AF in previously known heart failure obviously presents little challenge in determining cause and effect, the temporal sequence of events from the clinical history may not always be clear. Several, early clinical trials have
demonstrated that the restoration of sinus rhythm with successful catheter ablation improved LVEF irrespective of heart failure aetiology\textsuperscript{103,125-127}. However, these trials were complicated by non-standardised definitions of heart failure aetiology, such as the failure to distinguish between a causative diagnoses (for example myocardial infarction) and concurrent diagnosis (for example non-occlusive, or non-contributory coronary disease). Gentlesk et al, in a retrospective analysis, reported the outcomes of patients (n=50) with so called unexplained cardiomyopathy with LV function normalised in 72% post ablation\textsuperscript{127}. A meta-analysis suggested that pre-existing structural heart disease, such as prior myocardial infarction predicted reduced procedural efficacy \textsuperscript{128} and poor recovery of systolic function\textsuperscript{129}. In a retrospective analysis of 101 patients with persistent AF and heart failure (LVEF <45%), those patients (n=77) with no known aetiology for the LV dysfunction (idiopathic cardiomyopathy) had a 14% absolute improvement in LV function post ablation (p<0.001), with 38% of these patients normalising LVEF (>55%) at follow up\textsuperscript{129}. To date, there have been no prospective randomised trials evaluating the role of catheter ablation in patients with persistent AF and an otherwise unexplained cardiomyopathy.

2.4.2 Myocardial fibrosis

The presence of myocardial fibrosis, in particular ventricular myocardial fibrosis is increasingly recognised as an important determinant of outcome regarding improvement in ventricular function. Currently, although there is limited evidence that echocardiography can indirectly detect myocardial fibrosis via assessment of longitudinal strain (for example in hypertrophic cardiomyopathy\textsuperscript{130}), the mainstay of clinical detection of myocardial fibrosis is cardiac MRI.

2.4.2.1 Types of myocardial fibrosis

Three main types of myocardial fibrosis have been described, as expertly reviewed by Mewton et al\textsuperscript{131}. Reactive interstitial fibrosis, associated with increased extracellular matrix deposition of tissue in the setting of myocardial stress in disease states such as hypertension, diabetes, valvular disease and aging. Replacement fibrosis refers to dense collagen replacement of the extracellular space, in conjunction with necrosis of myocardiocytes. This follows conditions causing direct myocardial injury such as myocardial infarction, myocarditis, sarcoidosis, toxic injuries in addition to other conditions. Finally infiltrative interstitial fibrosis, is present in disease states
associated with deposition of toxic material in the extra-cellular space, such as amyloidosis and Fabry’s disease.

2.4.2.2 Detection of myocardial fibrosis with cardiac MRI
There are broadly speaking, two main forms of detection of ventricular myocardial fibrosis with cardiac MRI – late gadolinium enhancement and T1 mapping.

2.4.2.2.1 Late gadolinium enhancement (LGE)
A detailed description of the biophysiological mechanism of gadolinium is beyond the scope of this review. In brief, tissue gadolinium concentration results in changes T1 signal intensity by reducing the relaxation time. The final voxel intensity will be determined several other physiological determinants including local perfusion, extracellular matrix distribution, water exchange rates and the ‘wash out and wash in’ kinetics of gadolinium. Gadolinium accumulated in the extracellular space, which is expanded in the presence of myocardial fibrosis, and reduced capillary density in fibrotic tissue promotes the maintenance of high tissue concentrations of gadolinium. T1 shortening in this space displays this tissue with bright signal intensity. Typically, intensity parameters are set to display normal myocardium as black, highlighting abnormal tissue as white. In setting of idiopathic cardiomyopathy, Schalla et al have described that the presence of LGE was more associated with markers of inflammation rather than heart failure severity. Whilst chamber dimensions and both RV and LV ejection fraction compared favourably between the groups, inflammatory markers on endomyocardial biopsy, including CD3 and CD4 were significantly higher in those with LGE present132.

2.4.2.2.2 T1 mapping
T1 mapping is a technique allowing direct measurement of T1 relaxation times allowing a more standardised characterisation of myocardial tissue, independent of influences such as tissue windowing and variations in signal intensity. T1 times are generated from a curve generated by differing pulse sequences. Algorithms are utilise to determine the best fitting curve for the acquired voxels with various commercially available protocols in use world wide, such Smart T1 and modified Look-Locker
Inversion-recovery (MOLLI). Nonetheless, a lack of standardisation across centres remains a significant drawback of this technique. T1 mapping has several advantages over late gadolinium enhancement. The quantitative nature allows more accurate tissue characterisation than late gadolinium enhancement with the potential to characterise less prominent forms of fibrosis such as diffuse or interstitial fibrosis. Also, the lack of requirement of normal myocardial tissue for comparison is also an important advantage, especially in the characterisation of non-ischaemic myocardial injury. Post contrast T1 mapping has been histologically correlated with diffuse fibrosis in several single centre studies, including specifically in the setting dilated cardiomyopathy\textsuperscript{133-134}. Given the ability of gadolinium to shorten T1 times, in post contrast T1 mapping, lower values represent increased myocardial fibrosis, whereas in non-contrast or native T1 mapping, higher values correlate with increased fibrosis.

2.4.2.3 Myocardial fibrosis and clinical outcome

Ling et al reported the outcomes of patients with persistent AF, idiopathic cardiomyopathy (LVEF<50%) and the absence of late gadolinium enhancement (LGE) on MRI imaging undergoing catheter ablation. They hypothesised that the absence of LGE was indicative of an arrhythmia-mediated cardiomyopathy whereas its presence signified an established cardiomyopathy in which AF was less likely to be responsible for LV impairment. Patients without LGE undergoing AF ablation showed an average improvement of 20% in absolute LVEF, with 94% normalising LV function. McLellan et al performed post contrast ventricular T1 CMR for the presence of diffuse myocardial fibrosis (interstitial fibrosis) in patients undergoing AF ablation. Both atrial fibrillation and heart failure independently predicted the presence of diffuse ventricular fibrosis on multivariate analysis suggesting either or both can contribute to fibrosis in the ventricle\textsuperscript{135-136}. This suggests that the relationship between AF, heart failure and myocardial fibrosis is likely interdependent and complex. The presence of myocardial fibrosis may also have important implications for long term outcomes as well. Addison et al retrospectively evaluated the outcomes of 172 patients with LVEF <50% undergoing catheter ablation all of whom has baseline cardiac imaging performed, with 25% having LGE present. After an average of 42 months follow-up, the presence of LGE was associated with a lack of recovery of LV function, increased AF recurrence in addition to worsened mortality and heart
failure hospitalisations\textsuperscript{10}. In addition, Iles et al prospectively recruited 103 patients receiving primary prevention ICD. After a mean follow up of 573 days, in those patients with non-ischaemic cardiomyopathy (31 patients, 51%), the presence of LGE was associated with significantly more appropriate ICD therapy, despite similar ejection fraction\textsuperscript{132}. Importantly, a meta-analysis by Anselmino, the absence of structural heart disease, predicted the best response to catheter ablation both with respect to LVEF improvement and long term freedom from AF\textsuperscript{128}.

2.4.2.4 Reversibility of myocardial fibrosis.
Only one study had evaluated the potential for diffuse fibrosis, as detected by T1 mapping, to improve following intervention. McLellan et al performed cardiac MRI including post contrast T1 mapping before and 6 months after renal denervation. In concert with a significant reduction in blood pressure (152/84 to 141/80mmHg, \( p<0.01 \)), T1 partition co-efficient was significantly reduced (0.39±0.07 to 0.31±0.09), consistent with a regression of diffuse myocardial fibrosis\textsuperscript{100}. Other studies have longitudinally evaluated diffuse fibrosis in various disease states such as aortic stenosis\textsuperscript{137}, and acute myocardial infarction\textsuperscript{138} and chronic stable cardiomyopathy\textsuperscript{139}. To date no other studies have demonstrated a change in diffuse fibrosis utilising serial MRI scanning following intervention.

2.4.3 Co-diagnosis of AF and heart failure
An initial clinical presentation with both AF and heart failure may be marker of an arrhythmia-mediated cardiomyopathy. In a prospective randomised controlled trial with a heterogeneous population of patients with heart failure and persistent AF (\( n=50 \)), Hunter et al demonstrated that catheter ablation significantly improved LVEF (+8.1\%, \( p=0.015 \)), and both subjective and objective functional capacity (\( p<0.001 \)). Similarly, Prabhu et al found that in those patients with an otherwise unexplained cardiomyopathy, who were also more likely to improve LVEF post ablation (+14\% vs +3\%, \( p<0.001 \)), were significantly more likely to have been co-diagnosed with AF and heart failure (49\% vs 17\%), \( p=0.004 \)\textsuperscript{129}. 
2.4.4 AF burden and heart failure

Whilst some implications regarding cause and effect can be extrapolated from clinical trials aimed at treating AF, longevity cohort studies provide some insight in predicting the onset of HF in patients with AF. Miyasaka et al followed 3288 patients with newly diagnosed AF for an average of 6.1 years. The presenting AF phenotype, determined the likelihood of eventual chronic heart failure in a dose dependant manner. Incident chronic AF predicted the onset of heart failure 11 fold at one year and 28 fold at 5yrs, compared to incident paroxysmal AF (1yr: 7 fold, 5yr: 18 fold), and lone AF, which were not associated with HF. This suggests that AF burden in particular chronic AF is more likely to be associated with heart failure.

2.5 Anatomical considerations and implications for AF treatments

Before exploring the crucial role of structural remodelling on atrial function and its implications for the AF treatments, it is worth appreciating the purely anatomical aspects of the left atrium, and implications this has for our understanding of AF development and treatment. The advent of catheter ablation for AF, which by its very nature requires an intimate navigation around the left atrial endocardium, has significantly advanced our anatomical and electrophysiological understanding left atrial structure and function. Nonetheless, despite this detailed biological characterisation of the left atrium, significant debate still exists about the fundamental mechanisms driving and sustaining AF in various clinical phenotypes.

2.5.1 Pulmonary vein isolation (AF ablation)

Given that AF ablation is a now readily established as a mainstream treatment modality for atrial fibrillation with efficacy consistently superior to medical therapy, a brief understanding of the procedural aspects of AF ablation is warranted. The cornerstone of the procedure is electrical isolation of the pulmonary veins by the targeted deployment of radiofrequency (or essentially heat energy) ablation lesions, around the pulmonary vein ostia. Ablation is performed percutaneously by the insertion of endovascular catheters into the heart from the femoral vein with an ablation and multi-electrode catheter accessed to the left atrium via fluoroscopically guided transeptal puncture, often with intra-cardiac or transoesophageal echocardiographic support. Catheter location and navigation is
guided by 3D anatomical mapping systems capable of visually displaying the catheters in a computerised model 3D atrial shell generated by surface contact information in addition to pre-procedural imaging. This facilitates catheter manipulation with minimal need for X ray guidance. A circular multi-polar catheter is advanced into each pulmonary vein to monitor pulmonary vein electrical activity to ensure electrical dissociation is achieved following ablation. Radiofrequency ablation catheters are continually irrigated to ensure adequate power delivery and minimise the potential for catheter tip thrombus formation. Recently cyro-tipped inflatable balloons have been utilised to rapidly deliver circumferential hypothermic injury around the pulmonary vein ostia to facilitate more rapid pulmonary vein isolation, with similar efficacy to radiofrequency energy but with different adverse effect profile. Significant variations in practice may occur based on institution or operator preference. In addition to pulmonary vein isolation, further lesions or lines of block may be delivered for the purposes of additional substrate modification (in persistent AF phenotypes), or in the process of mapping and ablating other atrial macro-reentrant or focal tachyarrythmias – although the optimal approach to this remains the focus of considerable debate.

2.5.2 Left atrial and pulmonary vein anatomy

The left atrium consists of four main components. The venous component consists of the four (usually) pulmonary veins and the intervening posterior wall of the LA. The vestibule consists of the superior and inferior portions of the atrium – connecting anteriorly with the mitral annulus. The inter-atrial septum and the left atrial appendage make up the remaining to atrial components located in the septal and lateral region respectively. Of these components, the pulmonary veins have been shown to play a crucial role in the development of ectopic foci capable of initiating atrial fibrillation in the susceptible atrium, as described by Haïssaguerre in his landmark paper and which formed the basis of the modern day AF ablation procedure in which electrical isolaion of the pulmonary veins remains the cornerstone. Post mortem studies of patients both with and without a history of AF, showed more atrial myocardial extensions into the pulmonary veins, which were also more likely to be discontinuous in patients with AF. Interestingly, the length of extensions appeared greater in the upper pulmonary veins compared to the lower veins consistent with the
finding that the superior veins are more likely to be implicated in triggering AF\textsuperscript{145}. Furthermore, the pulmonary veins were associated with intercellular fibrosis and myocyte hypertrophy, each extending variable distance both proximally and distally from the pulmonary vein ostia\textsuperscript{146}. In addition the sharp transition in fibre orientation in the vicinity of the pulmonary veins may intrinsically promote conditions for re-entry by virtue of high tissue anisotropy\textsuperscript{147}. The dense neural inputs in the region of the PV/LA junction, and their contribution to arrhythmogenesis in AF have been described above. These intrinsic anatomical and structural features promote relatively more rapid electrical and structural remodelling even in the settings of considerably modest AF burdens (such as ‘lone’ AF)\textsuperscript{97, 148-149}. Myocardial fibres along the intervenous ridges may be associated with epicardial connections facilitating PV-LA connections across an apparent circumferential line of block\textsuperscript{150}. In addition, the left lateral ridge (also known as the LAA/PV ridge) which divides the anterior region of the left pulmonary veins and the left atrial appendage, has been well described as an highly arrhythmogenic region. The oblique vein of Marshall runs along the epicardial region of the ridge and carries with it a mirriad of autonomic neural bundles with important implications for arrythmogenesis. Furthermore dense muscular connections between the upper ridge and left superior pulmonary veins may be important conduits for PV triggers to initiate AF\textsuperscript{151}.

Beyond the pulmonary veins, the septo-pulmonary bundle provides another substrate for AF by virtue of sudden alterations in atrial thickness particularly along its boundaries. Pulmonary vein potential have a predisposition to ‘wave break’ at these sites, making these site particularly arrhythmogenic even the absence of other remodelling\textsuperscript{152}.

2.5.3 Implications for AF ablation (Figure 3)

2.5.3.1 Ablation approach

These anatomical challenges have impacted the approach to AF ablation since its inception in order to improve its efficacy. Given the degree of arrhythmogenic substrates in close proximity to the PV/LA ostia, a significant development in AF ablation strategy is the delivery of a progressively wider (or more antral) circumferential ablation lines in order to encompass a larger proportion of this potentially arrhythmogenic substrate, as well as minimising the potential for
pulmonary vein stenosis – a recognised complication of ostial (also termed segmental) pulmonary vein ablation. However, results have been somewhat mixed. A recent meta-analysis of ostial versus wide circumferential ablation strategies showed a markedly improved freedom from AF recurrence at long term follow up\textsuperscript{153}. In contrast, a previous meta-analysis which had a longer average follow up time (3yrs vs 1 yrs) suggested no benefit in ostial versus wide antral approach\textsuperscript{154}. This may reflect the fact that a more antral approach may make achievement of PV isolation more challenging as it requires more ablation lesions to achieve, and possibly less durable in the long term by increasing the chance for gaps in the ablation line – predisposing to PV reconnection (see below). A recent multicentre study by our group has demonstrated that the pulmonary vein requiring ablation along the intervenous ridge to achieve isolation was associated with higher AF recurrence post ablation\textsuperscript{155}

2.5.3.1 *Pulmonary vein reconnection*

Pulmonary vein reconnection is the most common cause for recurrent AF post ablation and is regarded as the ‘Achilles heel’ of AF ablation. Given that the aim of the procedure is the containment of electrical activity behind a manufactured line of block or electrical buffer, even a seemingly innocuous gap in lesion coverage can be sufficient to allow complete conduction between the PV and LA. Gaps in the ablation line facilitating PV/LA reconnection may be due to: (1) inadequate (sub-transmural) lesion formation\textsuperscript{156}, (2) pseudo-block at the time of isolation presumably due resolution of peri-lesional oedema revealing viable tissues capable facilitating conduction\textsuperscript{156} or (3) as a consequence of tissue remodelling\textsuperscript{157}. Inadequate lesion formation was elegantly evaluated in a series of patients undergoing surgical maze procedure following recurrence of AF after an initial pulmonary vein isolation procedure. Areas of visible scar were sampled and pulmonary veins were assessed for reconnection. Transmural lesions were more likely to be associated with reconnected veins. The recent advent of ablation tip pressure sensing technology (such as Contact Force) has provided important real-time feedback regarding the ablation tip pressure on the endocardial surface, as tip pressure is a determinant of energy delivery and lesion size\textsuperscript{158}. Furthermore, parameters such as minimum contact force and minimum force time integral are strong predictors of lesion gap formation\textsuperscript{159}. Failure to recognise pseudo-block resulting in initial pulmonary vein isolation can be minimised
by sufficient waiting period following initial PV isolation, or the administration of adenosine (see below). This may facilitate unmasking of acute reconnection as peri-lesional oedema settles. The absence of acute reconnection following at least a 30-minute waiting period was associated with reduced AF recurrence\textsuperscript{160}. Interestingly, even when reconnection is demonstrated, further ablation to reisolate does not appear to improve outcome to those with no evidence of acute reconnection\textsuperscript{161}.

### 3. Clinical trials in atrial fibrillation and heart failure

Several studies have explored the role catheter ablation in patients with heart failure. A growing body of evidence is accruing demonstrating the important role of catheter ablation as an anti-failure treatment for patients with reduced systolic function.

#### 3.1 Early studies

The landscape in this area was characterised largely by two large multicentre controlled trials evaluating the role of pharmacological rhythm control in patients with AF. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial randomised 4,060 patients with AF to a pharmacological rhythm or rate control study with the clinical endpoint of all cause mortality. At mean follow-up of 3.5 years, there was no significant difference between the groups (23.8% vs 21.3%, p=0.08) with respect to all cause mortality\textsuperscript{162}. This study pre-dated the era of catheter ablation, with amiodarone the agent of choice for rhythm control (62%). A further post hoc analysis by Corley et al, demonstrated the mortality benefit from sinus rhythm was largely negated by the worsened survival attributable to anti-arrhythmic use\textsuperscript{163}. Roy et al performed a similar study in 1,367 patients with systolic dysfunction (48% ischaemic cardiomyopathy) and randomised each to either pharmacological rhythm control (principally with amiodarone, 82%) or rate control. Again catheter ablation was utilised in a minority of patients (not specified by the authors). That study again showed no difference in mortality (27% vs 25%, p=0.59). Reasons for the lack of difference may be attributable to the heterogeneous make-up of the study population, the poor efficacy of pharmacological rhythm control, the toxicity of anti-arrhythmic medications and overall low burdens of AF in the study population.
3.2 Catheter ablation in heart failure

Since the advent of catheter ablation, a growing number of studies have demonstrated an important role of catheter ablation in heart failure. These include both non-randomised and randomised studies. Table 1 provides a brief summary of key clinical trials of catheter ablation in heart failure to date.

3.2.1 Non-randomised studies

Hsu et al published one of the first trials to demonstrate the benefit of catheter ablation in improving heart function. Fifty-eight consecutive patients with heart failure (LVEF<45%) undergoing catheter ablation were compared to 58 matched controls (based on age, sex and AF phenotype), with cardiac dimensions, ejection fraction, functional capacity and quality of life assessed pre and post ablation. They found patients with heart failure had improved ejection fraction (+21 ± 13%), reduction in cardiac chamber dimensions, improvements in functional capacity and quality of life. Importantly, this benefit appeared to persist despite the adequacy on baseline rate control and the presence of known structural heart disease. Chen et al retrospectively compared the outcomes in 377 patients undergoing catheter ablation, 94 of which had LV dysfunction (average LVEF=36%). Compared to controls with normal LV function (n=283, LVEF=54%), there was a non-significant improvement in LVEF (36% to 41%, p=0.1) but a significant improvement in quality of life scores. Importantly, multi-procedural success was similar between the groups (94% vs 96%, p=0.2). Gentlesk et al performed a similar retrospective analysis in 366 patients undergoing catheter ablation, 67 (18%) of whom had LV dysfunction (LVEF=42±9%). With comparable AF control between the groups (86% vs 87%, p=NS), the heart failure group showed significant improvement in LVEF (42±9% to 56±8%, p<0.001), despite adequate rate control at baseline. The absence of known structural heart disease such as myocardial infarction or valvular heart disease also predicted the best outcome. As discussed above, in a meta-analysis of randomised, non-randomised and observational studies, incorporating the results from 1,838 patients, Anselmino et al highlighted the relative safety of catheter ablation in heart failure, in addition to a average improvement of LVEF of 13%, in addition to a reduction in biomarkers (BNP).
3.2.2 Randomised studies

There have been five randomised controlled studies comparing catheter ablation to medical rate control in heart failure. These are summarised in Table X below.

3.2.2.1 Early studies

Khan et al randomised 81 patients to either catheter ablation (n=41) or Bi-ventricular pacing with AVN ablation (n=40). The primary endpoint, consisting of a composite of LVEF improvement, improvement in 6 minute walk test distance and quality of life measure was satisfied with all three measures showing significant individual improvement form baseline. At six months, ejection fraction had improved by 8±8% p<0.001 in addition to 6 minute walk distance 340m vs 297m, p<0.001) and the Milwaukee Living With Heart Failure Score (82±14 vs 60±8, p<0001)\(^{165}\). In contrast, Macdonald et al randomised 41 patients with heart failure (49% ischaemic) to catheter ablation (n=22) or ongoing medical rate control (n=19). The baseline LVEF was 18%. These was no significant improvement in LVEF between the groups (4.5% vs 2.8%, p=0.6) as measured by cardiac MRI, although 50% of patients in the ablation arm did not maintain sinus rhythm. In addition, no significant improvement clinical biomarkers, 6 minute walk test or quality of life. A serious complication rate of 15% was also reported\(^{166}\). The relative severity of the heart failure of patients included in this study may have influenced the findings. Jones et al randomised 52 patients with heart failure (33% ischaemic) to catheter ablation (n=26) or medical rate control (n=26). The catheter ablation group showed significantly improved objective functional capacity with a greater improvement in VO2max (+3.07ml/kg/min, p=0.018), although ejection fraction, BNP and 6 minute walk test distance only showed non-significant improvements at 12 months\(^{126}\).

3.2.2.2 Recent studies

More recently, Hunter et al randomised 50 patients with systolic dysfunction (26% ischaemic) to catheter ablation (n=26) or medical rate control (n=24). In addition to the catheter ablation group demonstrating a significant improvement in ejection fraction (+8.1% vs -3.6%, p<0.001), there was also a greater improvement in
VO2max (22 vs 18ml/kg/min, p=0.014) and improvement in quality of life (MLWHF score 47 vs 24, p=0.001). Di Biase et al recently compared the efficacy of catheter ablation versus amiodarone in maintain sinus rhythm in patients with heart failure. To date this is the largest randomised controlled clinical trial of catheter ablation in heart failure patients. Two hundred and three patients were randomised to catheter ablation (n=102) or amiodarone therapy (n=101). At 2 year follow up, in addition to demonstrating the superiority of catheter ablation as rhythm control strategy with respect to freedom from recurrent AF (78% vs 34%, p<0.001), those patients in either arm who maintained sinus rhythm significantly improved LVEF compared to those with AF recurrence (+4.2%, p<0.001). They also had greater 6 minute walk test differences and improved quality of life. Recently, the CASTLE-AF study (Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction, NCT00643188) reported their outcomes at the European Society of Cardiology Congress in Barcelona in August 2017. This multi-centre international randomised controlled clinical trial compared catheter ablation (n=179) to conventional therapy (n=184) over 5 years of follow-up with the primary endpoint being a composite of all cause mortality and heart failure hospitalisation. At 5 years, AF burden was significantly lower in the catheter ablation group (25% vs 60%, p<0.001) and ejection fraction was significantly higher (+8% vs 0%, p=0.005). The primary endpoint strongly favoured catheter ablation. The primary endpoint strongly favoured catheter ablation with a 38% risk reduction (HR=0.62, p=0.007). In addition, individual endpoints also favoured catheter ablation including all cause mortality (HR=0.53, p=0.011), heart failure admissions (HR=0.56, p=0.004), cardiovascular death (HR=0.49, p=0.009) and cardiovascular hospitalisation (0.72, p=0.050). This is also the first trial to demonstrate a benefit of catheter ablation with respect to hard clinical endpoints such as mortality and hospitalisation. At the time of submission, this study was yet to be published.

4. Pulmonary vein electrical activity in persistent AF

Pulmonary vein isolation remains the cornerstone of AF ablation for all phenotypes of AF. However, more persistent forms of AF have proven challenging to treat with catheter ablation with success rates consistently lagging behind those for paroxysmal AF. In a recent meta-analysis, Genesan et al showed that long-term single procedure
success in patients with paroxysmal AF was 54.1% at 2-6 years post ablation compared to 41.8% in patients with persistent AF\textsuperscript{167}. More recent analyses have suggested that success rates with a pulmonary vein isolation strategy alone in patients with persistent AF and the absence of structural heart disease yield 12 month freedom from AF around 67%, as described by Voskoboinik et al in a meta-analysis of 956 patients across 14 studies\textsuperscript{168}. The STAR-AF-2 randomised clinical trial, to date the prospective multi-centre clinical trial of catheter ablation, demonstrated no benefit of further substrate modification (in the form of linear ablation or CFAE ablation) over pulmonary vein isolation alone. Five hundred and eight nine patients with persistent AF were randomised in a 1:4:4 fashion to each ablation strategy. At 18 months post ablation, single procedure success was 60% in the pulmonary vein isolation arm\textsuperscript{169}. These studies demonstrate that in the setting of persistent atrial fibrillation, pulmonary vein isolation alone is effective in achieving freedom from AF in about two thirds of patients. Thus being able to identify those patients in which pulmonary vein activity may play a role in maintaining AF, may improve patient selection for PVI in patients with persistent AF, currently, the only ablation strategy to date to demonstrate consistent benefit in this patient group. In this context, it is worth exploring the role of PV electrical activity during sinus rhythm, and studies aimed at characterising it role in maintain the AF substrate.

\subsection{Animal studies}

Few animal studies have evaluated PV activity during AF. Wu et al induced sustained AF in 6 canines using a rapid pacing model, and characterised the activation of the pulmonary vein and ligament of Marshall and determined relative AF cycle lengths using computerised atrial epicardial mapping. They noticed mean AF cycle length was longer in the right atrial free wall (126 ± 17ms) compared to the left atrial free wall (95 ± 5ms, p=0.006), which was in turn longer than that measured at the ligament of Marshall (84 ± 5ms, p<0.001), and the left inferior and superior pulmonary veins (81 ± 4ms, p=0.001; 85 ± 7, p=0.003). The dominant AF frequency was measured at the pulmonary veins and the ligament of Marshall (11.2 to 13.3Hz). They argued that rapid activations in the pulmonary veins and ligament of Marshall region may play a role in sustaining atrial fibrillation\textsuperscript{170}. 

\addcontentsline{toc}{section}{4.1 Animal studies}
4.2 Human studies

Human studies can be divided into two main areas; studies looking at the mechanistic implications of pulmonary vein activity upon AF maintenance, and clinical studies evaluating the utility of PVCL measurement in determining clinical outcomes following AF ablation.

4.2.1 Mechanistic human studies

Kumagai et al evaluated PVCL activity in 32 patients undergoing catheter ablation of ‘focal’ AF with a proven triggering focal activations from the pulmonary veins. In patients with sustained AF (>10 minute), no difference between mean cycle length in the triggering PV was not significantly different to that measured in the other pulmonary veins and rapid focal activity was continually observed. In contrast, in patients with non-sustained AF (5-120 seconds), rapid focal activation of the originating PV was significantly shorter than that of the other veins, and would terminate AF when ablation. The authors concluded that ‘rapid conduction’ of rapid focal activation from one source to others may be necessary to maintain AF, and hence PV activity can contribute to the maintenance of AF in this manner171. Oral et al describes a more complex interplay between left atrial and pulmonary vein electrical activity during AF. In 56 patients undergoing segmental pulmonary vein isolation had cycle lengths during in the pulmonary veins and left atrium determined during AF. Pulmonary vein tachycardia was present during AF most commonly in the left superior pulmonary vein (93%, average CL = 130 ± 30ms), and site of shortest cycle length alternated between the pulmonary veins and body of the left atrium between 1 and 13 times per minute. Pulmonary vein tachycardias were seen to resolve following pulmonary vein isolation. The authors argued that this represented a dynamic interplay between the pulmonary vein and the left atrium with “intermittent bursts of pulmonary vein tachycardia being dependant on left atrial input and with the probability of persistent AF diminishing when pulmonary vein tachycardias are eliminated with PVI”172. Takahashi et al examined the impact of vagal activation during AF ablation upon pulmonary vein and AF cycle length. They analysed the cycle length in the pulmonary veins and coronary sinus during AF ablations in which vagal activation was apparent, by the occurrence of sinus bradycardia or AV block during ablation. During vagal activation, both coronary sinus and pulmonary vein
cycle length decreased with drop in the pulmonary vein cycle length preceded and decreased to a greater magnitude than that of the coronary sinus. The authors argued that this demonstrated the ability of rapid pulmonary vein activity to drive AF.

4.2.2 Human clinical outcome studies
There have been only few clinical studies which have sought to correlate pulmonary vein activity with post ablation outcome. Seitz et al evaluate the outcomes of 121 patients (84% persistent), after determining the pulmonary vein and left atrial cycle length. The authors characterized veins as either passive or active based on whether the PV cycle length was shorter (active) or longer (passive) than that measured in the left atrial appendage. They concluded that ‘passive’ PVs, in which PV activity was passively driven by drivers beyond the PV, were more common in persistent or long-standing persistent AF (76% vs 0%, p<0.001). Furthermore, a post ablation single procedure success of 85% was achieved with non-PV substrate based approach in which PV isolation was not systematically performed. Pascale et al retrospectively evaluated 97 patients undergoing catheter ablation for persistent AF. Pulmonary vein and left atrial appendage cycle length was calculated for each patient. The investigators found no relationship between absolute pulmonary vein cycle length and multi-procedure success. However, the ratio of the fastest measured PV cycle length to left atrial appendage cycle length if less than 69% was predictive of intra-procedural termination of AF after pulmonary vein isolation (74% PPV, 95% NPV), and long term freedom from AF (80% vs 43%, p<0.001).

4.3 Cycle length and atrial remodelling
One study has attempted to correlate AF cycle length with invasive assessment of the atrial substrate with electro-anatomical mapping. Walters et al evaluated 23 patients who presented in AF for AF ablation and determined the fibrillatory cycle length using digital ECG filtering to isolate the fibrillatory baseline in V1. Mean and dominant AF cycle length was determined. In addition, AF cycle length at the coronary sinus was also calculated. In this study, AF cycle length correlated significantly with the proportion of complex electrograms in the left atrium (R=0.6, p=0.02), and with conduction velocity as evidenced by coronary sinus activation time (R=0.63, p=0.01) although no correlation with LA voltage was found. The
investigators concluded that slowed AF cycle length was associated with atrial remodelling. Although not specifically evaluating the pulmonary vein cycle length, this novel study was the first to correlate rate of AF electrical activity with invasive measures of atrial remodelling\textsuperscript{175}.

5. Use of adenosine to unmask dormant conduction in AF ablation

An interesting tool utilised to improve catheter ablation of AF is the use of adenosine of ATP (adenosine tri-phosphate) to unmask dormant pulmonary vein conduction following intra-procedural acute pulmonary vein isolation. However, considerable controversies exist regarding the clinical utility of this approach. A brief review of the relevant literature is included below with a particular focus on the appropriate dosing of adenosine for use during catheter ablation.

5.1 Pulmonary vein reconnection

Pulmonary vein reconnection is the most common cause for recurrent AF post ablation and is regarded as the ‘Achilles heel’ of AF ablation. Given that the aim of the procedure is the containment of electrical activity behind a manufactured line of block or electrical buffer, even a seemingly innocuous gap in lesion coverage can be sufficient to allow complete conduction between the PV and LA. Gaps in the ablation line facilitating PV/LA reconnection may be due to: (1) inadequate (sub-transmural) lesion formation\textsuperscript{156}, (2) pseudo-block at the time of isolation presumably due resolution of peri-lesional oedema revealing viable tissues capable facilitating conduction\textsuperscript{156} or (3) as a consequence of tissue remodelling\textsuperscript{157}. Inadequate lesion formation was elegantly evaluated in a series of patients undergoing surgical maze procedure following recurrence of AF after an initial pulmonary vein isolation procedure. Areas of visible scar were sampled and pulmonary veins were assessed for reconnection. Transmural lesions were more likely to be associated with reconnected veins. The recent advent of ablation tip pressure sensing technology (such as Contact Force) has provided important real-time feedback regarding the ablation tip pressure on the endocardial surface, as tip pressure is a determinant of energy delivery and lesion size\textsuperscript{158}. Furthermore, parameters such as minimum contact force and minimum force time integral are strong predictors of lesion gap formation\textsuperscript{159}. Failure to
recognise pseudo-block resulting in initial pulmonary vein isolation can be minimised by sufficient waiting period following initial PV isolation, or the administration of adenosine (see below). This may facilitate unmasking of acute reconnection as perilesional oedema settles. The absence of acute reconnection following at least a 30-minute waiting period was associated with reduced AF recurrence. Interestingly, even when reconnection is demonstrated, further ablation to reisolate does not appear to improve outcome to those with no evidence of acute reconnection.

5.2 Role of Adenosine in AF ablation

5.2.1 Mechanism of adenosine induced restoration of dormant PV conduction
A relatively recent development in AF ablation is the use of intravenous bolus doses of adenosine to unmask dormant conduction in the pulmonary veins in order to identify acute reconnection. This technique utilises unique electrophysiological properties of the pulmonary veins and ablated atrial tissue to transiently establish conduction so that ablation gaps can identified and targeted for further ablation. Datino et al elegantly explored the electrophysiological action of adenosine in restoring conduction in dormant veins post ablation in the canine model. They identified that previously described G protein coupled adenosine sensitive potassium channels ($I_{KAdo}$) were in higher abundance in PV myocytes relative to those in the body of the LA. Radiofrequency injury to PV cells causes an increase in resting membrane potential of the cells to approximately $-60mV$ at which voltage dependant Na channels are known to inactivated – rendering these cells inexcitable. In the presence of adenosine, PV myocytes with dormant conduction and capable of responding to adenosine undergo hyperpolarisation via adenosine induced activity of $I_{KAdo}$. This removes inactivation of sodium channels and facilitates the capacity reconduction of these myocytes, until the influence of adenosine is removed.

5.2.2 Clinical utility of adenosine in AF ablation.
Initial data regarding the use routine of adenosine during AF ablation following acute pulmonary vein isolation was from non-randomised mostly single centre studies. These studies, including the dosing strategies utilised are outlined in Table 2. At that stage a meta-analysis of 6 non-randomised studies and 544 patients concluded that
routine usage of adenosine was associated with improved freedom from AF compared to no use. Interestingly, the identification of dormant pulmonary vein reconnection predicted a greater likelihood of recurrence even despite further targeted ablation to eliminate dormant reconnection\textsuperscript{178}. The first prospective randomised multi-centre trial evaluating the role of additional ablation in patients with adenosine unmasked dormant conduction recently reported results\textsuperscript{179}. Dormant PV reconnection was identified in 284 of 534 recruited patients who were then randomised to further ablation or no further ablation and followed up for 1 year with trans-telephonic monitoring, with single procedure freedom from AF the primary outcome. A random selection of patients with no PV reconnection was selected as a comparator group for extended follow up. Patients with dormant conduction randomised to further ablation had greater single procedure success at 1 year compared to those receiving no further ablation (69.4\% vs 42.3\%, \textit{p}=0.0192), and had significantly reduced requirement for repeat procedures (20.4\% vs 35\%, \textit{p}=0.006). The investigators concluded that elimination of adenosine unmasked dormant conduction conferred an overall 14\% improvement in procedural success\textsuperscript{180}. This result suggests that routine adenosine usage may have a role in standard AF ablation practice. These findings however have been challenged by the UNDER-ATP trial by Kobori et al randomised 2,113 patients undergoing catheter ablation to strategy of ATP guided or non-ATP guided ablation. In this study, there was no difference seen between the groups with respect to single procedure success post ablation (68.7\% vs 67.1\%, \textit{p}=0.25). Importantly, the requirement to achieve AV block following adenosine administration was not specified in this study.

### 5.3 Systematic dosing evaluation

None of the above studies have systematically looked at the effect of variable doses of adenosine on the ability to unmask dormant pulmonary vein conduction. Trial have utilised doses ranging from 12mg-60mg of adenosine – however no trials have provided a detailed dosing protocol as to the parameter determined to guide dosing. Table 2 below describes the dose ranges in the range of identified trials.

Miyazakei et al noted the effect of high dose dipyridamole (an inhibitor of the breakdown of adenosine) in prolonging the effect of adenosine and dormant pulmonary
vein conduction where it was identified. However, if dormant conduction was identified by an adenosine bolus, the addition of dipyridamole did not identify further sites of reconnection. Importantly, whether the effect of dipyridamole in this circumstance is equivalent to increasing bolus doses of adenosine, was not evaluated.

5.4 Safety of adenosine dosing
Adenosine is rapidly taken up by red blood cells and metabolised rapidly with a half-life of 10 seconds. With respect to the safety of adenosine injection, majority of studies utilised similar or higher doses compared to those utilised at our institution (as outlined in the above table). The most noticeable clinical side effect is transient hypotension which has no reported long term sequale. Indeed, several studies have shown the safety of adenosine at very high doses for the purposes of transient cardioplagia in endovascular structural procedures. These studies illustrate the proposed doses to be utilised for this study are comparable to those used in previous studies and is negligible clinical consequence.
6. Tables and Figures

6.1 Tables

Table 1. Clinical trials of AF ablation in patients with heart failure an outcome upon LV function

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. Patients</th>
<th>HF type</th>
<th>AF type (HF group)</th>
<th>LVEF Outcome (ablation arm)</th>
<th>Other outcomes</th>
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<tr>
<td>Hsu, 2004, NEJM</td>
<td>Prospective, single centre</td>
<td>116 patients</td>
<td>LVEF&lt;45% Dilated CM</td>
<td>Persistent (91%)</td>
<td>LVEF improved +21±13%, p&lt;0.001</td>
<td>Reduced LVED diam Reduced LA size Improved QOL Improved exercise capacity</td>
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<td>Non-randomised.</td>
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<td>Dilated CM</td>
<td>Paroxysmal (9%)</td>
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<td>Ablation in HF vs Ablation in normal LV 12 month F/U</td>
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<td>(55%) Ischaemic CM</td>
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<td>(16%) Congential CM</td>
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<td>Reduced LA size</td>
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<td>Improved QOL</td>
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<td>Improved exercise capacity</td>
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<tr>
<td>Chen, 2004, JACC</td>
<td>Prospective, single centre</td>
<td>377 patients</td>
<td>LVEF ≤40% Dilated or ischaemic or valvular (91%)</td>
<td>Persistent (57%)</td>
<td>Non-significant LVEF improvement (+5%, p=0.1)</td>
<td>Improved QOL</td>
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<td>Non-randomised 6 months F/U</td>
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<td>(43%)</td>
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</tr>
<tr>
<td>Gentlesk, 2007, JCE</td>
<td>Retrospective, non-randomised</td>
<td>366 patients</td>
<td>LVEF≤50% Dilated CM</td>
<td>Persistent (30%)</td>
<td>Mean LVEF improved (+12%, p=0.001)</td>
<td>Reduced LVED and LVES dimensions Reduced atrial size</td>
</tr>
<tr>
<td></td>
<td>single centre. 20±9 month F/U</td>
<td></td>
<td>(70%)</td>
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<tr>
<td>Structural heart disease (ischaemic and valvular) excluded.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mean LVEF improved (+15%, p=0.001)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>72% normalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacDonald, 2011, Heart</td>
<td>Prospective, multicentre, randomised. 12 month F/U</td>
<td>41 patients with HF</td>
<td>LVEF&lt;50% Dilated CM</td>
<td>Persistent (100%)</td>
<td>No change in MRI measured LVEF. Improvement in GBPS LVEF (+8.2 vs +1.4%, p=0.032)</td>
<td>No change in BNP, 6MWT distance or QOL.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(22%) Ischaemic (49%) Other (29%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Persistent (100%)</td>
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<tr>
<td></td>
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<td></td>
<td>No change in MRI measured LVEF.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Improvement in GBPS LVEF (+8.2 vs +1.4%, p=0.032)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jones, 2013, JACC</td>
<td>Prospective, multi-centre, randomised trial 12 month F/U</td>
<td>52 patients</td>
<td>LVEF≤35% Dilated CM</td>
<td>Persistent (100%)</td>
<td>Non-significant LVEF improvement (+5.6%, p=0.06)</td>
<td>Improved VO2max Improved QOL Reduced BNP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(73%) Ischaemic CM</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Persistent (100%)</td>
<td></td>
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<td></td>
<td>Non-significant LVEF improvement</td>
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<td></td>
<td></td>
<td></td>
<td>(+5.6%, p=0.06)</td>
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<tr>
<td>Ling, 2013, Heart</td>
<td>Prospective, single centre</td>
<td>16 patients with HF referred for</td>
<td>LVEF &lt; 50% Dilated CM</td>
<td>Persistent (75%)</td>
<td>LVEF improved +20±10%</td>
<td>Reduced LVESV Reduced LA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paroxysmal</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LVEF improved +20±10%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced LVESV</td>
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<td>Reduced LA</td>
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<td></td>
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<td></td>
<td>Improved QOL</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Improved exercise capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhythm</td>
<td>6 months</td>
<td>ablation</td>
<td>(100%) All LGE negative</td>
<td>(25%)</td>
<td>p&lt;0.001</td>
<td>volume</td>
</tr>
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</tr>
<tr>
<td>Hunter, 2014, Circ AE</td>
<td>Prospective, single centre, randomised trial 6 month F/U</td>
<td>50 patients 24 rate control 26 AF ablation</td>
<td>LVEF&lt;50% Dilated CM (31%) Hypertension (31%) Ischaemic CM (23%) Other (16%)</td>
<td>Persistent (100%)</td>
<td>LVEF improved (+8.1±5.1%, p&lt;0.001)</td>
<td>Improved VO2max Reduced BNP Improved QOL</td>
</tr>
<tr>
<td>Anselmino, 2014, Circ AE</td>
<td>Meta-analysis, 26 studies (various) 23±11 months F/U</td>
<td>1838 patients with HF</td>
<td>LVEF&lt;50% Paroxysmal (45%) Persistent (55%)</td>
<td>LVEF improved (13%, p&lt;0.001) % patients LVEF &lt;35% (25% vs 10%)</td>
<td>Reduced NT-pro-BNP Increased recurrence</td>
<td></td>
</tr>
<tr>
<td>Prabhu, 2016, JCE</td>
<td>Retrospective, multi-centre analysis 3 years</td>
<td>101 patients with HF referred for ablation</td>
<td>LVEF ≤45% Dilated CM (76%) Ischaemic CM (16%) Valvular CM (4%) Hypertrophic CM (4%)</td>
<td>Persistent (78%) Paroxysmal (22%)</td>
<td>IDC: LVEF improved (+14%, p&lt;0.001) Known HD: No signif. Change LVEF (+3%, p=0.25)</td>
<td>IDC: Improved AF control Improved NYHA status Improved Less mortality KHD: Improved NYHA</td>
</tr>
</tbody>
</table>
### Table 2 – Varying dosing strategies of adenosine utilised in clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Adenosine Dosing</th>
<th>Comments</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrade et al (2013)¹⁸³</td>
<td>≥ 12mg</td>
<td>Adenosine titrated to achieve ≥1 blocked p wave or ≥ 3 sec sinus pause</td>
<td>High output pacing was resulted in less dormant conduction and comparable long term outcomes compared to adenosine guided ablation</td>
</tr>
<tr>
<td>Anter et al (2014)¹⁶⁰</td>
<td>12-48mg</td>
<td>Dosing protocol not detailed</td>
<td>Acute reconnection predicted AF recurrence</td>
</tr>
<tr>
<td>Brunelli et al (2013)¹⁸⁴</td>
<td>15-60mg</td>
<td>Titrated until ‘at least some effect on AV node conduction was seen’</td>
<td>Dormant reconnection seen in up to 88% of veins isolated with PVAC catheter</td>
</tr>
<tr>
<td>Cheung et al (2012)¹⁸⁵</td>
<td>12mg</td>
<td>Single dose only used</td>
<td>Reconnection associated with bradycardic phase of adenosine activity</td>
</tr>
<tr>
<td>Elayi et al (2013)¹³⁶</td>
<td>18-24mg</td>
<td>Used in conjunction with isuprel to identify non-PV triggers</td>
<td>Adenosine may induce non-PV triggers with improved outcome with further ablation</td>
</tr>
<tr>
<td>Kaitani et al (2014)¹⁸⁷</td>
<td>40mg (ATP*)</td>
<td>Given in conjunction with isuprel</td>
<td>Carina identified as a common site of adenosine mediated dormant conduction.</td>
</tr>
<tr>
<td>Matsuo et al (2011)¹⁸⁹</td>
<td>20mg (ATP)</td>
<td>Given in conjunction with isuprel</td>
<td>Dormant condition occurs evenly in all AF phenotypes</td>
</tr>
<tr>
<td>Miyazaki et al (2012)¹⁹¹</td>
<td>40mg (ATP)</td>
<td>Single dose given</td>
<td>Further ablation to eliminate adenosine mediated dormant conduction did not improve AF freedom</td>
</tr>
<tr>
<td>Miyazaki et al (2013)¹⁹²</td>
<td>30mg (ATP)</td>
<td>Single dose given</td>
<td>Dipyridamole can safely prolong the activity of adenosine</td>
</tr>
<tr>
<td>Spotnitz et al (2014)¹⁹³</td>
<td>≥ 12mg</td>
<td>Dose up titrated but protocol unspecified</td>
<td>Adenosine can be used to identify dormant conduction in accessory pathways post ablation</td>
</tr>
</tbody>
</table>

* ATP = adenosine triphosphate which has a similar effect as adenosine but at a slightly lower dose¹⁸⁸.   Favale S Fau - Di Biase, M.; Di Biase M Fau - Rizzon, U.; Rizzo U Fau - Belardinelli, L.; Belardinelli L Fau - Rizzon, P.; Rizzon, P., Effect of adenosine and adenosine-5'-triphosphate on atrioventricular conduction in patients. (0735-1097 (Print)).
6.2 Figures

Figure 1 – Physiological pathways in electrical remodelling including pharmacological targets.

Figure 1: The interplay of processes contributing to electrical remodeling in AF. Panel A: Ionic remodeling. The bar graph indicates the ionic currents active during the atrial myocyte action potential. Green bars indicate inward current, red bars outward current. Panels B and C highlight the processes in calcium processing and inter-cell electrical coupling respectively. The green boxes highlight the various pharmacological strategies and their site of action against electrical remodeling. APD = action potential duration, ERP = effective refractory period, RMP = resting membrane potential, I_{TO} = transient outward current, I_{Kur} = ultra-rapid delayed rectifier current, I_{CaL} = L-type Ca^{2+} current, I_{Kr} = rapid delayed rectifier current, I_{Ks} = slow delayed rectifier current, I_{K1} = inward rectifier current, I_{Kach} = acetylcholine-activated inward rectifier current, RyR2 = ryanodine receptor 2, SERCA = sarcoplasmic reticulum clacium-ATP-ase.
Figure 2 – Physiological processes implemented in structural remodelling in atrial fibrillation

**Figure 2:** The complex interplay of physiological processes involved in structural remodeling in AF. ACE = angiotensin converting enzyme, PUFA = poly-unsaturated fatty acids, (R)AGE = (Receptor) for advanced glycalation end-products, PPAR = peroxisome proliferator-activated receptor, TGF = transforming growth factor, NF-Kappa-B = nuclear factor kappa light-chain-enhancer of activated B cells.
Figure 3 – The interplay of factors contributing to and maintaining atrial fibrillation and heart failure.
Figure 4: The interplay of factors impacting upon the overall procedural success of AF ablation. HF = heart failure, SP = septo-pulmonary, LAA = left atrial appendage, PV = pulmonary vein, LA = left atrium.
CHAPTER 2: The Impact of Known Heart Disease on Long Term Outcomes of Catheter Ablation in Patients with Atrial Fibrillation and Left Ventricular Systolic Dysfunction – A Multicenter International Study.

1. Introduction
Atrial fibrillation (AF) and heart failure (HF) are growing epidemics in most developed countries. A complex interplay of clinical and physiological factors characterise the relationship of AF and HF, with each condition promoting the progression of the other\(^{194-195}\). The poor efficacy of pharmacological approaches in restoring and maintaining sinus rhythm has confounded the ability to demonstrate a benefit of rhythm control in this patient population\(^{196}\). Randomised studies have shown improvements in left ventricular function, heart failure symptoms and VO2 max in patients with LV dysfunction who undergo catheter ablation compared to medical therapy\(^{103,126,128,197}\). Importantly, these benefits are predicated on successful restoration of sinus rhythm following catheter ablation, thus factors influencing the effectiveness of AF ablation in HF warrant exploration. A recent meta-analysis highlighted the role of pre-existing known heart disease (KHD) on the efficacy of catheter ablation in HF, yet the impact of this factor on HF outcomes (such as LV ejection fraction and functional capacity) has not been systematically evaluated. The aim of the present study was to evaluate the impact of the etiology of the cardiomyopathy on freedom from AF, LVEF and New York Heart Association (NYHA) functional class following catheter ablation.

We hypothesised that patients with a so called idiopathic cardiomyopathy were more likely to have an arrhythmia-mediated mechanism underlying the cardiomyopathy and consequently obtain greatest benefit from catheter ablation.

2. Methods

2.1 Patient selection
The study population included consecutive patients with AF referred for catheter ablation between 2002 to 2014. Patients were included if aged >18 years, NYHA class \(\geq 2\) on optimal medical therapy with adequate rate control. Patients were excluded for analysis if had had previous left atrial ablation, or an intervening
procedure (such as revascularisation or CRT) that may have impacted upon LVEF improvement. The study was approved by the institutional ethics bodies of the Alfred Hospital Melbourne, Royal Melbourne Hospital and St Bartholomews Hospital, London, United Kingdom.

2.2 Definitions
Patients were classified based on the presence or absence of a known cause for the LV dysfunction. Known heart disease was defined as a recognised cause of left ventricular dysfunction such as myocardial infarction, valvular heart disease or hypertrophic cardiomyopathy (HCM). Ischemic heart disease was defined by the presence of regional wall motion abnormalities consistent with a prior myocardial infarction represented on echocardiographic, nuclear or cardiac magnetic resonance (CMR) imaging in the presence of documented occlusive coronary disease. Valvular heart disease was defined by standard echocardiographic evidence of severe valvular dysfunction considered primarily responsible for the left ventricular dysfunction. Hypertrophic cardiomyopathy was defined according to standard criteria with concurrent left ventricular dysfunction. Although other less common causes of left ventricular dysfunction were recognised, only ischemic, valvular and HCM were present in the study population. IDC was defined as no recognised cause of LV dysfunction, with a typical imaging appearance of global systolic impairment, in the absence of valvular or occlusive coronary disease. Secondary causes were excluded as per current heart failure management guidelines.

A super response was defined as an absolute improvement in LVEF of 15% or greater from the pre-procedural assessment. Baseline NYHA class was determined at time of initial pre-procedural clinical review and follow-up as documented at the last clinical review.

2.3 Ablation procedure
Individual ablation practices differed between centres however consisted of the following general approaches. Trans-oesophageal echocardiography was performed to exclude intra-cardiac thrombus. Anticoagulation was ceased 2-5 days prior to ablation or continued (in the case of vitamin K antagonists) at operator discretion, with intravenous heparin utilised intra-procedurally. Ablation was performed with a 4mm
irrigated ablation catheter (Biosense Webster Inc. or St Jude Medical) with 3D
electroanatomical mapping CARTO3 (Biosense Webster Inc.) or Ensite Velocity (St
Jude Medical), with a multipolar catheter utilised to confirm PV isolation. PV
isolation with bidirectional block was the procedural endpoint in all cases with
additional ablation for substrate modification or the treatment of organised atrial
arrhythmias performed at the discretion of the operator. A three month blanking
period post procedure for arrhythmia monitoring was observed.

2.4 Follow up
Patients were routinely reviewed at 6 weeks then every 6 months with a combination
of (1) ECG, (2) 24 hour holter monitoring, (3) interrogation of dual lead implantable
device or implantable loop recorder where available.
AF control was defined as freedom from AF or marked (>90%) reduction in AF
burden on or off previously ineffective antiarrhythmic therapy\textsuperscript{127}. LVEF assessment
was determined by echocardiography, cardiac MRI or gated blood pool scan.
Echocardiographic LV assessment was performed using the Simpson’s biplane
technique utilising 4 chamber and 2 chamber LV views. CMR LVEF assessment was
performed via the summation of disc methods. Only patients with pre and post
ablation LVEF assessments utilising the same modality were included to avoid the
impact of discrepancies between different modalities in the measurement of LVEF.
Follow-up LVEF was performed a minimum of 6 months post index ablation
procedure.

2.5 Statistical analysis
Data are expressed as mean±standard deviation (SD) unless otherwise indicated.
After assessment of normal distribution with the Kolmogorov–Smirnov test, two-
group comparisons were made using Student’s t test for continuous variables, or the
Chi-squared test for categorical variables. The independent samples Mann-Whitney
U test was used for non-normally distributed variables. Binary logistic regression
analysis was utilised to assess the association of continuous and categorical variables
with multi-procedural freedom from AF and greater than 15% absolute LVEF
improvement at follow up in univariable and multivariable models. A two-tailed p
value of <0.05 was considered significant. Analyses were conducted using SPSS software (version 23, IBM, Chicago, Illinois).

3. Results

3.1 Study Population (table 1)

A total of 2,484 patients were screened across the 3 centres with 118 patients meeting the inclusion criteria. A consort diagram is presented in figure 1. Seventeen patients were excluded due to incomplete clinical records, with 101 patients (IDCM in 77 and KHD in 24 patients) included. In the KHD group myocardial infarction was present in 16 (68%), HCM in 4 (16%), and severe valvular disease in 4 (mitral regurgitation in 2 and aortic valvular disease in 2).

Patients in the KHD were significantly older (61±7 vs. 55±11 years, p=0.005), with more coronary artery disease (67% vs. 12%, p<0.001) and a higher average CHADS2 score (2.0±0.8 vs. 1.6±0.7, p=0.016). In addition the KHD group were more likely to be prescribed amiodarone (54% vs. 31%, p=0.041), and ACE inhibitors (83% vs. 57%, p=0.021) at baseline, and more likely to have an implantable cardiac defibrillator (38% v 9%, p<0.001). In the present study a rhythm control strategy using cardioversion and/or amiodarone had been instituted in 76% the IDCM group and 83% in the SHD group (p=0.41).

Implantable cardiac devices capable of detecting atrial arrhythmia (ILR or any implantable device with a functioning atrial lead) were present in 42% of the KHD group and 18% of the (p=0.018).

The groups were otherwise well matched including for duration of continuous AF, AF type, LA dimensions and NYHA class. Patients in the IDCM group were far more likely to be co-diagnosed with HF and AF on initial presentation (49% vs. 17%, p=0.004). CMR imaging was performed at baseline in 26% of patients in the IDCM group and 13% in the KHD group (p=0.17), and at follow up in 9% of the IDCM group and in none of the KHD group (p=0.13). In the present study a rhythm control strategy using cardioversion and/or amiodarone had been previously instituted in 76% the IDCM group and 83% in the KHD group (p=0.41).
3.2 Procedural Characteristics (table 2)
Pulmonary vein isolation was successfully achieved in 100 of 101 patients. Additional substrate modification did not differ significantly between the two groups (IDCM in 77% and KHD in 83%, p=0.49 see table 2). Procedure duration (IDCM vs KHD; 240±86 minutes vs 256±111 minutes, p=0.54) and radiation doses (22745±26998 vs 12903±15465 DAP mGycm², p=0.16) did not differ significantly between the two groups.

3.3 AF control
After a mean follow up of 36 ± 22months multi-procedural AF control was documented in 82% in the IDCM group vs. 50% in KHD group (p=0.002). The mean number of procedures was 1.6±0.75 in the IDCM group and 1.8±0.9 in the KHD group (p=0.13).

Univariate analysis identified age, coronary artery disease, myocardial infarction, KHD, CHADS2 score, initial AF and HF co-diagnosis, amiodarone and ACE inhibitor therapy as predictive of AF control. Following a binary logistical regression model the absence of KHD was the only predictor of AF control at final follow-up (p=0.033).

The two groups were well matched for follow up duration (IDCM: 35±22 months vs KHD: 33±19 months, p=0.81).

3.4 Functional Status Post Ablation (Figure 3)
There was no significant difference in baseline NYHA functional class between the groups. Both groups demonstrated a significant improvement in average NYHA functional class from baseline to last follow-up post ablation. At follow up, those without KHD had a significantly lower degree of function limitation than those with IDCM (mean NYHA Class 2.0±0.8 vs 1.5±0.7, p=0.005).

3.5 Left Ventricular Ejection Fraction (Figures 5A, 5B and Table 3)
At baseline the LVEF did not differ between the groups (IDCM vs. SHD, 36±8% vs. 35±8%, p=0.59). However at follow up those with IDCM had a significantly greater LVEF than those with KHD (mean LVEF 50±11% vs 38±10%, p<0.001). The
absolute improvement in LVEF in the IDCM group was 14% (p<0.001) compared to 3% in the KHD group (p=0.25, Figure 4). Furthermore, significantly more patients had a normalised LVEF (≥55%) post ablation in the IDCM (38%) compared to the KHD group (6%, p=0.0015). In the IDCM group, there was no significant difference in LVEF improvement when stratified according to baseline heart rates of greater than (Δ average LVEF: +16%) vs less than 100bpm (+14%, p=0.64, See Table 3). After exclusion of patients with baseline resting heart rates >100bpm, (23 patients in the IDCM group, 7 in the KHD group), AF control (85% vs 41%, p=0.0017) and LVEF improvement (+13.4% vs +4.5%, p<0.001) remained significantly greater in the IDCM group. The degree of dyspnea (as estimated by NYHA class) or palpitations on presentation were not predictive of the adequacy of rate control in the IDCM group (See table 3).

The lack of improvement in LVEF in the SHD group at final follow-up, was independent of AF control (KHD group with AF control: (n=12) Δ average LVEF=+1.8%, p=0.67, KHD group without AF control: (n=12) Δ average LVEF=+4.6%, p=0.24). Super responders were more likely to have IDCM (p<0.001), a reduced baseline LA diameter (45±5mm vs 48±7mm, p=0.022) and lower baseline LVEF (33±9% vs 37±7%, p=0.014). A significant reduction in LA diameter was noted in the super responders at follow up assessment (45±5mm vs 42±7mm, p=0.04). On multivariate analysis, the presence of IDCM was the only significant predictor of super responder status (p=0.008, Figure 5A). Super responders were associated with a significantly greater AF control than the rest of the study cohort (89% vs. 61% in LVEF improvement<15%, p<0.001, Figure 5B).

Twenty-two of 77 patients in the IDCM group, (28.5%) underwent CMR data, of which only 5 (23%) had late gadolinium enhancement (LGE). All LGE was localised to the mid wall, a common association with idiopathic cardiomyopathy. Two of 24 patients in the KHD group underwent CMR data. Both patients had hypertrophic cardiomyopathy with transmural mid wall enhancement. Fifteen patients in the KHD group (62.5%) who did not undergo CMR had evidence of a myocardial infarction on echocardiography.

There was a significant improvement in LVEF in the LGE positive (n=5: 34% to 44%, p=0.03) and LGE negative groups n=17: 37.2% to 51.5%, p<0.001).
3.6 Mortality
All cause mortality was significantly higher in the KHD group (17% vs. 1.3%, p=0.002). There were 5 deaths in total - 4 deaths in the KHD group and 1 death in the IdCM group. The single death in the IdCM group was from an electro-mechanical dissociative (EMD) arrest. In the KHD group, one death was an EMD arrest, another from malignancy and remaining two from unknown causes. No deaths occurred within 30 days of an index or redo AF ablation procedure.

4. Discussion
Catheter ablation offers the potential benefits of restoring sinus rhythm without the deleterious effects of antiarrhythmic medications in patients with atrial fibrillation and left ventricular dysfunction. However there is significant variation in procedural outcomes and the impact on heart failure symptoms and LV function. In this multicentre international study, we evaluated the outcomes of a cohort of patients with concurrent LV dysfunction and AF undergoing catheter ablation stratified according to the presence of known heart disease. Patients with AF and an unexplained or IDCM demonstrated:

1. a significantly higher AF control (82%) compared with known heart disease (50%, p=0.0017) at a mean follow up of 3 years;
2. a significantly greater improvement in NYHA functional class;
3. an absolute improvement in LVEF of 14% (p<0.001); compared with 3% in KHD group (p=0.25);
4. a lower total mortality (1.3%) compared with 17% in the KHD group (p=0.002).

4.1 Freedom from AF and Structural Heart Disease
Catheter ablation has become an important strategy for the management of atrial fibrillation in heart failure. A large randomised multicentre study did not support a pharmacologic strategy of rhythm control over rate control however catheter ablation was not included\textsuperscript{162}.\textsuperscript{196} Haissaguerre and co-workers reported substantial improvements in heart failure symptoms and LV function in 58 patients with an average LVEF or 35±7%, of which 26 patients were categorised as KHD. There was no significant difference in multi-procedural freedom of AF at an average of 12±7
months post ablation to those with ‘dilated cardiomyopathy alone’ (73% vs. 81%, p=0.46)\textsuperscript{125}. Further single centre studies have reported on the efficacy of catheter ablation in patients with atrial fibrillation and LV dysfunction however the impact of structural heart disease on outcome has been limited by small numbers or excluding patients with KHD and inconsistent definitions\textsuperscript{103, 126-127, 201}. A meta-analysis of AF ablation outcomes in the heart failure population included 1838 patients from 26 studies and reported a reduction in AF recurrence in patients free of known heart disease\textsuperscript{128}. The present multicentre study is consistent with the findings from the earlier meta analysis in that patients with an idiopathic cardiomyopathy who underwent AF ablation had a significantly higher freedom from AF. However, the present study has some important differences. Firstly, the study population included a greater proportion of persistent (78% vs 55%) and long standing persistent AF patients (47% vs 5%) compared with the meta analysis. Secondly, the meta-analysis reported studies with a conventional definition of AF recurrence (documented > 30 seconds of AF or atrial tachycardia) and found increased recurrence in patients with KHD. The present study applied a definition of AF control defined as greater than 90% reduction in AF burden\textsuperscript{202-204}. Lastly significant improvements in heart failure symptoms and LV function were demonstrated compared with KHD group.

\textbf{4.2 Functional Improvement}

Functional improvement following AF ablation in the heart failure population is well established and proportional to the maintenance of sinus rhythm\textsuperscript{103, 126, 197}. Although earlier studies have demonstrated improvements in NYHA functional class\textsuperscript{103, 125} and quantitative functional capacity\textsuperscript{103, 126} post AF ablation, the impact of LV dysfunction etiology has not been determined. Nedios et al reported an attenuated improvement in NYHA class post catheter ablation in 26 patients with coronary artery disease between those with and without regional wall motion abnormalities\textsuperscript{202}. To our knowledge the present study is the first to report a significant difference in functional status improvement in patients with idiopathic CM compared with known KHD.

\textbf{4.3 Improvement in Left Ventricular Ejection Fraction}

Several studies have demonstrated significant improvements in LVEF following AF ablation, particularly in patients with no known cause of cardiomyopathy\textsuperscript{103, 126, 166, 205-207}, although few have sought specifically to evaluate the population with KHD. Hsu
et al found patients with ‘concurrent structural heart disease’ had significant improvements in LVEF post ablation although to a significantly lesser extent than those without (16±14% vs. 24±10%, p=0.007 for comparison). Nedios et al reported that the presence of structural heart disease was not a significant multivariate predictor of LVEF improvement post ablation, particularly in those with regional wall motion abnormalities. The magnitude of improvement in LV function is predominantly determined by the long term maintenance of sinus rhythm, rather than other HF therapy. The present study found no significant improvement in LVEF in patients post AF ablation with KHD. The findings from the subgroup of patients who underwent CMR suggests that the presence of LGE may have a role in predicting LV recovery following catheter ablation in patients with IDCM, however the study was underpowered to draw meaningful conclusions.

4.4 Atrial and Ventricular Remodeling in Cardiomyopathy Post AF ablation

The physiological relationship between AF and HF is complex. Kalman and colleagues demonstrated that advanced atrial electrical and structural remodeling is present in patients with LV dysfunction. In patients diagnosed with an idiopathic cardiomyopathy in which an arrhythmia mediated mechanism is in fact responsible for the LV dysfunction, improvement in LVEF following the restoration of sinus rhythm may be followed by reverse ventricular and atrial remodeling. KHD may be associated with progressive irreversible replacement fibrosis in the ventricular myocardium, irrespective of cardiac rhythm. Replacement fibrosis can be quantified by the extent of late gadolinium enhancement (LGE) on cardiac MRI and is associated with poor recovery of LV function, in addition to adverse cardiac events and prognosis. Similarly, fibrosis in the setting of other SHD such as hypertrophic cardiomyopathy and severe valve disease has been described and limits reverse remodeling. Persisting left ventricular dysfunction maintains elevated atrial pressure and chronic stretch likely explains the vulnerability to AF recurrence. A distinct pattern of mid wall replacement fibrosis is often present in IDCM and can predict LVEF recovery. Ling et al have previously demonstrated that the absence of MRI detected fibrosis in patients with IDCM can predict LV remodeling post AF ablation.
4.5 Mortality

The finding of a significant difference in mortality between the groups should be interpreted with caution given small numbers and limited details regarding the nature of the deaths. The mortality demonstrated in the KHD group may reflect the attributable mortality in a HF population with significant co-morbidities whose LVEF remains essentially unaltered over several years\textsuperscript{212}. Nonetheless the anticipated mortality in the IDC\textsubscript{M} with AF of 10-30\%\textsuperscript{196} over the follow-up period was well above that demonstrated in this study (1.7\%), in which 85\% of patients had some improvement in LVEF, with nearly half of these normalizing LVEF over the period. The impact of AF ablation on long term mortality in the heart failure population remains the focus of an ongoing international randomized controlled trial\textsuperscript{213}.

4.6 Limitations

This is a retrospective study with inherent limitations of this study design. We await with interest the outcome of large randomized controlled trials in this area such as CASTLE AF\textsuperscript{213}. As with earlier studies there is a selection bias as only patients referred for AF ablation were included. As such this heart failure population may not be truly reflective of the wider heart failure population and as such the findings in this study may not be applicable to the broader heart failure population. The proportion of implantable devices capable of continuous atrial monitoring for the detection of atrial arrhythmia, were significantly higher in the KHD group (42\% vs 18\%, \textit{p}=0.018). However, there was no significant difference between the primary endpoint of AF control when comparing those with and without atrial monitoring (atrial monitor (n=24) vs no atrial monitor (n=77); 70\% vs 75\%, \textit{p}=0.66), across the cohort. Given the limited number of patients with AF control in the KHD group, no definitive conclusion can be made regarding the impact of AF ablation on LVEF improvement in this patient population.
5. Conclusion

The presence of KHD contributing to LV dysfunction is associated with a reduction in the maintenance of sinus rhythm post ablation, functional improvement and improvement in LVEF. Conversely, the absence of KHD identifies a HF population who receive greater benefit from catheter ablation for AF and should be strongly considered.
6. Table and Figures

6.1 Tables

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Idiopathic CM (n=77)</th>
<th>Known HD (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55 ± 11</td>
<td>61 ± 7</td>
<td>P=0.005</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>91% (70)</td>
<td>80% (19)</td>
<td>P=0.15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47% (36)</td>
<td>63% (15)</td>
<td>P=0.19</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10% (8)</td>
<td>21% (5)</td>
<td>P=0.19</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>1.3% (1)</td>
<td>8.3% (2)</td>
<td>P=0.08</td>
</tr>
<tr>
<td>Average LVEF (%)</td>
<td>36 ± 8</td>
<td>35 ± 8</td>
<td>P=0.59</td>
</tr>
<tr>
<td>Average NYHA class</td>
<td>2.3±0.7</td>
<td>2.5±0.3</td>
<td>P=0.30</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>5% (4)</td>
<td>4% (1)</td>
<td>P=0.83</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>30 ± 5</td>
<td>29 ± 5</td>
<td>P=0.38</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>46 ± 6</td>
<td>49 ± 8</td>
<td>P=0.06</td>
</tr>
<tr>
<td>LA area (mm^2)</td>
<td>31 ± 7</td>
<td>33 ± 9</td>
<td>P=0.38</td>
</tr>
<tr>
<td>Average CHADS2</td>
<td>1.6±0.7</td>
<td>2.0±0.8</td>
<td>P=0.016</td>
</tr>
<tr>
<td>Median CHADS2</td>
<td>2</td>
<td>2</td>
<td>P=1.0</td>
</tr>
<tr>
<td>Amiodarone therapy</td>
<td>31% (24)</td>
<td>54% (13)</td>
<td>P=0.04</td>
</tr>
<tr>
<td>Duration of follow up (months)</td>
<td>35 ± 22</td>
<td>33± 19</td>
<td>P=0.62</td>
</tr>
<tr>
<td>Symptoms to procedure (months)</td>
<td>41 ± 46</td>
<td>37 ± 23</td>
<td>P=0.69</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>78% (60)</td>
<td>79% (19)</td>
<td>P=0.88</td>
</tr>
<tr>
<td>Longstanding persistent AF</td>
<td>47% (36)</td>
<td>62.5% (15)</td>
<td>P=0.18</td>
</tr>
<tr>
<td>Duration of cont. AF pre-ablation (persistent AF)</td>
<td>27 ± 44</td>
<td>32 ± 21</td>
<td>P=0.64</td>
</tr>
<tr>
<td>Average resting HR at time of LV assessment (bpm)</td>
<td>89 ± 20</td>
<td>83 ± 21</td>
<td>P=0.34</td>
</tr>
<tr>
<td>ICD implanted</td>
<td>9.1% (7)</td>
<td>38% (9)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Any implantable recording device</td>
<td>22% (17)</td>
<td>50% (12)</td>
<td>p=0.008</td>
</tr>
<tr>
<td>Implantable device with atrial monitoring (ILR or atrial lead)</td>
<td>18% (14)</td>
<td>42% (10)</td>
<td>p=0.018</td>
</tr>
<tr>
<td>AF &amp; HF co-diagnosed</td>
<td>49% (38)</td>
<td>17% (4)</td>
<td>p=0.004</td>
</tr>
</tbody>
</table>
Table 2 – Procedural characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Idiopathic CM (n=77)</th>
<th>Known HD group (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of procedures</td>
<td>1.6 ± 0.75</td>
<td>1.8 ± 0.9</td>
<td>P=0.13</td>
</tr>
<tr>
<td>Right PV isolation</td>
<td>99% (76)</td>
<td>100% (24)</td>
<td>P=0.57</td>
</tr>
<tr>
<td>Left PV isolation</td>
<td>100% (77)</td>
<td>100% (24)</td>
<td>P=NS</td>
</tr>
<tr>
<td>Any substrate modification</td>
<td>77% (59)</td>
<td>83% (20)</td>
<td>P=0.49</td>
</tr>
<tr>
<td>Roof line</td>
<td>73% (56)</td>
<td>75% (18)</td>
<td>P=0.87</td>
</tr>
<tr>
<td>Inferior Line</td>
<td>58% (45)</td>
<td>50% (12)</td>
<td>P=0.33</td>
</tr>
<tr>
<td>Posterior wall isolation</td>
<td>56% (43)</td>
<td>50% (20)</td>
<td>P=0.59</td>
</tr>
<tr>
<td>Mitral line</td>
<td>23% (18)</td>
<td>21% (5)</td>
<td>P=0.70</td>
</tr>
<tr>
<td>CFAE ablation</td>
<td>35% (27)</td>
<td>46% (11)</td>
<td>P=0.07</td>
</tr>
<tr>
<td>CTI ablation</td>
<td>52% (40)</td>
<td>46% (11)</td>
<td>P=0.77</td>
</tr>
<tr>
<td>Intra-procedure cardioversion</td>
<td>61% (47)</td>
<td>67% (16)</td>
<td>P=0.85</td>
</tr>
<tr>
<td>SR at case end</td>
<td>95% (73)</td>
<td>96% (23)</td>
<td>P=0.80</td>
</tr>
</tbody>
</table>
Table 3 – Comparison of LVEF outcomes in the IDCM group stratified by heart rate

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Average HR</th>
<th>NYHA class</th>
<th>Palpitations</th>
<th>Baseline (BL) LVEF</th>
<th>Follow-up (FU) LVEF</th>
<th>P value (BL vs FU)</th>
<th>Absolute % change</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. IDCM (HR ≥100bpm)</td>
<td>23</td>
<td>112 ± 14 bpm</td>
<td>2.5 ± 0.7</td>
<td>61%</td>
<td>33.3 ± 10.4%</td>
<td>49.4 ± 11.7%</td>
<td>P&lt;0.001</td>
<td>16.1%</td>
</tr>
<tr>
<td>B. IDCM (HR &lt;100bpm)</td>
<td>54</td>
<td>77.1 ± 11.1 bpm</td>
<td>2.2 ± 0.6</td>
<td>71%</td>
<td>37.4 ± 6.2%</td>
<td>50.9 ± 10.6%</td>
<td>P&lt;0.001</td>
<td>13.5%</td>
</tr>
<tr>
<td>P value (A vs B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.2 Figures

Figure 1: Patient Selection Flow Chart

Figure 1: Consort diagram indicating the development of the study population. LVEF = left ventricular ejection fraction, UK = United Kingdom, KHD = known heart disease, IdCM = Idiopathic cardiomyopathy, MI = myocardial infarction, HCM = hypertrophic cardiomyopathy.
Figure 2: AF control by cardiomyopathy etiology. IDCM = idiopathic cardiomyopathy, KHD = known heart disease.
Figure 3: NYHA Functional Class Pre and Post Ablation

**Average NYHA Class**

<table>
<thead>
<tr>
<th>Baseline NYHA Class</th>
<th>Post ablation NYHA class</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM group</td>
<td>2.3</td>
</tr>
<tr>
<td>KHD group</td>
<td>2.49</td>
</tr>
</tbody>
</table>

P=0.005

P=0.021

P=NS

**Figure 3**: NYHA functional class before and after AF ablation. NYHA = New York Heart Association, IDCM = idiopathic cardiomyopathy, KHD = known heart disease.
Figure 4: Average LVEF pre and post ablation for each etiology. LVEF = left ventricular ejection fraction, IDCM = idiopathic cardiomyopathy, KHD = known heart disease.
Figure 5A: Super responders and Non-super responders by aetiology

Figure 5A: The proportion of each etiology in super-responders (absolute LVEF improvement > 15%) and non-super responders. LVEF = left ventricular ejection fraction, IDC = idiopathic cardiomyopathy.
Figure 5B: A comparison of AF control at final follow up in super responders and non-super responders
CHAPTER 3: Catheter Ablation versus MEdical Rate control in Atrial fribillation and systolic dysfunction (CAMERA-MRI)--An MRI guided multi-centre, randomised controlled trial.

1. Introduction

Atrial fibrillation (AF) and heart failure are burgeoning cardiovascular epidemics\textsuperscript{214-215} and frequently co-exist\textsuperscript{98}. AF in patients with left ventricular systolic dysfunction (LVSD) is associated with worsening heart failure, stroke and mortality\textsuperscript{140,216}. It is a common clinical conundrum for cardiologists and general physicians alike to determine the “chicken and egg” relationship between AF and heart failure as each can lead to the other. Given the morbidity and mortality associated with AF in heart failure it may be expected that the restoration of sinus rhythm may be beneficial. However, a large multicentre trial did not show superiority of a pharmacologic rhythm versus rate control strategy\textsuperscript{8}. Recently, catheter ablation (CA) for AF has emerged as a superior alternative strategy to pharmacologic rhythm control\textsuperscript{217}. However randomised trials of CA in LVSD have shown mixed results with no or only modest improvements in LVEF\textsuperscript{103, 126, 165-166, 217}. Consequently, current guidelines have no specific recommendations for CA in patients with LVSD, with medical rate control (MRC) the accepted standard treatment\textsuperscript{218}. A recent meta-analysis suggested that improvements in LVEF may be greater in those with idiopathic cardiomyopathy\textsuperscript{128} where prevalence of AF is up to 20\%\textsuperscript{216,219}. A critical drawback of prior randomised trials has been the heterogeneous nature of the study cohorts, with aetiologies such as ischaemic and valvular heart disease largely responsible for LVSD. AF in this instance, is more likely a secondary phenomenon than a primary cause limiting the effect of CA. Therefore, this randomised study sought to determine whether the restoration of sinus rhythm with CA could improve LVSD compared to MRC where the aetiology of the underlying cardiomyopathy was otherwise unexplained, apart from the presence of AF.
2. Methods

2.1 Study design
This was a prospective, parallel group, open labelled, multi-centre randomised clinical trial. Recruitment took place over three tertiary hospitals in Australia (The Alfred Hospital, The Royal Melbourne Hospital and Monash Medical Centre), with ablations performed at the Alfred and Royal Melbourne Hospitals. Ethics committee approval was obtained at each participating centre. The study protocol is available online via the ANZCTR website.

2.2 Study Population
Patients meeting inclusion criteria were recruited. Patients were included if they were (1) age 18 to 85 years; (2) New York Heart Association (NYHA) class ≥ II; (3) had persistent AF; (4) had an left ventricular ejection fraction (LVEF) ≤45% on baseline Cardiac MRI (CMR); (5) had significant coronary artery disease excluded via conventional or CT guided angiography or functional imaging and (6) had no other identifiable cause explaining the LV dysfunction. Patients were excluded if they (1) were unable or unwilling to consent or commit to follow up requirements; (2) had any contra-indication to AF ablation; (3) had any contra-indication to cardiac MRI or (4) had paroxysmal AF. The upper age limit was raised to 85 years during the study to facilitate recruitment. All participants provided written informed consent to partake in the study.

2.3 Randomisation and masking
Following CMR, provided LVEF was ≤45%, patients were block randomized 1:1 to either CA or ongoing MRC. Randomization was performed electronically, using commercially available software from an independent third party. Block randomization (block size, n=8) was used in order to ensure the equal distribution key baseline characteristics including the presence of ventricular late gadolinium enhancement. Randomization was performed centrally. The study investigator performing the randomization was blinded to block size in order to minimize potential selection bias. Patients and investigators performing ablation necessarily could not be blinded to treatment allocation. Investigators and physicians reporting CMR and
echocardiography were blinded to treatment allocation, but could not be blinded to cardiac rhythm or the presence of implantable loop recorders (ILR). Investigators reporting imaging were not involved in the performance of ablation procedures or clinical management. Investigators performing CA were blinded to the LGE status and this data was withheld or masked on CMR reports.

2.4 Procedures
Patients meeting the inclusion criteria underwent baseline echocardiography, CMR, 24hr holter monitoring, six minute walk test (6MWT), 36-Item Short Form Survey (SF-36), serum brain natriuretic peptide (BNP) and clinical review prior to randomisation. Clinical review was repeated at 6 weeks, 3 and 6 months; SF-36 and 6MWT were repeated at 3 and 6 months and CMR, BNP and echocardiography repeated at 6 months. Late procedural complications were reassessed at 6 months. Following study completion, patients in the MRC arm could undergo CA at physician discretion.

2.4.1 Cardiac MRI
Prior to CMR, rate control was optimized for 4 weeks aiming for an average ventricular rate <100bpm on 24 holter monitoring. Baseline and 6-month CMR were performed on a clinical 1.5-T MRI scanner (Signa HD 1.5-T, GE Healthcare, Waukesha, WI, USA, WI). Sequences were acquired during breath-holds of 10–15 seconds. Initial cine CMR sequences were performed in 3 standard long-axis (4-, 3-, and 2-chamber views) and short-axis (basal, mid, and apical) slices, kept identical for each subsequent sequence throughout the CMR examination. To calculate LV volume and function, a contiguous short-axis steady-state free precession stack was acquired (8-mm-thick slice, no gap), extending from the mitral valve annulus to the LV apex. Late gadolinium enhancement (LGE) was obtained in both long- and short-axis views 10 minutes after a bolus (0.2 mmol/kg body weight to a maximum of 20 mmol) of gadolinium- diethylenetriamine pentaacetic acid (Magnevist, Schering, Germany) to identify regional fibrosis by using a T1-weighted inversion-recovery gradient echo technique. LGE was quantified by manually contouring regions of increased signal intensity consistent with scar, using commercially available software (CVI42; Circle
Cardiovascular Imaging, Inc., Calgary, Canada). For the purposes of this analysis, LGE negative was defined as <1% LGE present in the myocardium.

2.4.2 Medical rate control
Patients randomised to ongoing MRC underwent 24hr holter monitoring at 3 months and 6 months following randomisation, with medical therapy titrated to achieve a resting rate <80bpm, an average 24 hour ventricular rate of <100bpm and post exercise (6MWT) rate of <110bpm in accordance with current guidelines. Crossover to CA prior to 6 month CMR assessment was discouraged, however was permitted at the discretion of the treating physician.

2.4.3 Catheter ablation procedure
Catheter ablation was performed within one month of randomisation. Oral anticoagulation was discontinued 24 hours pre-procedure with the exception of vitamin K antagonists or dabigatran, which was continued. Anti-arrhythmic medication was discontinued 5 half lives pre-procedure with the exception of amiodarone. All procedures were performed under general anaesthesia with the assistance of a 3D mapping system (CARTO, Biosense Webster). After exclusion of intra-cardiac thrombus, trans-oesophageal echocardiographic guided double trans-septal punctures were performed. Unfractionated heparin was administered to achieve an activated clotting time of >350 seconds. Mapping of the left atrium and pulmonary veins was performed with a 20 pole circular mapping catheter, and ablation with a 3.5mm irrigated-tipped catheter (SmartTouch Thermocool, Biosense Webster) following direct current cardioversion (DCCV) to restore sinus rhythm (power range: 25W (posteriorly) to 30W, contact force range: 10-40g anteriorly and 10-25g posteriorly). Pulmonary vein isolation was achieved with wide antral circumferential ablation with additional roof and inferior lines performed to achieve posterior wall isolation (Figure 2B). In general, antiarrhythmic medications were continued if present, or commenced following early recurrence. Repeat procedure was permitted for symptomatic recurrence occurring beyond 3 months post index procedure. AF recurrence was monitored via ILR (CONFIRM™, St Jude Medical, USA or REVEAL LINQ™, Medtronic, USA) implanted at the time of procedure. Recurrence was defined as documented AF or atrial tachycardia >30seconds occurring beyond a 4
AF burden was expressed as the percentage of total time in AF from time of implant beyond blanking period.

2.5 Primary and secondary endpoints

Primary endpoint was change LVEF from baseline at 6 months on CMR. All CMR’s were performed and assessed centrally. The effect of LGE status upon LVEF improvement was a pre-specified secondary endpoint. Other secondary endpoints included: (1) change in CMR chamber dimensions, (2) New York Heart Association (NYHA) class, (3) BNP, (4) 6MWT distance, (4) physical and (5) mental composite scores (SF-36), (6) AF recurrence, (7) AF burden and (8) procedural complications.

2.6 Statistical Analysis

The sample size calculation for the primary endpoint of LVEF assumed an average expected standard deviation of baseline LVEF of 10% based on preliminary data. For the primary endpoint, we aimed to detect a minimum absolute change in LVEF of 10% between CA and MRC groups, requiring a minimum of 16 patients in each group to provide a power of 0.8 at an alpha value of 0.05. Estimating the short-term success of restoring sinus rhythm by CA of 80%, 20 patients in each comparative group would be required. In addition, a secondary endpoint was to assess the effect of CA versus MRC in patients with or without LGE (n=20 for each of 4 groups). However, due to the lower than anticipated incidence of LGE in the study population, this secondary endpoint recruitment target was abandoned and the study was terminated after 68 patients were randomised. Data are expressed as mean ± standard deviation (SD) unless otherwise indicated. Cardiac chamber dimensions are indexed to body surface area. Two-group comparisons were made using Student’s t-test for continuous variables, or the Chi-squared test, or Fisher’s Exact test for categorical variables. The independent samples Mann–Whitney U test was used for non-normally distributed variables. Confidence intervals for the difference of two independent proportions were calculated using Newcombe-Wilson score method (uncorrected). McNemar’s test was used for comparisons of proportions of paired samples. Primary outcome analysis was performed on an intention to treat basis. Other outcome analyses have been specified in the text. Procedural outcomes are reported for all...
patients undergoing CA, regardless of treatment assignment unless otherwise specified. Analyses were conducted using SPSS software (version 24, IBM, Chicago, Illinois, USA). The trial was registered with the Australia New Zealand Clinical Trials Registry (Trial No: ACTRN12613000880741).

3. Results

3.1 Study population
Patient recruitment was from 3rd September 2013 until the 23rd December 2016. The first patient was enrolled on 27th November 2013 and the last on 6th October 2016. Of 301 patients screened, most (132) were excluded due to ischaemic cardiomyopathy, or MRI incompatible implanted cardiac devices. 68 patients were randomised to CA (n=34) or MRC (n=34). Two patients were excluded post randomisation. One patient in the CA arm withdrew from the study and did not complete follow-up. One patient in the MRC arm was excluded due to screening failure (paroxysmal AF). Overall, 66 patients were analysed (33 in each arm). Three patients in the MRC arm, crossed over to CA prior to follow-up CMR due to uncontrolled heart failure symptoms (Figure 1).

3.2 Baseline characteristics
Study participants had an average baseline LVEF of 33±8.6%, CHA₂DS₂VASc score of 2.4±0.9, moderately enlarged left atria (LA volume = 54±17ml/m²), failed previous DCCV in 95% well established on anti-failure therapy (renin angiotensin aldosterone system inhibition 94%, beta-blockade 97%) and well controlled rate (resting HR = 78±18 bpm, 24 hour mean HR = 86±15bpm, post 6MWT HR = 94±21bpm). All patients had persistent AF with the majority (74%) having long-standing persistent AF. There were 2.1±0.76 DCCV attempts per person (median =2, IQR=1) with 76% having two or more attempts and 23% having three or more. A single attempt may include up to 3 DCCVs to establish sinus rhythm. In addition, 86% had failed or been intolerant of amiodarone. Baseline characteristics following randomisation are shown in Table 1.
3.3 Catheter ablation outcome

In those undergoing catheter ablation (n=36), pulmonary vein isolation was achieved in 100% and posterior LA wall isolation attempted in 94% and achieved in 85%. The average procedure time was 200±47 minutes; radiation dose: 46±53 mGy; dose area product (DAP): 22407±11552 mGy.cm²; fluoroscopy time: 15.4±5.4 minutes and ablation time 43±12 minutes. The single procedure freedom from AT/AF (> 30 seconds) after 1 month blanking period off AAD was 56% and on AAD was 75%. The average AF burden at six months was 1.6%±5.0% with an AF burden of > 10% in two patients. Antiarrhythmic therapy was continued post ablation in 33% (12/36) (amiodarone 72%, sotalol 28%) and 14% (5/36) required DCCV beyond the blanking period. All patients in the MRC arm remained in AF for the duration of the study period. All patients in the catheter ablation group were in SR at time of repeat CMR assessment.

3.4 Medical rate control outcome

In the MRC group, the average ventricular rate was well controlled from baseline (85 ± 18bpm) to 6 months (80±10bpm, p=0.10). The post 6MWT HR significantly improved at 3 months (95±19 vs 85±15bpm, p=0.0325) and was maintained at 6 months (86±17bpm, p=0.0434). In the CA group, the restoration of sinus rhythm with CA significantly improved resting heart rate (62±10 vs 79±16bpm, p=0.0001), mean heart rate (67±9.1 vs 86±14bpm, p=0.0001), and post 6MWT heart rate (92±24 vs 73±12bpm, p=0.0001) at 6 months compared to baseline, with improvement evident at 3 months. All measures were significantly lower in CA group at 6 months (post 6MWT: p=0.0009, resting and mean heart rate: p<0.0001).

3.5 Primary endpoint (Table 2).

On an intention to treat analysis (Figure 2A), the CA group, demonstrated a significant improvement in LVEF (+18.3%, p<0.0001) at 6 months. The MRC group also significantly improved LVEF (+4.4%, p=0.0145) at 6-months. The improvement in LVEF was significantly greater in the CA group (p<0.0001). At 6 months, 58% of patients undergoing CA had normalised systolic function (LVEF ≥50%) compared to 9% in the MRC group (p=0.0002). In the CA group, the proportion of patients with
severe systolic dysfunction (LVEF <35%) was significantly reduced from 52% to 9% (p=0.0001) at 6 months but not in the MRC group (45% to 36%, p=0.61).

3.6 Secondary endpoints (Table 2)

3.6.1 Cardiac chamber dimensions
Left ventricular end systolic volume (LVESV) was significantly decreased in the CA group (-24±24 ml/m²) compared with the MRC group (-8.0±20ml/m², p=0.007) with more also reducing by ≥15% (73% vs 27%, p=0.0011). Left ventricular end diastolic volume (LVEDV) decreased from baseline in the CA group but not the MRC group with no difference between the groups. Left atrial volume significantly decreased in the CA group with no change in the MRC group (ΔLA volume: -12±13 vs +1.7±14ml/m², p<0.0001).

3.6.2 Other secondary endpoints
Serum BNP significantly decreased in the CA group compared to the MRC group. Additionally, NYHA class reduced significantly in the CA group compared the MRC group (p<0.0001). The 6MWT distance and physical component summary scores significantly improved from baseline in both groups, and mental component summary scores in CA group only, but with no significant difference between the groups.

3.6.3 Late gadolinium enhancement and LVEF improvement post ablation
Ventricular LGE was present on baseline CMR in 36% (n=24) of patients (36% in CA group and 36% in the medical rate control group). A mid wall fibrosis pattern (Figure 4) was seen in the majority 83% (20/24) with the remainder displaying either a sub-endocardial or diffuse patchy enhancement pattern. There was no significant difference in LVEF between LGE positive (31±9%) and negative patients (34±8.5%, p=0.13) however, LVESV and LVEDV were significantly larger in LGE positive patients (p=0.0114, 0.0138 respectively).

In those undergoing CA (n=36), the LGE negative group (n=22) had a significantly greater improvement in absolute LVEF at 6 months compared to LGE positive (n=14) patients (11.6% vs 22.3%, p=0.0069). LGE negative patients were more likely to
normalise LV function (73% vs 21%, p=0.0093, PPV=73% (58%, 84%), NPV=71% (49%, 87%)) and reduce indexed LVESV by ≥15% (86% vs 43%, p=0.0057, PPV=86% (70%, 95%), NPV=57% (38%, 75%)) at 6 months compared to LGE positive patients (Table 3). The proportion of patients with LVEF <35% decreased from 50% to 0% (p<0.0001) in the LGE negative group compared to 64% to 21% (p=0.022) in the LGE positive group (between group difference, p=0.051). We performed a univariable and multivariable analysis of significant predictors of LVEF normalization (including, baseline LVEF, baseline mean heart rate, age, longstanding persistent AF, BMI, AF duration, LGE status, indexed LVEDV and LVESV) at 6 months in patients undergoing catheter ablation. The presence of LGE (p=0.0296), indexed LVESV (p=0.0203) and indexed LVEDV (0.0195) were significant univariable predictors of LVEF normalization. On multivariable analysis, only the absence of LGE predicted LVEF normalization (p=0.0342).

In those undergoing CA, the percentage of ventricular myocardium LGE was determined (range 0.98–22%, mean=8.6±7.3%). Two patients were excluded from analysis due to artefact from ILR precluding accurate quantification. LGE percentage inversely correlated with the absolute improvement in LVEF as determined by CMR (R=−0.67, p=0. 0.0094, Figure 3B).

3.7 Complications
There were four unplanned admissions in the MRC group compared to none in the CA group (excluding admission for elective DCCV for early AF recurrence.). Two patients required treatment for decompensated heart failure and two patients required an implantable cardiac defibrillator (ICD) (p=0.11).

There were two procedural complications in the CA group. One patient had groin and ILR implantation site bleeding requiring blood transfusion. The other had post-procedural pneumonia. There were no deaths or thrombo-embolic complications.
4. Discussion
This is the first randomised clinical trial to compare LVEF improvement following the restoration of sinus rhythm with CA to ongoing AF with adequate MRC in patients with persistent AF and idiopathic cardiomyopathy. The key findings were:

1. On intention to treat analysis, CA was associated with a significant improvement in LVEF. This was accompanied by reductions in atrial and ventricular chamber dimensions, BNP and NYHA class.
2. The absence of ventricular LGE on cardiac MRI imaging was associated with a greater improvement in LVEF, and a higher likelihood of normalisation of LV function.

These findings indicate that in these patients, AF may either significantly contribute to, or indeed be entirely responsible for LVSD. Importantly the benefits of sinus rhythm with CA as confirmed on implantable loop recorder were present in spite of adequate rate control supporting the concept that an AF mediated cardiomyopathy may occur independently of rapid ventricular rates. Furthermore, those patients without LGE on CMR, showed significantly greater improvement in systolic function with the restoration of sinus rhythm suggestive of an underlying arrhythmia mediated cardiomyopathy.

Importantly, this study population had largely failed pharmacological rhythm control, principally with amiodarone (86%), with 96% of patients having had an average of two separate DCCV attempts. In this study, catheter ablation offered an effective rhythm control strategy for these patients, with previously ineffective anti-arrhythmic medications used in concert in a third of patients. This is consistent with the findings of the recent a recent large multi-centre randomized trial which found catheter ablation superior amiodarone in maintaining sinus rhythm in patients with systolic dysfunction.

4.1 Prior studies
Five randomised clinical trials have evaluated the role of CA in patients with AF and LVSD. Khan et al randomised 81 patients with either paroxysmal or persistent AF (46%/51%) and predominately ischaemic cardiomyopathy (71%) to either CA (n=41) or bi-ventricular pacing and AV node ablation (n=40), and showed a significant albeit modest improvement in LVEF (+8±8%)\textsuperscript{165}. MacDonald et al randomised 41 patients
with more severe LVSD (LVEF=20±5.5, ischaemic 48%) to CA (n=22) or MRC (n=19) and found no significant improvement in LVEF, although the reduced procedural success (50%) in this advanced heart failure population may have explained these findings. Jones et al randomised 52 patients with LVSD (LVEF=23.5±7.5%, 23% ischaemic) to CA or MRC. Despite a significant improvement in VO2max, quality of life and BNP, there was no significant improvement in LVEF. Hunter et al randomised 50 patients to either catheter ablation (n=26) or medical rate control (n=24, ischaemic 26%). Ablation was associated with a modest but significant improvement in LVEF (+8.1±5.1% vs -3.6±4.1%, p<0.001), quality of life, functional capacity (VO2max) and BNP at 6 months. Recently, the AATAC-AF trial, randomised 203 patients with AF and LVSD (LVEF = 30±6%, 46% non-ischaemic), to either rhythm control with CA or amiodarone. In addition to demonstrating the superiority of CA as a rhythm control strategy, those patients in either arm that maintained sinus rhythm demonstrated improvements in median LVEF (+9.6% vs +4.2%, p<0.001), 6MWT distance, and heart failure symptoms. Other non-randomised studies, have also demonstrated variable improvements in LVEF following CA, likely explained by the contribution of ischemic injury or ventricular fibrosis to LVSD. A meta-analysis of 1,838 patients showed that whilst overall CA modestly improved LVEF the greatest improvements were in the idiopathic or dilated cardiomyopathy group. Prabhu et al retrospectively evaluated the outcomes of 101 patients with reduced LVEF undergoing CA stratified by aetiology. Patients with an idiopathic cardiomyopathy demonstrated significant improvements in LVEF compared to those with a known cause of LVSD, such as myocardial infarction or valvular disease. The present study is the first to specifically evaluate patients with persistent AF and an idiopathic cardiomyopathy in a prospective randomised fashion with ILRs to confirm the presence of sinus rhythm with CA. Based on the current findings, we report that the restoration of sinus rhythm with CA results in substantial improvements in systolic function and that AF is an underestimated cause of LVSD in this patient population.

### 4.2 Late gadolinium enhancement and LVEF improvement

Within this patient population, further stratification may identify those patients who benefit most from the restoration of sinus rhythm. In the present study, over two-
thirds of patients were co-diagnosed with AF and LVSD upon first presentation. Frequently, the clinical history cannot determine the temporal relationship both conditions. A non-invasive tool such as CMR may provide further insights. In the present study the absence of ventricular fibrosis (as determined by LGE) on CMR was associated with a significantly greater improvement, including normalisation, of LVEF in the CA group. There is an eight fold increase in risk of heart failure hospitalisation, appropriate ICD therapy or cardiac related death in non-ischaemic LGE positive cardiomyopathy. In a retrospective analysis of patients undergoing CA for AF, the presence of ventricular LGE was associated with lack of recovery of LVEF. Normalisation of LVEF in this population was associated with a reduction in heart failure hospitalisation and mortality. Furthermore, the reduction in LVESV of ≥15% demonstrated in the CA group has been previously correlated with improved survival in LVSD. Ling et al, prospectively evaluated improvement in LVEF following CA in 16 patients with LVSD (LVEF <50%) and the absence LGE on baseline CMR imaging demonstrating an absolute improvement in LVEF of 20±10% at repeat CMR in 6 months. This is consistent with the findings of this study with a similar magnitude of improvement in LVEF in the LGE negative patients. A lesser improvement in LV function was seen in LGE positive patients (Figure 3A). Some improvement may be expected as ventricular fibrosis is not a binary phenomenon supported by a significant inverse correlation demonstrated between the extent of ventricular LGE and the magnitude of LV recovery (Figure 3B). As such these findings should not necessarily be used to proscribe CA in LGE positive cardiomyopathy as significant improvements in LVEF may still occur. Rather, it should be a consideration in clinical decision-making.

4.3 Impact on primary prevention ICD therapy

The potential to prospectively identify those patients likely to respond to CA may have important implications for primary prevention device therapy in this patient population. Catheter ablation reduced the number of patients meeting current guideline criteria for primary prevention implantable cardiac defibrillator (LVEF <35%) by almost one third compared to MRC (p=0.0082). Additionally, no patients in the LGE negative group undergoing CA met guideline criteria at 6 months compared to 21% in the LGE positive group.
4.4 ‘Arrhythmia’ versus ‘tachycardia’ mediated cardiomyopathy

Reduced systolic function in the setting of AF has been termed “tachycardia mediated cardiomyopathy” however, although the rate improvement with the restoration of sinus rhythm was notable, the present study clearly supports the role of several other mechanisms by which AF may lead to systolic impairment\(^{105}\). Irregular ventricular activity\(^{107,119}\) and the loss of atrial contraction\(^{108}\) also contribute to reduced cardiac output, whilst shared mechanisms, such as activation of neuro-hormonal\(^{223}\) and profibrotic\(^{134-135}\) pathways, also play a significant role. Despite the presence of adequate rate control at baseline, which improved over the course of the study in the rate control group, there was only a modest improvement in LVEF compared to the substantial recovery of LVEF following CA with accompanying improvements in NYHA class, reductions in BNP and cardiac dimensions. The term ‘arrhythmia mediated cardiomyopathy’ may be more appropriate to describe LVSD attributable to AF.

4.5 Study limitations

Several limitations need to be acknowledged with this study. The exclusion of patients with non-MRI compatible cardiac devices (predominately defibrillators), may have added selection bias to the study population. Catheter ablation was associated with an AF burden of 1.5% at 6 months which is unlikely to represent the long term single procedure success of catheter ablation as AF recurrence continues to occur over time. Further improvements in reverse remodelling may have been seen if patients were followed up for longer than 6months. Patients with paroxysmal AF were excluded as significant variation in AF burden may impact the likelihood of AF contributing to the underlying systolic dysfunction. Although this study is the largest randomised study to date comparing CA and pharmacological rate control in AF and LVSD, the endpoints are surrogates for clinical outcomes and the study was underpowered to detect outcomes such as heart failure hospitalisation and mortality which should become the focus of larger longer term randomised studies in this specific population.
5. Conclusion

A significant proportion of patients with persistent AF and otherwise unexplained LVSD have an under recognised arrhythmia mediated cardiomyopathy present despite adequate ventricular rate control. The restoration of sinus rhythm with catheter ablation is associated with considerable improvements in LVEF, cardiac remodelling and functional capacity. The absence of CMR detected ventricular fibrosis identifies “super responders” to catheter ablation. Catheter ablation in conjunction with cardiac MRI should be considered in patients with persistent AF and otherwise unexplained systolic dysfunction. These findings challenge the current treatment paradigm that rate control is adequate in AF and heart failure.
6. Tables and Figures

6.1 Tables

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics (n=66)</th>
<th>Catheter ablation (n=33)</th>
<th>Medical rate control (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 11</td>
<td>62 ± 9.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>94% (31)</td>
<td>88% (29)</td>
</tr>
<tr>
<td>CHA₂DS₂VASc score</td>
<td>2.42 ± 0.87</td>
<td>2.36 ± 0.96</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>39% (13)</td>
<td>36% (12)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12% (4)</td>
<td>15% (5)</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>27% (9)</td>
<td>27% (9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 7.5</td>
<td>31 ± 4.1</td>
</tr>
<tr>
<td>Obstructive sleep apnoea (%)</td>
<td>36% (12)</td>
<td>21% (7)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>6.1% (2)</td>
<td>0% (0)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
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<tr>
<td>ACE inhibitor or ARB (%)</td>
<td>94% (31)</td>
<td>94% (31)</td>
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<tr>
<td>Cardio-selective beta-blocker (%)</td>
<td>88% (29)</td>
<td>85% (28)</td>
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<td>Any beta-blocker (%)</td>
<td>97% (32)</td>
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<td>Spironolactone (%)</td>
<td>33% (11)</td>
<td>48% (16)</td>
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<td>Anti-arrhythmic therapy (%)</td>
<td>24% (8)</td>
<td>24% (8)</td>
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<tr>
<td>Anticoagulation (%)</td>
<td>100% (33)</td>
<td>100% (33)</td>
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<tr>
<td><strong>Atrial fibrillation history</strong></td>
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<tr>
<td>Mean duration of continuous AF (months)</td>
<td>23 ± 18</td>
<td>21 ± 15</td>
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<td>Long standing persistent AF (%)</td>
<td>72% (24)</td>
<td>76% (25)</td>
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<tr>
<td>Previous DCCV (%)</td>
<td>97% (32)</td>
<td>94% (31)</td>
</tr>
<tr>
<td>Average number DCCV attempts per patient</td>
<td>2.1 ± 0.8</td>
<td>2.0 ± 0.7</td>
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<tr>
<td>Amiodarone therapy ineffective or intolerant</td>
<td>91% (30)</td>
<td>82% (27)</td>
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<tr>
<td>Resting HR (bpm)</td>
<td>79 ± 17</td>
<td>77 ± 19</td>
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<tr>
<td>24hr average HR (bpm)</td>
<td>86 ± 14</td>
<td>85 ± 17</td>
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<tr>
<td>Post 6MWT HR (bpm)</td>
<td>93 ± 23</td>
<td>95 ± 20</td>
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<td><strong>LV systolic dysfunction history</strong></td>
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<tr>
<td>Co-diagnosis of AF and LV systolic dysfunction</td>
<td>70% (23)</td>
<td>67% (22)</td>
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<td>AF preceded LV systolic dysfunction</td>
<td>24% (8)</td>
<td>27% (9)</td>
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<tr>
<td>LV systolic dysfunction preceded AF</td>
<td>6.1% (2)</td>
<td>6.1% (2)</td>
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<td><strong>Cardiac MRI findings</strong></td>
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<tr>
<td>LVEF</td>
<td>32 ± 9.4%</td>
<td>34 ± 7.8%</td>
</tr>
<tr>
<td>LVEF &lt; 35% (%)</td>
<td>52% (17)</td>
<td>45% (15)</td>
</tr>
<tr>
<td>Late gadolinium present (%)</td>
<td>36% (12)</td>
<td>36% (12)</td>
</tr>
<tr>
<td><strong>Echocardiography findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>35 ± 9.8%</td>
<td>35 ± 9.3%</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>20 ± 8.4%</td>
<td>18 ± 8.8%</td>
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<tr>
<td>LV end diastolic diameter (mm)</td>
<td>59 ± 7.7</td>
<td>59 ± 6.4</td>
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<tr>
<td>LV end systolic diameter (mm)</td>
<td>45 ± 10</td>
<td>47 ± 9.2</td>
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<tr>
<td>LA diameter (mm)</td>
<td>48 ± 5.5</td>
<td>47 ± 8.2</td>
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### Table 2 – Primary and secondary endpoints

<table>
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<tr>
<th>Primary and secondary endpoints</th>
<th>Catheter ablation (n=33)</th>
<th>Medical rate control (n=33)</th>
<th>Comparison treatment arms</th>
<th>between arms</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>Baseline</td>
<td>6 months</td>
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<tr>
<td><strong>Primary endpoint</strong></td>
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<td></td>
<td></td>
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<tr>
<td>LVEF (MRI) (%)</td>
<td>31.8 ± 9.4</td>
<td>50.1 ± 11§</td>
<td>34.1 ± 7.8</td>
<td>38.5 ± 8.7‡</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
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<td></td>
<td></td>
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<tr>
<td>LVEF (echocardiography) (%)</td>
<td>35.0 ± 9.8</td>
<td>52.7 ± 11.9§</td>
<td>34.8 ± 43.7</td>
<td>43.7 ± 12.7‡</td>
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<td>LV end systolic volume (ml/m²)</td>
<td>79.5 ± 33.3</td>
<td>55.3 ± 30.5§</td>
<td>76.3 ± 27.2</td>
<td>68.2 ± 26.3†</td>
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<tr>
<td>LV end diastolic volume (ml/m²)</td>
<td>114 ± 40</td>
<td>106 ± 33§</td>
<td>113 ± 32</td>
<td>109 ± 39</td>
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<td>LA volume (ml/m²)</td>
<td>54.4 ± 16.1</td>
<td>43.4 ± 13.3§</td>
<td>53.9 ± 18.9</td>
<td>55.6 ± 14.6</td>
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<td>LV stroke volume (ml/m²)</td>
<td>34.9 ± 12.7</td>
<td>50.5 ± 10.1§</td>
<td>38.6 ± 12.5</td>
<td>40.5 ± 14.8</td>
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<td>Average NYHA Class</td>
<td>2.55 ± 0.62</td>
<td>1.33 ± 0.48§</td>
<td>2.45 ± 0.56</td>
<td>2.06 ± 0.50†</td>
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<td>BNP (log[ng/L])</td>
<td>2.34 ± 0.38</td>
<td>1.84 ± 0.37§</td>
<td>2.27 ± 0.43</td>
<td>2.14 ± 0.56</td>
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<tr>
<td>BNP (ng/L)</td>
<td>266 ± 210</td>
<td>98 ± 77</td>
<td>256 ± 208</td>
<td>247 ± 197</td>
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<tr>
<td>6 minute walk test distance (m)</td>
<td>491 ± 147</td>
<td>546 ± 82§</td>
<td>489 ± 132</td>
<td>518 ± 119†</td>
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<td>SF-36 Physical component scores</td>
<td>41.6 ± 11.6</td>
<td>48.5 ± 8.2§</td>
<td>38.8 ± 10.4</td>
<td>44.6 ± 11.2†</td>
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<tr>
<td>SF-36 Mental component scores</td>
<td>49.1 ± 10.6</td>
<td>53.3 ± 7.7‡</td>
<td>50.3 ± 11.2</td>
<td>52.9 ± 8.9</td>
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</table>

* p value for comparison of mean difference from baseline to 6 months between catheter ablation and medical rate control treatment arms
† p value <0.05 for comparison between baseline and six months
‡ p value <0.01 for comparison between baseline and six months
§ p value <0.0001 for comparison between baseline and six months
Il Non-normally distributed therefore confidence intervals not displayed. P value determined by Mann-Whitney U test
Table 3: Improvement in LVEF stratified by LGE status – Actual treatment analysis

<table>
<thead>
<tr>
<th>Comparison within each group (LGE positive vs LGE negative)</th>
<th>Patients undergoing catheter ablation (n=36)</th>
<th>LGE positive (n=14)</th>
<th>LGE negative (n=22)</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVEF</td>
<td>32.1 ± 8.7%</td>
<td>31.7 ± 9.4%</td>
<td>0.4% (-5.9%, 6.8%)</td>
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<td>6 month LVEF</td>
<td>43.7 ± 11.2%</td>
<td>54.0 ± 8.5%</td>
<td>+10.3% (3.3%, 17.0%)</td>
<td>0.0036</td>
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<tr>
<td>Change in LVEF from baseline</td>
<td>+11.6 ± 10.3%</td>
<td>+22.3 ± 11.3%</td>
<td>+10.7% (3.2%, 18.3%)</td>
<td>0.0069</td>
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<tr>
<td>LVEF ≥50% at 6 months (%)</td>
<td>29% (4)</td>
<td>73% (16)</td>
<td>44.2% (10.7%, 66.1%)</td>
<td>0.0093</td>
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<tr>
<td>Improvement in LVEF by ≥15%</td>
<td>29% (4)</td>
<td>82% (18)</td>
<td>53.2% (20.2%, 73.3%)</td>
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<table>
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<tr>
<th>Comparison between treatment arms (catheter ablation and medical rate control)</th>
<th>LGE positive (n=30)</th>
<th>LGE negative (n=20)</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Baseline LVEF</td>
<td>29.0 ± 7.8%</td>
<td>36.8 ± 7.0 %</td>
<td>7.7% (2.1%, 13.3%)</td>
<td>0.0089</td>
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<tr>
<td>6 month LVEF</td>
<td>33.8 ± 7.3%</td>
<td>39.3 ± 9.8%</td>
<td>5.5% (-1.0%, 12.0%)</td>
<td>0.09</td>
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<tr>
<td>Change in LVEF from baseline</td>
<td>+4.8 ± 8.5%</td>
<td>+2.9 ± 9.8%</td>
<td>2.3% (-5.1%, 9.7%)</td>
<td>0.54</td>
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<tr>
<td>LVEF ≥50% at 6 months (%)</td>
<td>0% (0)</td>
<td>10% (2)</td>
<td>10% (-25%, 33%)</td>
<td>0.30</td>
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<tr>
<td>Improvement in LVEF by ≥15%</td>
<td>0% (0)</td>
<td>10% (2)</td>
<td>10% (-25%, 33%)</td>
<td>0.30</td>
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</table>

<table>
<thead>
<tr>
<th>Comparison between treatment arms (catheter ablation and medical rate control)</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Change in LVEF from baseline</td>
<td>+6.8%</td>
<td>-1.5%, 15.0%</td>
<td>0.10</td>
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<tr>
<td>LVEF ≥50% at 6 months (%)</td>
<td>29%</td>
<td>-3.9%, 54.7%</td>
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</table>

<table>
<thead>
<tr>
<th>LGE negative</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Change in LVEF from baseline</td>
<td>+19.8%</td>
<td>13.1%, 26.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF ≥50% at 6 months (%)</td>
<td>63%</td>
<td>30.0%, 80.4%</td>
<td>&lt;0.0001</td>
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</table>
6.2 Figures

Figure 1 – Trial profile

Figure 1: CONSORT diagram illustrating the recruitment for this study.
Figure 2 - Change in absolute LVEF from baseline by treatment arm

**Figure 2 (A and B):** Panel A: Graph illustrating the primary endpoint: LVEF change from baseline in catheter ablation versus the medical rate control group – on a per protocol analysis. Bars represent 95% confidence intervals. Panel B: An integrated CT image depicting a typical ablation strategy utilised in this study. Posterior wall or ‘box isolation’ involves the addition of a roof line and inferior line between the superior and inferior aspects of the wide encirclement ring to achieve electrical isolation of the posterior wall. LSPV = left superior pulmonary vein, LIPV = left inferior pulmonary vein, RSPV = right superior pulmonary vein, RIPV = right inferior pulmonary vein LAA = left atrial appendage.
Figure 3 – Late gadolinium enhancement and change in absolute LVEF

**Figure 3**: Panel A: Graph illustrating the LVEF change from baseline in those patients undergoing catheter ablation stratified according to the presence or absence of LGE on cardiac MRI. Bars represent 95% confidence intervals. Panel B: Correlation between the percentage of ventricular LGE and ΔLVEF following catheter ablation.
**Figure 4** – MRI detected mid wall ventricular fibrosis in idiopathic cardiomyopathy

<table>
<thead>
<tr>
<th>Late gadolinium enhancement demonstrating regional mid-wall fibrosis in dilated cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="LGE Positive" /> <img src="image2" alt="LGE Negative" /></td>
</tr>
</tbody>
</table>

**Figure 4**: An example of mid wall fibrosis as detected by the presence of late gadolinium enhancement on cardiac MRI. The left picture shows a short axis view demonstrating mid wall fibrosis highlighted in white along the inter-ventricular septum (arrows). The right picture shows a patient with no detectable LGE.
CHAPTER 4: Regression of Diffuse Ventricular Fibrosis following restoration of sinus rhythm with catheter ablation in Patients with Atrial Fibrillation and Systolic Dysfunction: a Sub-Study of the CAMERA MRI Trial

1. Introduction

Myocardial fibrosis is the hallmark of many cardiac diseases\textsuperscript{100,224}, including systolic heart failure\textsuperscript{134} and atrial fibrillation (AF)\textsuperscript{135,225}, and is the end result of a myriad of adverse remodelling processes. Atrial fibrillation is a well-described cause of systolic dysfunction in selected patients. Catheter ablation for AF in heart failure is associated with a reduction in mortality and heart failure hospitalisation\textsuperscript{217,226}. In the CAMERA-MRI study, patients with AF and unexplained LV systolic dysfunction randomised to catheter ablation demonstrated significant improvements in LV systolic dysfunction compared with medical rate control\textsuperscript{128,227}. The improvement in LVEF following the restoration of sinus rhythm with catheter ablation was greater in the absence of ventricular LGE on cardiac MRI. The extent of myocardial fibrosis has been associated with adverse outcomes in both AF and idiopathic cardiomyopathy\textsuperscript{10}. Diffuse or interstitial fibrosis can be detected by T1 mapping on cardiac MRI\textsuperscript{134} and may be a precursor to more irreversible forms of replacement fibrosis\textsuperscript{228}. The reversibility of systolic impairment in this population affords a unique opportunity to examine the impact upon diffuse fibrosis in idiopathic cardiomyopathy. The extent or otherwise that diffuse fibrosis in heart failure is capable of regression with any form of therapy is unclear. This study aimed to determine the impact upon diffuse ventricular fibrosis of recovery of systolic function following catheter ablation in AF mediated cardiomyopathy, compared to those with ongoing rate controlled atrial fibrillation in a randomised control trial.

2. Methods

2.1 Study design

This was a pre specified secondary analysis of patients enrolled in the Catheter Ablation versus MEdical Rate control in Atrial fibrillation and systolic dysfunction
MRI guided multi-centre randomised controlled trial (CAMERA-MRI)\textsuperscript{227}. Ethics committee approval obtained at each participating centre.

2.2 Study Population

The inclusion criteria were as previously published\textsuperscript{227}. In summary: (1) age 18 to 85 years; (2) New York Heart Association (NYHA) class ≥ II; (3) persistent AF; (4) an left ventricular ejection fraction (LVEF) ≤45% on baseline CMR; (5) significant coronary artery disease excluded via conventional or CT guided angiography or functional imaging and (6) no other identifiable cause explaining LV systolic dysfunction. Patients were excluded if they (1) were unable or unwilling to consent or commit to follow up requirements; (2) had any contra-indication to AF ablation; (3) any contra-indication to cardiac MRI or (4) had paroxysmal AF. An additional 16 age-matched patients with no evidence of atrial fibrillation, structural heart disease or heart failure, underwent CMR scanning with native T1 mapping as normal controls. All participants provided written informed consent to partake in the study.

2.3 Procedures

Patients meeting the inclusion criteria underwent baseline echocardiography, 24hr holter monitoring, six minute walk test (6MWT), 36-Item Short Form Survey (SF-36), serum brain natriuretic peptide (BNP) and clinical review. 6MWT, 36 Item Short Form Survey (SF-36) and clinical review were repeated at 3 and 6 months, and CMR, BNP and echocardiography at 6 months.

2.3.1 Cardiac MRI

Prior to CMR, rate control was optimized aiming for an average ventricular rate <100bpm on 24 holter monitoring. Baseline and 6 month CMR was performed by using a clinical 1.5-T magnetic resonance imaging scanner (Signa HD 1.5-T, GE Healthcare, Waukesha, WI, USA, WI). Sequences were acquired during breath-holds of 10–15 seconds. Initial cine CMR sequences were performed in 3 standard long-axis (4-, 3-, and 2-chamber views) and short- axis (basal, mid, and apical) slices, kept identical for each subsequent sequence throughout the CMR examination. To
calculate LV volume and function, a contiguous short-axis steady-state free precession stack was acquired (8-mm-thick slice, no gap), extending from the mitral valve annulus to the LV apex. Late gadolinium enhancement (LGE) was obtained in both long- and short-axis views 10 minutes after a bolus (0.2 mmol/kg body weight to a maximum of 20 mmol) of gadolinium-diethylenetriamine pentaacetic acid (Magnevist, Schering, Germany) to identify regional fibrosis by using a T1-weighted inversion-recovery gradient echo technique. LGE was defined quantitatively by manually contouring regions of increased signal intensity consistent with scar, using commercially available software (CVI42; Circle Cardiovascular Imaging, Inc., Calgary, Canada). For the purposes of this analysis, LGE negative was defined as <1% LGE present in the myocardium.

2.3.1.2 T1 mapping technique

Myocardial T1 times were estimated of by means of a prototype SMART MAP sequence (Global Applied Science Laboratory, GE Healthcare). Each sequence was acquired within an end-expiration breath-hold using an electrocardiogram-triggered single-shot acquisition with a balanced steady-state free precession readout in a single mid short-axis slice. A series of images at the mid-LV short-axis level were acquired sequentially at increasing inversion times, pre-contrast (for non-contrast myocardial T1 time; TI range, 75 to 2 000 ms) during a single breath hold. After image acquisition, the short-axis images of varying TIs were transferred to an external computer for analysis using a dedicated research software package with a curve-fitting technique to generate T1 maps (cvi42, Circle Cardiovascular imaging, Calgary, Canada). T1 measurements were taken at the mid short-axis level by taking a region within the septum as has previously been described\textsuperscript{229} and away from magnetic field distortions created by susceptibility effects. Additionally, we chose to measure T1 times in the mid septum to avoid the risk of partial voluming due to variable triggering in AF. We excluded participants whose susceptibility artefact involved the septum. Any mid-wall fibrosis (typical of DCM) was included, with the consideration that this represents a continuum with diffuse interstitial fibrosis\textsuperscript{228, 230}. For each patient, T1 mapping data was independently assessed as being of sufficient quality (ie
free from blood pool contamination and/or loop recorder artifact) in both the baseline and follow-up scans, for that patient to be included in the analysis.

2.3.2 Medical rate control
Patients randomised to ongoing rate control underwent 24hr holter monitoring at 3 months and 6 months following randomisation, with medical therapy titrated to achieve a resting rate <80bpm, and average 24 hour ventricular rate of <100bpm and post exercise (6MWT) ventricular rate of <110bpm or maximal tolerated dose to achieve symptomatic control, in accordance with current guidelines\textsuperscript{218}.

2.3.3 Catheter ablation procedure
Catheter ablation was performed within one month of randomisation as previously described\textsuperscript{227}. In brief, oral anticoagulation was discontinued 24 hours pre-procedure with the exception of vitamin K antagonists or dabigatran, which was continued. All procedures were performed under general anaesthesia with the assistance of a 3D mapping system (CARTO, Biosense Webster) and image integration. After exclusion of intra-cardiac thrombus, a deca and quad polar catheter were positioned in the coronary sinus and His position respectively. Tran-oesophageal echocardiographic guided double trans-septal punctures were performed (BRK-1XS needle, SL1 8, 8.5F sheaths). Unfractionated heparin was administered to achieve an activated clotting time of >350 seconds. Mapping of the left atrium and pulmonary veins (PVs) was performed with a 20 pole circular mapping catheter, and ablation with a contact-force enabled 4mm irrigated-tipped catheter (SmartTouch Thermacool Biosense Webster) following electrical cardioversion to restore sinus rhythm (25-30W). Pulmonary vein isolation was achieved with wide antral circumferential ablation (WACA) with additional roof and inferior lines to achieve posterior left atrial wall isolation. Anti-arrhythmic medication use post ablation was at operator discretion.

2.4 AF monitoring
In patients undergoing catheter ablation, AF recurrence was monitored via implantable loop recorder (CONFIRM\textsuperscript{TM}, St Jude Medical, USA or REVEAL LINQ\textsuperscript{TM}, Medtronic, USA) implanted at the time of procedure. Recurrence was
defined as documented AF or atrial tachycardia >30 seconds occurring beyond a 4 week blanking period post procedure. Recorded rhythms were manually verified by study investigators during clinical assessments at 6 weeks, 3 months and 6 months post catheter ablation. AF burden was determined using manufacturers’ automated algorithm and expressed as the percentage of total time in AF from time of implant.

2.5 Statistical Analysis
Data are expressed as mean ± standard deviation (SD) unless otherwise indicated. Two-group comparisons were made using Student’s t test for continuous variables, or the Chi-squared test, or Fisher’s Exact test for categorical variables. Confidence intervals for the difference of two independent proportions were calculated using Newcombe-Wilson score method (uncorrected)\(^2\). McNemar’s test was used for comparisons of proportions of paired samples. Analyses were conducted using SPSS software (version 24, IBM, Chicago, Illinois, USA). The trial was registered with the Australia New Zealand Clinical Trials Registry (Trial No: ACTRN12613000880741).

3. Results

3.1 Baseline characteristics
Of the 66 patients analysed in the CAMERA-MRI study, 36 patients (18 in each arm) had both baseline and six month T1 mapping performed at CMR at baseline and six months has T1 data suitable for inclusion in this study. The baseline characteristics of included patients are shown in Table 1. Demographics, co-morbidities and risk factors were well matched between the groups. Baseline anti-failure, anti-arrhythmic drug therapy and rate control (including resting, mean and post exercise) were also well established and well matched between the groups. In the medical rate control group, average ventricular rates at baseline (82 ± 19 bpm), were maintained at 3 months (81 ± 14 bpm) and at 6 months (79 ± 8.7 bpm). There was no significant difference in LVEF or cardiac dimensions between the groups. At baseline, there was no significant difference between the myocardial T1 times between the groups, although both groups had significantly higher values than normal controls (CA: p<0.001, MRC: p=0.002). Late gadolinium enhancement was present in 42% (15 patients) of patients with no difference between the groups (p=0.6, Table 1). The predominant pattern of
fibrosis was mid-wall in 87% (13 patients) involving the septum (53%, 8 patients), inferior wall (53%, 8 patients) and the lateral wall (40%, 6 patients). There were no cross-overs between catheter ablation and medical rate control in this cohort.

3.2 Procedural characteristics and AF outcome

In those patients undergoing catheter ablation (n=18), pulmonary vein isolation was achieved in all patients, with additional posterior wall isolation attempted in 94% (17) of patients and achieved in 76% (13/17). Additional cavo-tricuspid isthmus ablation was performed in 11% (2). At 6 months, AF burden in the catheter ablation group was 0.8 ± 2.9%, with 89% (16) patients with an AF burden <0.1%. Thirty-nine percent (7 patients) of patients undergoing CA continued or commenced anti-arrhythmic drug therapy post ablation. No patients underwent repeat catheter ablation during the 6 month follow up period. In the CA group, groin haematomas occurred in 2, with one requiring blood transfusion and one patient developed pneumonia. There were no reported complications in the MRC group.

3.3 Diffuse ventricular fibrosis (Tables 2 and 3, Figures 1 and 2)

At 6 months there was a significant decrease in the myocardial T1 times in the catheter ablation group compared to the medical rate control group (-124ms, 95%CI(-23, -225ms), p=0.017) with no significant difference at baseline (see Table 1). Although myocardial T1 times improved significantly in the catheter ablation group they remained significantly higher compared to normal controls (1192 ± 77.1 vs 1103 ± 71.8ms, p=0.0015, Figure 2) at six months. Myocardial T1 times were higher in the medical rate control group compared to normal controls at baseline (p=0.0017) and six months (p=0.0024). Myocardial T1 times in patients with an absolute improvement in LVEF≥15% from baseline decreased an average of -99±159ms compared to 2.0±154ms in those improving LVEF< 15% (p=0.09). In those undergoing CA, there was no difference in reduction in myocardial T1 times between those improving LVEF by ≥15% (-102±167ms) and those not (-83±88ms, p=0.77). In the LGE positive group a significantly greater reduction in T1 time was demonstrated with CA compared to the MRC (-145 ± 137ms vs +29 ± 185ms, p=0.05). In the LGE
negative group there was no significant difference in change in T1 time (CA vs MRC: -42 ± 117ms vs +31 ± 159ms, p=0.26).

3.4 Reverse ventricular remodelling (Tables 2 and 3)

At six-months, LVEF had significantly improved in the catheter ablation group compared to the medical rate control group (47 ± 11% vs 37 ± 7.6%, p=0.00377), with an absolute improvement in LVEF from baseline of +14 ± 11% vs +1.5 ± 11% in MRC (p=0.0004). Six patients (33%) in the catheter ablation group had normalised LV function at 6 months, compared to none in the medical rate control arm. Serum BNP significantly reduced in the catheter ablation group compared to the medical rate control group (-216 ng/L, p=0.013). No significant improvement in LVEF, BNP or other cardiac dimensions was seen in the medical rate control group (Table 3). At six months, the presence of sinus rhythm in the catheter ablation group was associated with superior rate control compared with the medical rate control group (-17 bpm, p=0.002).

4. Discussion

This sub-study of the CAMERA-MRI trial aimed to determine the recovery of diffuse fibrosis (native T1 mapping) in patients with persistent AF and otherwise unexplained cardiomyopathy who were randomised to catheter ablation or medical rate control and underwent cardiac MRI assessment at baseline and at 6 months. The primary findings were:

1. a regression in diffuse fibrosis in the sinus rhythm group who underwent catheter ablation, compared to patients undergoing medical rate control In concert with this there were significant improvements in LVEF, ventricular and atrial chamber dimensions, BNP and functional capacity.
2. Despite regression in diffuse fibrosis, myocardial T1 mapping values in those patients undergoing catheter ablation remained higher than those of normal controls without a history of AF.
4.1 Diffuse fibrosis in idiopathic cardiomyopathy and atrial fibrillation

Quantitative measures of diffuse fibrosis such as extra-cellular volume calculation and T1 mapping have been validated against collagen content on histology\textsuperscript{231-233}. In the setting of heart failure, Iles et al correlated the presence of diffuse fibrosis with reduced systolic function at cardiac biopsy and CMR\textsuperscript{134}. Other studies have histologically validated the use of native T1 mapping for the detection of diffuse fibrosis in the setting of idiopathic cardiomyopathy\textsuperscript{232, 234}, with a recent study suggesting that native T1 mapping as the most robust approach to assessing diffuse fibrosis in the setting of non-ischaemic cardiomyopathy\textsuperscript{235}. Both atrial fibrillation and idiopathic cardiomyopathy have been independently associated with diffuse fibrosis. Ling et al evaluated the incidence of diffuse ventricular fibrosis using post contrast T1 mapping in 90 patients (23 controls, 40 with paroxysmal AF and 27 with persistent AF) and demonstrated an increase in diffuse fibrosis with the presence of AF in a dose dependant manner. On multivariate analysis, age, AF phenotype and ejection fraction independently predicted post contrast T1 time\textsuperscript{135}. Furthermore, Mclellan et al demonstrated that diffuse fibrosis independently predicted single procedure success in patients undergoing catheter ablation for AF\textsuperscript{225}. Elevated T1 times have also been demonstrated with CMR using native T1 in patients referred for AF ablation\textsuperscript{139}.

4.2 Regression of diffuse fibrosis

It is unclear whether diffuse fibrosis, as determined by CMR, in the setting of heart failure is reversible. Several studies demonstrated that myocardial collagen content, as determined on myocardial biopsy, can be decreased following prolonged angiotensin converting enzyme inhibition\textsuperscript{236} or mineralocorticoid receptor antagonism\textsuperscript{237}, which was also associated with a reduction in LV chamber stiffness\textsuperscript{238}. Mclellan et al demonstrated a reduction in myocardial T1 times following successful blood pressure reduction in hypertensive patients undergoing renal denervation\textsuperscript{100}. Other studies have longitudinally evaluated diffuse fibrosis in various disease states such as aortic stenosis\textsuperscript{137}, and acute myocardial infarction\textsuperscript{138}. The present study prospectively assessed the impact of successful treatment of systolic dysfunction upon diffuse fibrosis with serial CMR. Arrhythmia mediated cardiomyopathy, when successfully treated with catheter ablation, results in significant improvements in
ventricular function, and reverse cardiac remodelling. As both AF itself and reduced systolic function may be responsible for diffuse fibrosis, the treatment of both with successful catheter ablation affords a unique opportunity to examine the impact of sinus rhythm and reverse remodelling upon diffuse fibrosis. Interestingly, the improvements in T1 times in those both with and without ≥15% improvements in LVEF (-102ms vs -83ms, p=0.77), suggests that elimination of AF may itself regress fibrosis even in the absence of a large accompanying improvement in LVEF. This may in part explain the reduction in mortality seen with catheter ablation in CASTLE-AF where the absolute improvement in LVEF was 8%. Additionally, a more significant reduction in T1 time was demonstrated in the LGE positive group as there was a greater initial burden of fibrosis and therefore have a greater capacity for reversibility of fibrosis following the restoration of sinus rhythm with CA. The present study demonstrated regression of MRI detected diffuse fibrosis in concert with the improvement in ventricular function following the restoration of sinus rhythm in arrhythmia-mediated cardiomyopathy. To our knowledge, this is the first time that reversibility of ventricular fibrosis in the setting of systolic dysfunction has been demonstrated in humans on CMR.

Nonetheless, at six months although improved from baseline, myocardial T1 values remained significantly higher than that of normal controls (p=0.0017). This may reflect the incomplete recovery of LVEF in the catheter ablation group. Alternatively the mechanisms responsible for diffuse fibrosis may be primarily related to that responsible for the underlying cardiomyopathy rather than being explained by atrial fibrillation alone; the well-recognized “chicken and egg” relationship between AF and heart failure. It is also possible that 6 months may be too short a time to permit complete resolution of diffuse fibrosis. Ling et al demonstrated that diffuse fibrosis was still detectable despite recovery of LV function at nearly 5 years following successful catheter ablation for atrial tachycardia mediated cardiomyopathy. Animal studies have suggested that the early LV recovery process may be associated with increased collagen deposition.
4.3 Clinical implications

There are several important clinical implications of these findings. The regression of diffuse fibrosis in concert with recovery of LV function in patients undergoing successful catheter ablation may explain the better than expected outcomes with ablation in the AF/heart failure population where procedural success is generally poorer\textsuperscript{128-129, 240}. The reversibility of diffuse fibrosis in the present study presents an opportunity to reduce the precursor to the more permanent form of replacement fibrosis or scar. Early intervention with catheter ablation in patients with AF and heart failure may not only reduce interstitial fibrosis but halt the progression to scar\textsuperscript{232}. The lack of complete resolution of diffuse fibrosis also has important clinical implications. Firstly, diffuse fibrosis may be a marker of a genetic predisposition to adverse remodelling. The genetic determinants involved in arrhythmia mediated cardiomyopathy are yet to be determined, however, given the majority with this common arrhythmia do not develop systolic dysfunction it seems probable that some inherent predisposition may exist\textsuperscript{114}. Finally, although systolic dysfunction may improve or even normalise, this finding suggests that the ultra-structural aspects of the ventricle may not ‘normalise’ following the restoration of sinus rhythm. Thus medical treatments for heart failure, such as renin-angiotensin aldosterone and adrenergic system inhibition, should be continued.

4.4 Limitations

The study has several limitations. Not all patients enrolled in the CAMERA-MRI trial had sufficient ventricular T1 data both pre and post catheter ablation due to patient tolerability of the longer scanning time or artefact from the implantable loop recorder. Although used widely in research and academic settings, the clinical utility of T1 mapping in the setting of heart failure has yet to be established. Whether regression of diffuse fibrosis as detected by myocardial T1 mapping translates to a reduction in clinical outcomes (such as hospitalisation and cardiac mortality) should be determined by adequately powered prospective studies.
5. Conclusion

The improvement in systolic function and reverse ventricular remodelling following successful treatment of AF mediated cardiomyopathy with catheter ablation is accompanied by regression of diffuse fibrosis. This may have important implications for the timely treatment of arrhythmia mediated cardiomyopathy to minimise irreversible ventricular remodelling.
6. Tables and Figures

6.1 Tables

Table 1 – Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics (n=36)</th>
<th>Catheter (n=18)</th>
<th>Ablation</th>
<th>Medical rate control (n=18)</th>
<th>P value</th>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age (years)</td>
<td>59 ± 13</td>
<td>63 ± 7.1</td>
<td>0.26</td>
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<tr>
<td>CHA²DS₂VASc score</td>
<td>2.6 ± 0.9</td>
<td>2.2 ± 1.1</td>
<td>0.20</td>
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<tr>
<td>Hypertension (%)</td>
<td>44%</td>
<td>22%</td>
<td>0.36</td>
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<tr>
<td>Diabetes (%)</td>
<td>17%</td>
<td>28%</td>
<td>0.73</td>
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<tr>
<td>Hyperlipidaemia (%)</td>
<td>33%</td>
<td>17%</td>
<td>0.51</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>31 ± 8.7</td>
<td>30 ± 2.7</td>
<td>0.42</td>
<td></td>
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<tr>
<td>Obstructive sleep apnoea (%)</td>
<td>28%</td>
<td>11%</td>
<td>0.45</td>
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<tr>
<td>Stroke/TIA</td>
<td>6%</td>
<td>0%</td>
<td>0.60</td>
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<td><strong>Medications</strong></td>
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<tr>
<td>ACE inhibitor or ARB (%)</td>
<td>95%</td>
<td>95%</td>
<td>1.0</td>
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<tr>
<td>Cardio-selective beta-blocker (%)</td>
<td>89%</td>
<td>95%</td>
<td>0.55</td>
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<td>Any beta-blocker (%)</td>
<td>100%</td>
<td>100%</td>
<td>1.0</td>
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<td>Spironolactone (%)</td>
<td>33%</td>
<td>61%</td>
<td>0.10</td>
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<td>Amiodarone (%)</td>
<td>22%</td>
<td>28%</td>
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<td>Anti-arrhythmic therapy (%)</td>
<td>28%</td>
<td>28%</td>
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<td>Anticoagulation (%)</td>
<td>100%</td>
<td>100%</td>
<td>1.0</td>
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<td><strong>Atrial fibrillation history</strong></td>
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<tr>
<td>Mean duration of continuous AF (months)</td>
<td>24 ± 21</td>
<td>18 ± 13</td>
<td>0.27</td>
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<td>Long standing persistent AF (%)</td>
<td>67%</td>
<td>77%</td>
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<td>Previous DCR (%)</td>
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<td>100%</td>
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<td>Resting HR (bpm)</td>
<td>79 ± 9.4</td>
<td>76 ± 20</td>
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<td>24hr average HR (bpm)</td>
<td>87 ± 18</td>
<td>83 ± 19</td>
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<td>Post 6MWT HR (bpm)</td>
<td>95 ± 23</td>
<td>91 ± 19</td>
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<td><strong>LV systolic dysfunction history</strong></td>
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<tr>
<td>Co-diagnosis of AF and LVSD</td>
<td>78%</td>
<td>61%</td>
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<td><strong>Cardiac MRI findings</strong></td>
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<tr>
<td>LVEF</td>
<td>33 ± 8.0%</td>
<td>36 ± 8.2</td>
<td>0.35</td>
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<tr>
<td>Late gadolinium present (%)</td>
<td>50%</td>
<td>28%</td>
<td>0.39</td>
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<td>Native T1 relaxation time (T1RT)</td>
<td>1285 ± 120</td>
<td>1224 ± 125</td>
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<td>LAVI (ml/m²)</td>
<td>54 ± 16</td>
<td>53 ± 21</td>
<td>0.89</td>
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<td>LVESV (ml/m²)</td>
<td>80 ± 34</td>
<td>75 ± 29</td>
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<tr>
<td>LVEDV (ml/m²)</td>
<td>118 ± 44</td>
<td>114 ± 36</td>
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### Table 2 – Change From Baseline in each Treatment Arm

<table>
<thead>
<tr>
<th>Comparison from baseline to 6 months</th>
<th>Baseline</th>
<th>6 months</th>
<th>P value</th>
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<tr>
<td><strong>Cardiac MRI parameters</strong></td>
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<tr>
<td>LVEF (MRI)</td>
<td>33.0 ± 8.0%</td>
<td>47.0 ± 11.3%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Myocardial T1 time (ms)</td>
<td>1286 ± 120</td>
<td>1192 ± 77.1</td>
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<td>LV end systolic volume (ml/m²)</td>
<td>80.4 ± 75.1</td>
<td>63.1 ± 34.3</td>
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<td>LV end diastolic volume (ml/m²)</td>
<td>118 ± 43.8</td>
<td>113 ± 37.1</td>
<td>0.32</td>
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<td>LA volume (ml/m²)</td>
<td>53.6 ± 15.6</td>
<td>44.9 ± 10.5</td>
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<td>LV stoke volume (ml/m²)</td>
<td>37.6 ± 13.9</td>
<td>50.2 ± 10.1</td>
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<td><strong>Other parameters</strong></td>
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<td>NYHA Class</td>
<td>2.56 ± 0.51</td>
<td>1.33 ± 0.49</td>
<td>&lt;0.0001</td>
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<td>BNP (ng/L)</td>
<td>321 ± 191</td>
<td>108 ± 74.7</td>
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<td>6 minute walk test distance (m)</td>
<td>490 ± 109</td>
<td>536 ± 67.8</td>
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<td>SF-36 Physical component scores</td>
<td>37.9 ± 10.7</td>
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<td>SF-36 Mental component scores</td>
<td>46.5 ± 10.2</td>
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<td><strong>Medical rate control (n=18)</strong></td>
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<tr>
<td>LVEF (MRI)</td>
<td>35.6 ± 7.6</td>
<td>37.1 ± 7.6%</td>
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<td>Myocardial T1 time (ms)</td>
<td>1224 ± 125</td>
<td>1255 ± 295</td>
<td>0.44</td>
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<tr>
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<tr>
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<td>110 ± 33.7</td>
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</tr>
<tr>
<td>LA volume (ml/m²)</td>
<td>52.7 ± 21.4</td>
<td>51.2 ± 13.5</td>
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</tr>
<tr>
<td>LV stoke volume (ml/m²)</td>
<td>39.4 ± 14.4</td>
<td>39.4 ± 10.9</td>
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<tr>
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<tr>
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<tr>
<td>BNP (ng/L)</td>
<td>210 ± 169</td>
<td>212 ± 176</td>
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<td>6 minute walk test distance</td>
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<td>532 ± 139</td>
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</tr>
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Table 3: Comparison between treatment arms

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6.2 Figures

Figure 1: Comparison of 6-month outcomes by treatment arm

A comparison of outcomes at 6 months by treatment arm. Catheter ablation was associated with a significant improvement in LVEF (Panel A), reduction in serum BNP (Panel B) and reduction in NYHA functional class (Panel C). This was accompanied by a reduction in myocardial T1 times consistent with a regression of diffuse fibrosis (Panel D). Bars represent 95% confidence intervals. LVEF = left ventricular ejection fraction, BNP = brain natriuretic peptide, NYHA = New York Heart Association.
Figure 2: Myocardial T1 times in the catheter ablation arm compared to normal controls.

**Figure 2:** The graph shown the myocardial T1 times at baseline and six months for the catheter ablation arm and for normal controls. Significant improvement are seen from baseline to six months, however T1 times are still significantly higher at 6 months compared to normal controls. Bars represent 95% confidence intervals.
CHAPTER 5: Bi-atrial Electrical and Structural Atrial Changes in Heart Failure: Electro-anatomic Mapping in Persistent Atrial Fibrillation in Humans

1. Introduction

Atrial fibrillation (AF) and heart failure (HF) are burgeoning epidemics contributing to significant morbidity and mortality and an increasing burden upon healthcare systems\(^2\). AF and HF co-exist in a significant proportion of patients, due to a significant overlap in the pathophysiological processes driving both conditions\(^1\). Recently, catheter ablation for AF has been purported as an effective treatment for selected patients with AF and HF\(^1\) with improvements in left ventricular function and functional class. However, the success of ablation in patients with HF is inferior to those with normal LV function\(^2\). AF and HF are both associated with atrial structural remodelling that adversely impacts long term outcomes following catheter ablation. However, within the persistent AF population, the specific contribution of left ventricular systolic dysfunction to atrial remodelling, over and above the contribution of persistent AF itself, has not been previously determined. We sought to characterise structural remodelling in patients with persistent AF, with and without LV systolic dysfunction using comprehensive detailed bi-atrial electroanatomic mapping.

2. Methods

2.1 Patient selection

Consecutive patients from two Australian centres undergoing catheter ablation for persistent AF were prospectively screened. Patients were included in the study if >18 yrs, symptomatic persistent AF of at least 3 months duration, an systolic left ventricular ejection fraction (LVEF) of ≤45% (HF group) or ≥55% (normal LV (NLV) group) on preprocedural cardiac imaging (either echocardiography or cardiac MRI). Patients were excluded if they had paroxysmal AF, a known structural cause of heart failure such as previous myocardial infarction or severe valvular disease, LVEF between 45 to 55%, or if unable to maintain sinus rhythm post electrical cardioversion to facilitate mapping. Persistent AF for this study was defined as AF duration greater
than 3 months to allow the assessment of PVCL without the risks of spontaneous reversion. Longstanding persistent AF was defined as continuous AF duration for > 1yr duration. All patients were adequately rate controlled for a minimum of 4 weeks prior to mapping and ablation. This study was approved by the human ethics committee at each study location.

2.2 Mapping technique
Anti-arrhythmic drugs were discontinued five half lives prior to procedure. Anticoagulation was ceased 2-5 days prior to ablation or continued (in the case of vitamin K antagonists) at operator discretion, with intravenous heparin utilised intra-procedurally aiming for ACT >350s. Following trans-esophageal echocardiography to exclude intra-cardiac thrombus, double transeptal access was performed. Left atrial geometry was constructed using a 20 pole lasso catheter (Biosense Webster Inc, CA, USA) and registered with the pre-procedural CT or MRI. In AF, PVCL was recorded in each PV and the LAA as described below. Electrical cardioversion to sinus rhythm was then performed. Mapping was performed prior to ablation using CARTO3 electro-anatomical mapping system (Biosense Webster Inc, CA, USA) during pacing from the coronary sinus at 600ms with a 3.5mm irrigated ablation catheter (Biosense Webster Inc, CA, USA) with contact force capability, aiming for an even distribution of at least 150 points across all atrial regions, up to and including the pulmonary vein (PV) ostia but excluding points within the PV. Only points with contact force >10g were included for analysis. Mapping was performed in an identical fashion in the right atrium following left atrial ablation, but prior to any right atrial ablation (such as a cavotricuspid isthmus ablation).

2.3 Electrogram Analysis
Electrogram analysis was performed offline post procedure. Points were analysed at 200mm/s sweep speed for fractionation, voltage and scar. Complex fractionated electrograms (CFE) were defined as electrograms with ≥ 3 deflections and ≥ 50ms duration. Unipolar and bipolar voltage was recorded for each point as the maximum voltage difference between the highest and lowest amplitude deflections. Points with bipolar voltage <1.5mV were defined as reduced voltage, <0.5mV as low voltage and <0.05mV as scar. For the purposes of regional analysis, the atria were divided into
four (for the RA) or five (for the LA) segments (see figure 1). The PV antrum was
defined as the LA region within a circumferential ring 2 cm proximal to the PV ostia –
approximating a typical wide encirclement ablation line (as marked in green in
figure 1). Percentages represent the proportion of total points across the entire atria
(for global analysis) or within each region (for regional analysis) meeting the defined
criteria for CFE, low voltage or scar. Global and regional voltage was determined by
the average voltage across the entire atria for global analysis or within each region for
regional analysis.

2.4 Conduction velocity
Conduction velocity (CV) in each region was determined using methodology
previously described\textsuperscript{100}. In brief, pairs of points were selected in each region
perpendicular to isochrones measured at five isochronal steps in areas of least
isochronal crowding. CV was determined by dividing the measured shortest surface
distance between point pairs by the difference in local activation time. Regional CV
was determined as the average CV measured from five different point pairs in each
region. Global CV consisted of the average of each regional CV within each atrium.

2.5 Pulmonary vein cycle length
Pulmonary vein cycle length (PVCL) was measured utilising the methodology
described by Pascale et al\textsuperscript{242}. In brief, prior to ablation, the multipolar catheter was
placed in each PV for 60 seconds. Average PVCL for each vein was determined as
the average of 100 consecutive PV cycle lengths. Average PVCL for each patient was
the average of each measured PV’s. Average left atrial appendage (LAA) CL was
utilised as a surrogate for LA AF cycle length and was measured in an identical
manner.

2.6 Statistical analysis
Data are expressed as mean ± standard deviation (SD) unless otherwise indicated.
After assessment of normal distribution with the Kolmogorov–Smirnov test, two-
group comparisons were made using Student’s t test for continuous variables, or the
Chi-squared test for categorical variables. The independent samples Mann-Whitney
U test was used for non-normally distributed variables. Correlation was performed using a Pearson’s correlation test. A two-tailed p value of <0.05 was considered significant. Analyses were conducted using SPSS software (version 24, IBM, Chicago, Illinois).

3. Results

3.1 Study Population (Table 1)

Forty patients with persistent AF underwent biatrial mapping (20 in the HF group and 20 in the NLV group). The baseline characteristics are presented in Table 1. The HF group had an average LVEF of 33 ± 8.4% compared to 61 ± 3.6% in the NLV group (p<0.001). Both groups were well matched with respect to age, gender, body mass index, co-morbidities, bi-atrial dimensions and AF burden – although expectedly, the HF group had a higher average CHADS2 (1.38 ± 0.86 vs 0.79 ± 0.71, p=0.011), and CHA2DS2-VASc score (2.19 ± 1.21 vs 1.00 ± 0.82, p=0.001) compared to the NLV group.

There were expected differences in medications with anti-heart failure medical therapy including beta-blocker usage (100% vs 45%, p<0.001), spironolactone (45% vs 0%, p<0.001), ACE inhibitor or ARB therapy (95% vs 65%, p=0.018) and diuretic therapy (50% vs 0%, p<0.001) significantly more frequent in the HF group. The use of any anti-arrhythmic was equivalent (55% vs 65%, p=0.52). Fifty per cent of patients (9/18) in the HF group had MRI detected late gadolinium enhancement. In the NLV group the average E/e’ was 7.5 ± 1.3 with no patients with an E/e’ ≥ 9.2 and, suggesting significant HF with preserved ejection fraction as unlikely243-244.

3.2 Electro-anatomical mapping (Table 2, Figure 3)

There was no difference in the number of mapping points between the groups in both the LA and RA (HF vs NLV; LA: 221±79 vs 210±59, p=0.62; RA: 200±36 vs 224±59, p=0.14).
3.2.1 Tissue voltage

In the LA, global unipolar and bipolar voltage was significantly lower in the HF group (Unipolar: 2.36±0.92mV and Bipolar: 1.47±0.60mV) compared to the NLV group (Unipolar 3.58±1.07mV, p<0.001; and Bipolar 2.28±0.69mV, p<0.001). Voltage heterogeneity, as measured by covariance (SD/mean), was significantly increased in the HF compared to NLV group (Unipolar: 0.60 ± 0.12 vs 0.47 ± 0.07, p<0.001; Bipolar: 0.75 ± 0.15 vs 0.61 ± 0.07, p<0.001).

In the RA, global unipolar and bipolar voltage was significantly lower in the HF group (Unipolar: 1.88±0.44mV and Bipolar: 1.45±0.36mV) compared to the NLV group (Unipolar 2.67±0.84mV, p=0.001; and Bipolar 2.13±0.75mV, p=0.001). Voltage heterogeneity, as measured by covariance (SD/mean), was also increased in the HF compared to NLV group (Bipolar: 0.80 ± 0.11 vs 0.70 ± 0.11, p=0.006).

Heart failure, in both atria, was associated with a significant increase in reduced voltage (≤1.5mV) points (LA: 59.9 ± 19.9% vs 35.6 ± 20.2%, p<0.001; RA: 64.2 ± 12.9% vs 44.8 ± 20.0%, p=0.001) and low voltage (≤0.5mV) points in the (LA: 23±17% in HF vs 6.3±5.9% in NLV, p<0.001; 20±11% vs 11±7.9%, p=0.006 ) compared to the NLV group.

Scar points (bipolar voltage ≤0.05) were found more frequently in the HF group in the LA (1.4±1.5% vs 0.2±0.9%, p=0.005) and RA (1.7±3.9% vs 0%, p=0.09). However, in both atria, a significantly higher proportion of patients in the HF group had scar present (LA: 75% vs 10%, p<0.001; RA: 50% vs 0%, p<0.001).

With in the HF group, atrial tissue voltage was significantly higher in patients with tachycardia or arrhythmia medicated cardiomyopathy (TCMP), as defined by an improvement in LVEF to ≥50% following catheter ablation (n=11), compared with those not demonstrating LV recovery (non-TCMP, n=9). The bipolar voltage was 1.72±0.64 in TCMP vs 1.20±0.44mV in non-TCMP (p=0.045); unipolar voltage was 2.67 ± 0.95 in TCMP vs 1.92 ± 0.60mV in non-TCMP (p=0.048); and low voltage (<0.5mv) was 17±16% in non-TCMP vs 31±14% in non-TCMP (p=0.05).
3.2.2 Conduction Velocity
In the HF group, global conduction velocity was significantly slower in the RA (0.91±0.17ms⁻¹ vs 1.03±0.08ms⁻¹, p=0.026) with a non significant difference in the LA (0.98±0.21ms⁻¹ vs 1.06±0.15ms⁻¹, p=0.22) (Table 3).

3.2.3 Complex Fractionated Electrograms
Heart failure was associated with a significant increase in CFEs in both atria compared to the NLV group (LA: 31±17% vs 9.1±8.5%, p<0.001, RA: 28%±14 vs 11±8.5%, p<0.001).

3.3 Regional assessment of atrial substrate (Tables 3 and 4)

3.3.1 Pulmonary venous antrum
Bipolar voltage was significantly reduced in the antrum in the HF group compared to the NLV group (1.18±0.51mV vs 2.00±0.68mV, p<0.001). Within the HF group antral bipolar voltage was significantly lower in the antral compared to the non-antral region (1.18±0.51 vs 1.76±0.80mV, p=0.016). Within the NLV group there was no significant difference between antral and non-antral voltage (2.01±0.68 vs 2.39±0.75mV, p=0.10). CFEs were significantly increased in the antrum in the HF group compared to the NLV group (40±15% vs 15±14%, p<0.001). Again within the HF group, CFEs were most pronounced in the antrum vs the non-antral region (26±13%, p=0.022). Within the NLV group there was no significant difference between antral and non-antral regions (8.2±7.1%, p=0.10). Heart failure was associated with a significantly increase in low voltage (25±25% vs 9.5±11% in NLV group, p<0.016) within the PV antrum.

3.3.2 Other Regional LA analysis
Tissue voltage was reduced in the HF group in all sub-regions (Figure 1) of the LA as shown in Table 3 and Figures 3A and 3B. In the posterior LA, HF was associated with a significant reduction in voltage (bipolar: 1.34 ± 0.57 vs 2.18 ± 0.77, p<0.001; unipolar: 2.23 ± 0.89 vs 3.59 ± 1.1±9, p<0.001), and regional low voltage(p<0.001). Atrial scar was more frequent in proportion (p=0.005), and number of patients in HF (50% vs 10% in NLV, p=0.006). In the posterior LA in the HF group CFEs were
significantly greater (32±19% vs 8.8±8.3% in NLV, p<0.001). Significantly reduced tissue voltage in the HF group was also pronounced in the septum.

3.3.3 Pulmonary vein cycle length assessment
In AF, the average PVCL was significantly longer in the HF group compared to the NLV group (185±27ms vs 165±19ms, p=0.016, Figure 3B). The average PVCL of the fastest PV (PV\textsubscript{FPV Average}) was also significantly slower in the HF group (172±24 vs 155±17, p=0.013). The average of each parameter relative the LAA cycle length was also significantly higher in HF vs NLV groups (PV\textsubscript{FPV Average}/LAA: 1.06±0.09 vs 0.99±0.10, p=0.028; PV\textsubscript{FPV Average}/LAA: 1.03±0.12 vs 0.93±0.10, p=0.015; PV\textsubscript{Fast}/LAA: 0.71±0.11 vs 0.57±0.10, p<0.001). Significantly more patients in the HF group had a ratio of PV\textsubscript{FPV Average}/LAA or PV\textsubscript{FPV Average}/LAA greater than 1 (PV\textsubscript{FPV Average}/LAA: 95% vs 45%, p<0.001; PV\textsubscript{FPV Average}/LAA: 60% vs 25%, p=0.025). There was a significant correlation between PV\textsubscript{FPV Average} and bipolar voltage (R=-0.62, p<0.001) and complex fractionated activity (R=0.46, p=0.001) in the antrum (Figure 2).

4. Discussion
Atrial fibrillation and HF frequently co-exist, however whether HF confers a cumulative impact upon atrial structural remodelling over and above the impact of AF itself, has not been previously explored. In the present study, we undertook detailed bi-atrial substrate analysis in patients with persistent AF both with and without LV dysfunction. In persistent AF, patients with HF demonstrated a significant:

1. Reduction in bi-atrial unipolar and bipolar tissue voltage;
2. Increase in bi-atrial voltage heterogeneity, low voltage and scar
3. Increase in bi-atrial complex fractionated activity;
4. Slowing in pulmonary vein electrical activity in AF which correlated with voltage and complex atrial activity at the pulmonary venous antrum.

4.1 Atrial substrate in heart failure
Pathophysiologic mechanisms responsible for AF and heart failure create a complex interplay and “chicken and egg” relationship between two common cardiac
conditions. Sanders et al elegantly demonstrated the structural remodelling in the RA in patients with HF in the absence of AF. Heart failure was associated with reduced bipolar voltage, increased low voltage and scarring together with conduction slowing. The present study supports these earlier findings however extends mapping to the left atrium and pulmonary veins in the persistent AF population. Previous studies looking at atrial structural remodelling as detected by atrial delayed gadolinium enhancement have shown mixed results. Oakes et al and McGann et al demonstrated no relationship between the extent of atrial delayed enhancement and systolic dysfunction. In contrast, Akkaya et al specifically compared the extent of left atrial delayed enhancement between patients with LVEF greater (n=or less than 50%) and found significantly higher percentage of delayed enhancement it the reduced LVEF group. Furthermore, the extent of enhancement predicted the extent of LV recovery. However no studies performed invasive assessment and all included mixed aetiologies of heart failure. Halder et al demonstrated a significant increase in atrial fractionation in patients with persistent AF and heart failure of variable aetiology. Although, consistent with the findings in the present study, this retrospective analysis was performed during AF rather than in sinus rhythm; HF aetiology included ischemic and valvular heart disease and substrate analysis was confined to fractionation alone. In the present study in patients with equivalent durations of persistent AF, HF was associated with bi-atrial electrical and structural remodelling with reductions in tissue voltage, low voltage and complex atrial activity. The adverse atrial remodeling demonstrated in the HF population in the present study may be representative of a primary global cardiomyopathy or driven by AF in patients vulnerable to systolic dysfunction. Conduction velocity (CV) was preserved in the LA despite demonstrating a significant reduction in the RA in the HF population. Differences in atrial architecture such as the crista terminalis may have enhanced conduction slowing in the RA and explain the observed differences between atrial chambers.

4.2 Pulmonary vein antrum and regional analysis
In the present study we demonstrated a significant reduction in voltage and increased fractionation in all regions of the LA in heart failure, most notably in the posterior and septal LA. In addition tissue voltage was significantly lower in the PV antrum
compared with surrounding non-antral sites with HF, a difference not observed in the NLV group\textsuperscript{245}. This study is the first to demonstrate that this remodelling in the PV antrum, associates with a slowing of PV electrical activity. This more extensive remodelling of the PV antrum, reinforces the role of wide encirclement rather than ostial ablative strategy in this patient population. Cabrera et al have demonstrated histological changes in the PV antral region, particularly the inter pulmonary and PV/left atrial appendage ridge, predisposing to the spread of AF activity\textsuperscript{104, 151}, and a recent clinical trial has highlighted the clinical implications of remodelling this region\textsuperscript{248}. Recent meta-analyses have demonstrated that wide antral approach to PVI may be more effective in achieving long-term freedom from AF in patients with persistent AF\textsuperscript{153, 249}.

Roberts-Thomson et al demonstrated the importance of the posterior LA in AF in an open chest epicardial human study in patients with structural heart disease and LV dysfunction\textsuperscript{250}. MRI detected atrial late gadolinium enhancement has similarly been shown to predominate in the posterior LA\textsuperscript{213, 245}. These findings have important clinical implications and may in part explain a recent observation from a randomised study of catheter ablation vs amiodarone in AF and HF. A retrospective analysis demonstrated that catheter ablation was more successful if PVI included posterior LA isolation compared with PVI alone (79\% vs 26\%, \textit{p}<0.001)\textsuperscript{217} in patients with HF. The presence of low voltage regions within the PV antrum and posterior LA provides mechanistic support to the observation of improved outcomes when isolation of the posterior LA is included with PVI during catheter ablation for AF in HF.

Pulmonary vein AF cycle length was significantly slower in heart failure patients with persistent AF. To our knowledge this has not been previously demonstrated. Pascale et al, demonstrated that the shortest measured PVCL relative to LAA AF cycle length was predictive of recurrence post AF ablation\textsuperscript{174}. Walters et al demonstrated that the AF cycle length within the coronary sinus correlated with LA structural remodelling (bipolar voltage, conduction velocity and complex electrograms) in patients with long-standing persistent AF. However, this study did not specifically correlate structural remodelling with PVCL and did not include patients with HF\textsuperscript{175}. Intriguingly in the present study there was a significant relationship between PVCL with PV antral voltage. Lower tissue voltage was associated with slowing of PVCL.
in AF in HF and one may speculate that reduced PV firing and more extensive atrial substrate may provide some insight into the reported lower success of PVI in patients with HF.\textsuperscript{240-241}

4.3 Clinical implications

In the present study patients with persistent AF and HF demonstrated bi-atrial electrical and structural changes that may in part explain the reduced success of pharmacotherapy and catheter ablation\textsuperscript{8, 240} compared with patients without systolic impairment. This has important implications as recent studies have suggested that catheter ablation in HF may have additional benefits of recovery of systolic dysfunction following restoration of sinus rhythm\textsuperscript{103, 126, 207, 128-129}. Liang et al demonstrated that patients with AF and systolic dysfunction without delayed ventricular enhancement on cardiac MRI normalise LV function following successful catheter ablation. In STAR AF II there was no significant difference in ablation outcomes for persistent AF with PVI vs PVI plus substrate modification however the proportion of patients with HF was just 4%\textsuperscript{169}. The presence of a slower PVCL and more extensive atrial substrate may require an alternate ablation strategy to improve outcomes in this population.

To date, there have been no randomized trials comparing ablation strategies in patients with normal and reduced ejection fraction although importantly, substrate modification strategies such as posterior wall isolation are yet to be prospectively evaluated in a randomised fashion. The AATAC-AF trial demonstrated the superiority of catheter ablation over amiodarone in patients with AF and HF. Retrospective analysis identified improved outcomes when posterior wall isolation was included beyond PVI alone (79% vs 36%, p<0.001)\textsuperscript{217}. This present study demonstrating extensive biatrial substrate in the AF/HF population offers a pathophysiologic explanation to support ongoing research into substrate modification strategies in this specific patient population.

The aim of the present study was to determine the bi-atrial substrate in patients with persistent AF and HF not explained by ischemia or valvular dysfunction. A significant proportion of HF patients in this study had an underlying arrhythmia mediated
cardiomyopathy with normalisation of LVEF following the restoration of sinus rhythm with catheter ablation. These patients displayed less advanced atrial substrate compared to those failing to normalise LV function following ablation. This may explain the improved freedom from AF with catheter ablation in patients with arrhythmia mediated cardiomyopathy\textsuperscript{10, 129} compared with known structural heart disease.

4.4 Study Limitations
The exclusion of patients with structural heart disease such as ischemic or valvular heart disease may limit the extrapolation of these findings to these cardiac conditions. In addition patients with paroxysmal AF were not included. This mechanistic study was designed to characterise the bi-atrial substrate in patients with persistent AF and HF, rather than outcome with catheter ablation. The use of a 3.5mm bipolar ablation catheter with a contact force of >10g may have result in both under sensing of local electrograms and over sensing of far field electrograms at the left atrial septum. The cut-off value for low voltage of <0.5mV, whist consistent with other substrate analysis studies has not to date, been histologically validated as marker of structural remodeling in humans.

5. Conclusion
HF is associated with a significant reduction in bi-atrial tissue voltage, fractionation and prolongation of AF cycle length within the pulmonary veins. More advanced bi-atrial remodelling may have implications for ablation strategies and explain relative ineffectiveness of antiarrhythmic therapy in patients with AF and HF.
6. Tables and Figures

6.1 Tables

Table 1 – Baseline characteristics of the study population

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<td>RA area (cm²)</td>
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<td>Average CHA₂DS₂-VASc score</td>
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<td>Average CHADS₂ Score</td>
<td>1.38 ± 0.86</td>
<td>0.79 ± 0.71</td>
<td>0.024</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>15%</td>
<td>10%</td>
<td>0.63</td>
</tr>
<tr>
<td>Average BMI (kg/m²)</td>
<td>28.8 ± 4.6</td>
<td>29.9 ± 3.2</td>
<td>0.46</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>95%</td>
<td>30%</td>
<td>0.011</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>100%</td>
<td>45%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spirinolactone</td>
<td>45%</td>
<td>0%</td>
<td>0.018</td>
</tr>
<tr>
<td>Diuretic</td>
<td>55%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any anti-arrhythmic</td>
<td>55%</td>
<td>65%</td>
<td>0.52</td>
</tr>
<tr>
<td>AF and HF co-diagnosed</td>
<td>65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF preceded HF</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF preceded AF</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia cardiomyopathy*</td>
<td>55%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* LVEF improved to ≥50% following ablation
## Table 2 – Bi-atrial electrophysiological parameters in heart failure and normal LV function groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>HF group (n=20)</th>
<th>NLV group (n=20)</th>
<th>Standard difference (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electroanatomical mapping</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left atrium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average total number of points</td>
<td>221 ± 79</td>
<td>210 ± 59</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage (mV)</td>
<td>1.47 ± 0.60</td>
<td>2.28 ± 0.69</td>
<td>0.81 (0.40, 1.22)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Co-variance of bipolar voltage</td>
<td>0.75±0.15</td>
<td>0.61±0.07</td>
<td>0.14 (0.07, 0.22)</td>
<td></td>
</tr>
<tr>
<td>Unipolar voltage (mV)</td>
<td>2.36 ± 0.92</td>
<td>3.58 ± 1.07</td>
<td>1.26 (0.64, 1.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Co-variance of unipolar voltage</td>
<td>0.60 ± 0.12</td>
<td>0.47 ± 0.07</td>
<td>0.12 (0.19, 0.07)</td>
<td></td>
</tr>
<tr>
<td>Reduced voltage (%)</td>
<td>59.9 ± 19.9%</td>
<td>35.6 ± 20.2%</td>
<td>24.3% (11.5, 37.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low voltage (%)</td>
<td>23.4 ± 16.5%</td>
<td>6.3 ± 5.9%</td>
<td>17.3% (9.3, 25.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Scarring (%)</td>
<td>1.4 ± 1.5%</td>
<td>0.2 ± 0.9%</td>
<td>-1.2% (-2.0, -0.38)</td>
<td></td>
</tr>
<tr>
<td>Presence of any scar (% of patients)</td>
<td>75%</td>
<td>10%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complex electrograms (%)</td>
<td>31.1 ± 11.8%</td>
<td>9.1 ± 8.5%</td>
<td>22.0% (15.3, 28.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conduction velocity (m/s)</td>
<td>0.98 ± 0.21</td>
<td>1.05 ± 0.15</td>
<td>0.10 (-0.01, 0.22)</td>
<td>0.21</td>
</tr>
<tr>
<td>Co-variance for CV (SD/mean)</td>
<td>0.33 ± 0.07</td>
<td>0.31 ± 0.07</td>
<td>-0.15 (-0.06, 0.03)</td>
<td></td>
</tr>
<tr>
<td><strong>Right atrium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average total number of points</td>
<td>200 ± 36</td>
<td>224 ± 59</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage (mV)</td>
<td>1.45 ± 0.37</td>
<td>2.13 ± 0.75</td>
<td>0.68 (0.29, 1.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>Co-variance of bipolar voltage</td>
<td>0.79 ± 0.11</td>
<td>0.70 ± 0.11</td>
<td>0.11 (0.03, 0.18)</td>
<td></td>
</tr>
<tr>
<td>Global unipolar voltage (mV)</td>
<td>1.93 ± 0.50</td>
<td>2.67 ± 0.84</td>
<td>0.79 (0.34, 1.22)</td>
<td>0.003</td>
</tr>
<tr>
<td>Co-variance of unipolar voltage</td>
<td>0.63 ± 0.10</td>
<td>0.57 ± 0.11</td>
<td>-0.06 (-0.13, 0.1)</td>
<td></td>
</tr>
<tr>
<td>Reduced voltage (%)</td>
<td>64.2 ± 12.9%</td>
<td>44.8 ± 20.0%</td>
<td>19.4 (8.21, 30.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low voltage, &lt;0.5mV (%)</td>
<td>19.8 ± 10.7%</td>
<td>10.5 ± 7.9%</td>
<td>10.1 (3.6, 16.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Scarring, &lt;0.05mV (%)</td>
<td>1.7 ± 3.9%</td>
<td>0%</td>
<td>-1.7 (-3.7, 0.28)</td>
<td></td>
</tr>
<tr>
<td>Presence of any scar (%) of patients</td>
<td>53%</td>
<td>0%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complex electrograms (%)</td>
<td>28.2 ± 13.9%</td>
<td>11.2 ± 8.5%</td>
<td>17.1 (9.4, 24.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conduction velocity (m/s)</td>
<td>0.91 ± 0.17</td>
<td>1.03 ± 0.08</td>
<td>0.12 (0.02, 0.22)</td>
<td>0.021</td>
</tr>
<tr>
<td>Co-variance for CV (SD/mean)</td>
<td>0.27 ± 0.07</td>
<td>0.34 ± 0.07</td>
<td>0.07 (0.02, 0.12)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 – Regional Tissue Voltage

<table>
<thead>
<tr>
<th></th>
<th>HF group (n=20)</th>
<th>NLV Group (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LA septum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage</td>
<td>1.13 ± 0.55</td>
<td>2.16 ± 0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unipolar Voltage</td>
<td>1.90 ± 0.91</td>
<td>3.22 ± 1.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LA anterior</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage</td>
<td>1.71 ± 0.9</td>
<td>2.33 ± 0.95</td>
<td>0.051</td>
</tr>
<tr>
<td>Unipolar Voltage</td>
<td>2.36 ± 1.26</td>
<td>3.45 ± 1.36</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>LA lateral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage</td>
<td>1.84 ± 0.90</td>
<td>2.54 ± 0.85</td>
<td>0.016</td>
</tr>
<tr>
<td>Unipolar Voltage</td>
<td>2.70 ± 1.13</td>
<td>3.85 ± 1.43</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>LA inferior</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage</td>
<td>1.79 ± 1.07</td>
<td>2.48 ± 1.19</td>
<td>0.060</td>
</tr>
<tr>
<td>Unipolar Voltage</td>
<td>2.96 ± 1.35</td>
<td>4.20 ± 1.63</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>LA posterior</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage</td>
<td>1.34 ± 0.57</td>
<td>2.18 ± 0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unipolar Voltage</td>
<td>2.23 ± 0.89</td>
<td>3.59 ± 1.19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 4: PV antrum and posterior left atrium: electrophysiological and electro-anatomical parameters

<table>
<thead>
<tr>
<th></th>
<th>Heart (n=20)</th>
<th>Failure (n=20)</th>
<th>Normal (n=20)</th>
<th>LV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary vein cycle length</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV 4Vaverage (4 vein average – over 100 cycles)</td>
<td>185 ± 27</td>
<td>165 ± 19</td>
<td></td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>PV FVaverage (fastest vein – over 100 cycles)</td>
<td>172 ± 24</td>
<td>155 ± 17</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>PV fast (shortest CL of any vein) (ms)</td>
<td>126 ± 23</td>
<td>94 ± 17</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAA average (ms)</td>
<td>170 ± 18</td>
<td>166 ± 15</td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>PV 4PVaverage (4 vein average) / LAA average</td>
<td>1.07 ± 0.09</td>
<td>0.99 ± 0.10</td>
<td></td>
<td></td>
<td>0.030</td>
</tr>
<tr>
<td>PV FPVaverage (fastest vein average) / LAA</td>
<td>1.01 ± 0.10</td>
<td>0.93 ± 0.10</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PV 4PVaverage / LAA average &gt; 1 (% patients)</td>
<td>95%</td>
<td>45%</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PV FPVaverage / LAA average &gt; 1 (% patients)</td>
<td>60%</td>
<td>25%</td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Electro-anatomical mapping (Pulmonary venous antrum)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage (mV)</td>
<td>1.18 ± 0.51</td>
<td>2.00 ± 0.68</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unipolar voltage (mV)</td>
<td>1.95 ± 0.80</td>
<td>2.98 ± 0.89</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complex electrograms (%)</td>
<td>40.0 ± 15.4%</td>
<td>14.5 ± 14.0%</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low voltage (%) (&lt;0.5mV bipolar)</td>
<td>25.4 ± 24.5%</td>
<td>9.5 ± 11.0%</td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Presence of any scar (&lt;0.05mV bipolar, % of)</td>
<td>50%</td>
<td>10%</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Conduction Velocity (m/s)</td>
<td>0.93 ± 0.20</td>
<td>1.05 ± 0.19</td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Electro-anatomical Mapping (Posterior Left Atrium)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage (mV)</td>
<td>1.34 ± 0.57</td>
<td>2.18 ± 0.77</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unipolar voltage (mV)</td>
<td>2.23 ± 0.89</td>
<td>3.59 ± 1.19</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low voltage (%)</td>
<td>26.0 ± 18.0%</td>
<td>5.7 ± 7.0%</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Scarring (%)</td>
<td>2.4 ± 3.3%</td>
<td>0.1 ± 0.4%</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Presence of any scar (% of patients)</td>
<td>50%</td>
<td>10%</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Complex electrograms (%)</td>
<td>31.5 ± 18.7%</td>
<td>8.8 ± 8.3%</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global conduction velocity (m/s)</td>
<td>0.89 ± 0.23</td>
<td>0.98 ± 0.19</td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
</tbody>
</table>
6.2 Figures

Figure 1 – Segmentation of the left atrium into regions.

**Figure 1**: The figure shows the division of the left atrium into anterior, posterior, inferior, septal, and lateral regions for the purposes of regional analysis. The antral region was defined at the circumferential region 2cm proximal to the pulmonary vein/left atrial junction. It encompasses a typical wide antral circumferential ablation to achieve PVI. The posterior region was identified as the posterior area between the right and left antral region, as shown in red. LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein, LAA=left atrial appendage.
Figure 2 – Relationship between antral voltage, complex fractionated activity and pulmonary vein cycle length

**Figure 2**: Correlation of antral bipolar tissue voltage (A), and antral complex electrograms (B) with average PVCL (average of all measured PVs). Antral region is that area defined in Figure 1 above.
Figure 3 – Bi-atrial bipolar voltage maps in heart failure and normal LV function.

Figure 3A
Figure 3: Bipolar voltage in the LA and RA in a patient with persistent AF and dilated cardiomyopathy (LVEF=31%) and a patient with persistent AF and normal LV function (LVEF=65%). Panel A indicates areas of low voltage in heart failure congregating around the posterior and antral regions. Panel B shows mean voltage across the RA and LA in HF and NLV. Sample of pulmonary vein activity with the average PVCL is also indicated for HF and NLV showing prolongation of PVCL in HF relative to NLV. PVCL=pulmonary vein cycle length, LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein, LAA=left atrial appendage.
CHAPTER 6: A Comparison of the Electrophysiologic and Electroanatomic Characteristics Between the Right and Left Atrium in Persistent Atrial Fibrillation: Is the Right Atrium a Window Into The Left?

1. Introduction
The atrial substrate, beyond the pulmonary veins, is fundamental to the maintenance and progression of paroxysmal to persistent atrial fibrillation\(^{251-252}\). Atrial fibrillation is associated with a range of conditions such as ageing, hypertension, obesity, heart failure and sleep apnoea which may be expected to produce biatrial changes and are associated with an increase in AF following catheter ablation\(^{78, 98, 100-101, 96}\). In clinical research, electroanatomic mapping of the right atrium can be safely performed without exposing patients to transeptal puncture without the justification of a clinical requirement. As such many studies\(^ {78, 98-101}\) exploring the atrial substrate associated with the risk factors for AF have been confined to the right atrium as a surrogate for the remodelling process in the left atrium. There are obvious structural differences between the two chambers with the vena cavae and the crista terminalis unique to the RA and the pulmonary veins a feature of the LA. However much of the atria is common to both including the body, the appendages and perivalvular tissue. Although biatrial mapping has been extensively performed, a detailed correlation of the electrical and structural remodelling processes between the atria has not been completed\(^ {78, 97}\). The aim of the present study was to determine if electrical and structural changes in the right atrium are truly representative of the left atrium.

2. Methods

2.1 Study population
Consecutive patients undergoing index AF ablation were prospectively enrolled across 2 centres. Patients were included if they had persistent AF of at least 3 months continuous duration and were in AF at time of ablation, as this burden of AF was expected to be associated with significant electrophysiologic and electroanatomic change. Patients were excluded if they (1) had paroxysmal AF; (2) were unable to be electrically cardioverted to sinus rhythm or; (3) had active or uncontrolled thyroid disease; (4) had undergone previous left atrial ablation or (5) were unable or unwilling to consent. The
study was approved by the human research and ethics committee at both of the centers involved in the study.

2.2 Mapping Technique

2.2.1 Peri-procedural management
Anti-arrhythmic medications were discontinued five half lives prior to procedure. Anticoagulation was ceased 2 days prior to ablation or continued (in the case of vitamin K antagonists) at operator discretion. Following trans-oesophageal echocardiography to exclude intra-cardiac thrombus, double transeptal access was performed and intravenous heparin administered to a target ACT >350s.

2.2.2 Electro-anatomical mapping
Left atrial geometry was constructed using a 20 pole lasso catheter (Biosense Webster Inc, CA, USA) and registered with the pre-procedural CT or MRI using CARTO3 electro-anatomical mapping system. Electrical cardioversion to sinus rhythm was then performed. Mapping was performed with a 4mm irrigated smart-touch ablation catheter (Biosense Webster Inc, CA, USA) with contact force capability prior to ablation during pacing from the coronary sinus at 600ms. At least 150 points across all atrial regions, up to but not including the pulmonary vein (PV) ostia were collected with the assistance of the Confidense™ module (Biosense Webster Inc, CA, USA) to ensure an even point distribution. Only points with contact force >10g were included for analysis. Mapping was performed in an identical fashion in the right atrium following left atrial ablation, but prior to any right atrial ablation such as a cavitricuspid isthmus ablation.

2.3 Electrogram Analysis
Electrogram analysis was performed offline post procedure. Points were analysed at 200mm/s sweep speed for complex fractionated electrograms(CFE), low voltage and scar. Complex fractionated electrograms (CFE) were defined as electrograms with ≥ 3 deflections and ≥ 50ms duration. Percentages represent the proportion of total points across the entire atria for global analysis or within each region according to the defined criteria for CFE, low voltage or scar. Global and regional voltage (unipolar and bipolar) was determined by the average voltage across the entire atria for global analysis or
within each region for regional analysis. For the purposes of regional analysis, the atria were divided into four discreet segments (see figure 1).

2.4 Tissue Voltage
Unipolar and bipolar voltage was recorded for each point as the maximum voltage difference between the highest and lowest amplitude deflections. Points with bipolar voltage \( \leq 0.5 \text{mV} \) were defined as low voltage.

2.5 Conduction velocity
Conduction velocity (CV) was determined using methodology previously described\textsuperscript{100}. In brief, five pairs of points were selected in areas of least isochronal crowding in each of 4 regions to obtain a global conduction velocity. Conduction was measured perpendicular to isochrones, at five isochronal steps. CV was determined by dividing the measured shortest surface distance between point pairs by the difference in local activation time. Regional CV was determined as the average CV measured from five different point pairs in each region. Global CV consisted of the average of each regional CV within each atrium.

2.6 Statistical analysis
Based on previous studies correlating bi-atrial volume as detected on CT in the setting of AF (as a surrogate for atrial remodeling), an expected R value of 0.51 was determined\textsuperscript{253-254}. For a statistical power of 80%, and two-tailed \( \alpha \) value of 0.05, a sample size of 28 was calculated. Data are expressed as mean ± standard deviation (SD) unless otherwise indicated. After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student’s t test for continuous variables, or the Chi-squared test for categorical variables. The independent samples Mann-Whitney U test was used for non-normally distributed variables. Coefficient of variation was determined by the mean divided by the standard deviation. Correlation was determined by Pearson’s correlation co-efficient. A two-tailed p value of \(<0.05\) was considered significant. Analyses were conducted using SPSS software (version 23, IBM, Chicago, Illinois).
3. Results

3.1 Study Population (Table 1)
40 patients undergoing AF ablation underwent biatrial mapping. The baseline characteristics of the patients are outlined in Table 1. The population was predominately male (90%) with a mean age of $59 \pm 9.2$ years, CHADS$_2$ score of $1.1 \pm 0.8$, and a BMI of $29.1 \pm 4.2$ kg/m$^2$. Persistent AF was long standing in 67.5% with an average duration of continuous AF of $12.9 \pm 9.2$ months and 85% of patients had undergone previous electrical cardioversion.

3.2 Electro-anatomical Mapping (Table 2, Figure 2)
The mean number of points was $220 \pm 66$ points in the LA and $216 \pm 54$ points in the RA with no difference between the atria (p=0.76).

3.2.1 Global Tissue Voltage (Figure 2A)
There was a significant correlation in global bipolar voltage between the left and right atria ($R=0.57$, p <0.001). There was no significant difference in global bipolar voltage between the left and right atria ($1.89 \pm 0.77$ vs $1.77 \pm 0.57$ mV, p=0.45) There was a strong correlation in global unipolar voltage between the left and right atria ($R=0.68$, p<0.001). Unipolar voltage was significantly higher in LA compared to the RA ($2.95 \pm 1.14$ vs $2.28 \pm 0.65$ mV, p<0.002). Within each atrium, there was a very strong correlation between global bipolar and unipolar tissue voltages (LA: $R=0.94$, RA: $R=0.95$, p<0.001 for each).

No significant regional variation in bipolar voltage was noted with the exception of the posterior segment, which was significantly lower in the RA compared to the LA ($1.18 \pm 0.48$ in RA vs $1.77 \pm 0.77$ mV, p<0.001). Compared to the LA, unipolar voltage in the RA was significantly lower in the posterior ($1.56 \pm 0.54$ vs $2.92 \pm 1.22$ mV, p<0.001) and lateral areas ($2.36 \pm 0.84$ vs $3.24 \pm 1.30$ mV, p<0.001) in the region of the crista terminalis. Bi-atrial bipolar and unipolar tissue voltage correlated well regionally (Table 3).
3.2.2 Low Voltage
The mean number of points in each atrial detecting low voltage or scar was 34 ± 23 points in the RA and 42 ± 44 points in the LA. There was a significant correlation in the proportion of low voltage (<0.5mV) between the RA and LA (R=0.48, p=0.002). There was no significant difference in the percentage of low voltage (<0.5mV) between the RA (15.7±10.3%) and LA (15.0±15.7%, p=0.84). Low voltage regions were present in the LA in 88%, the RA in 98% and bi-atrially in 95% of patients. Scar regions (bipolar voltage <0.05mV) were present in the LA in 45%, in the RA in 28% and bi-atrialy in 20% of patients (Table 2).

3.2.3 Complex Fractionated Electrograms (CFE’s)
There was a strong correlation in the presence of CFE’s between the RA and LA (R=0.73, p<0.001). There was no significant difference in the proportion of CFEs (20.0 ± 14.2% in the RA vs 20.0 ± 15.2% in the LA, p=0.73). Within regions of low voltage or scar fractionation was present in the LA in 8.7 ± 9.8% and RA in 8.0 ± 7.8%, p=0.73) which correlated significantly (R=0.53, p<0.001). Fractionation made up 40 ± 29% of low voltage or scar points in the RA and 44 ± 35% in LA (p=0.5), with no significant correlation between chambers(R=0.30, p=0.061).

3.3 Conduction Velocity (Table 2)
There was a significant correlation in global conduction velocity (CV) between the RA and LA (R=0.49, p=0.001, Figure 2B). CV correlated well regionally, with the exception of the septal region (Table 3). Global conduction velocity (CV) was notably slower in the RA compared to the LA (0.93 ± 0.15ms⁻¹ vs 1.01 ± 0.19ms⁻¹, p=0.02).

4. Discussion
We performed detailed high density electro-anatomical mapping using contact force in 40 patients with persistent AF undergoing AF ablation in order to compare the atrial substrate between the left and right atria. Although biatrial mapping has been previously performed, direct comparisons between atria have not been determined. In the present study there was a significant correlation between right and left atrium in:

1. Global unipolar and bipolar voltage;
2. Low voltage, scar and the presence of complex fractionated activity;
3. Global conduction velocity although conduction was significantly slower in the RA compared the LA.

To our knowledge, this is the first study to directly compare the atrial substrate between the left and right atria in a cohort of patients with persistent AF. Furthermore, our study is the first to undertake bi-atrial electro-anatomical mapping with the aid of contact force sensing technology, allowing a true differentiation of electrogram morphology from electrograms that may be explained by poor tissue contact. This provides a more accurate characterisation of the atrial substrate particular in regions of low voltage.

4.1 Does the right atrium represent the left?
A better understanding of the human atrial substrate in atrial fibrillation is the cornerstone in improving pharmacologic and ablation based strategies in persistent AF. Prior studies have provided a detailed characterisation of the electrical and structural changes in the right atrium alone in various disease states including hypertension, ageing, heart failure, mitral valve disease, as well as paroxysmal and persistent AF. Right atrial mapping is attractive in the research setting as access is generally uncomplicated, safer and avoids the need for transeptal access with its incumbent risks and ethical questionability in the setting of a purely non-clinical intervention. One may postulate that remodelling observed in the right atrium is an accurate representation of the left however, to our knowledge, this has not been specifically addressed. We sought to evaluate, whether such inferences maybe validly drawn.

4.2 Tissue Voltage and Fractionation
Although left atrial remodelling in the setting of persistent AF have been well described, few reports have performed bi-atrial mapping. Stiles et al performed biatrial mapping in no or low burden (‘lone’) AF (n=25) and demonstrated lower bipolar voltage, an increase in fractionation, with changes in AF comparable between the LA and RA (RA: $1.7 \pm 0.4$ mV, LA: $1.7 \pm 0.7$ mV). John et al performed bi-atrial substrate analysis in rheumatic mitral disease and also demonstrated comparable voltages between the RA and LA. Sanders et al performed RA substrate analysis in patients with LV dysfunction (in effect a bi-trial remodeling factor) and noted electrophysiological
changes mirroring those seen in high burden AF, including the presence of RA scar in 75% of patients with heart failure.

Remodelling is not confined to the left atrium which is not surprising given AF involves both atria and many of the associated disease states such as heart failure, aging, valvular disease and hypertension, stimulate neurohormonal pathways with systemic sequelae. These processes, which include AF itself, atrial stretch, inflammation, oxidative stress, autonomic neural activity and the activation of the renin-angiotensin system and sympathetic nervous system have been well described in human and animal models. Figure 3 illustrates the interplay of these processes in bi-atrial structural remodelling.

In the present study bi-atrial mapping was performed during paced rhythm as electrophysiological parameters are more reliable and reproducible compared with assessment during AF. Atrial voltage is significantly lower when measured in AF. Furthermore regions of CFE and low voltage apparent in AF frequently correlate with regions of normal conduction, electrogram morphology and voltage when reassessed in paced rhythm. The outcomes for catheter ablation for AF may also be improved when performed in sinus rhythm. Kochhäuser et al reported that the presence of sinus rhythm early during catheter ablation for persistent AF predicted greater freedom from AF at 18 months follow up. The authors hypothesised that improved signal voltage in sinus rhythm improved ablation endpoints.

In the present study, there was a significant correlation in complex fractionated activity (R=0.73, p<0.001), tissue voltage (Bipolar: R=0.57, p<0.001, Unipolar: R=0.68, p<0.001) and low voltage (R=0.55, p=0.002) between the RA and LA. These findings suggest that prior studies confined to the RA offer important insights and are an accurate representation of the left atrial substrate.

4.3 Conduction Velocity
To our knowledge, this study is the first to provide a direct comparison between the atria and demonstrate a significant reduction in conduction velocity in the RA relative to the LA in persistent AF. Although there was an absolute difference in CV between atria
a significant correlation remained both globally and regionally aside from the septum. There are important electroanatomic differences between the atria, which may in part explain this observation. In the right atrium there is the complex region of the crista terminalis which incorporates the sinus node complex and the junction of the smooth and trabeculated right atrium. In contrast, the left atrial endocardium houses the pulmonary veins, surrounding antrum and septopulmonary bundle hence differences in the posterior atria may be expected considering inherent anatomic differences. Slowing of right atrial conduction in the AF population is well recognised in the clinical coupling of sick sinus syndrome and atrial fibrillation. Conduction slowing in the RA relative to the LA may in part be explained by stretch mediated effects particularly at the vulnerable junction of the smooth and trabeculated region of the crista terminalis. Despite anatomical differences between the atria there was a significant correlation between the atria which may be attributable to systemic or neurohormonal mechanisms rather than local factors.

4.4 Mechanisms Responsible for Bi-atrial Structural Remodeling (Figure 3)

Although rapid firing from the pulmonary veins is the major source of triggers for AF the atrial substrate becomes increasingly important in the maintenance of persistent AF. Remodelling is not confined to the left atrium which is not surprising given AF involves both atria and many of the associated disease states such as heart failure, aging, valvular disease and hypertension, stimulate neurohormonal pathways with systemic sequelae. These processes, which include AF itself, atrial stretch, inflammation, oxidative stress, autonomic neural activity and the activation of the renin-angiotensin system and sympathetic nervous system have been well described in human and animal models. Figure 3 illustrates the interplay of these processes in bi-atrial structural remodelling. Similarly reverse remodelling following successful catheter ablation for AF results in a reduction in both LA and RA dimensions. In the present study electrical and structural remodelling in the right atrium correlated with findings in the left atrium in support of the right atrium as representative of the left and consistent with operation of bi-atrial remodelling processes. As such non-clinically indicated RA mapping studies provide useful insights into pathophysiologic processes occurring in the LA.
4.5 Clinical implications

There are several important clinical implications. Firstly, there was a significant correlation between the atria supporting assessment of the electrophysiological properties of the RA as a valid surrogate for the LA. As such the present study supports the conclusions of earlier substrate studies confined to the RA\textsuperscript{98-101} which demonstrated reductions in tissue voltage with the electrophysiologic sequelae of conduction slowing associated with ageing, heart failure and hypertension. Secondly, this study highlights that persistent AF and its inherent complicit co-morbidities are not confined to the LA but rather bi-atrial with electrophysiologic changes in part explained by a range of potential mechanisms including atrial stretch\textsuperscript{77-78}, inflammation\textsuperscript{258}, oxidative stress\textsuperscript{68}, autonomic neural activity\textsuperscript{28-29} and the activation of the renin-angiotensin system\textsuperscript{42,44} and sympathetic nervous system. Cardiac MRI using LGE provides a non invasive assessment of the atria and demonstrates an association between atrial fibrosis, CHADS\textsubscript{2} score and the outcomes of catheter ablation for atrial fibrillation although, to date, the atrial LGE imaging has largely been confined to a single centre\textsuperscript{213}.

4.6 Limitations

Several limitations of this study need to be acknowledged. The study population were patients with persistent AF selected for catheter ablation and may not represent the general population with long standing persistent AF. The patient population were persistent AF patients with a minimum duration of continuous AF of three months and as such may limit the generalizability of our findings to paroxysmal AF\textsuperscript{97}. However, we selected the persistent AF population as electrical and structural abnormalities are expected and a greater understanding of the atrial substrate in persistent AF may have implications for future substrate modification strategies\textsuperscript{169, 251}. The performance of mapping in sinus rhythm did restrict analysis to patients capable of maintaining sinus rhythm prior to catheter ablation. The conclusions from this study may not apply to conditions such as pulmonary vascular disease or valvular heart disease where direct hemodynamic factors would be expected to result in inherently less equal bi-atrial effects than the systemic effects of AF per se. The predominately male population in this study limits the generalizability of the findings to female AF patients, who may display a gender specific disease profile.
5. Conclusion

Electrical and structural remodeling within the right atrium correlates with that seen in the left atrium in patients with persistent AF. As such non-clinical mapping studies of the RA provide an important window into the LA without the risks of trans-septal access and as such provide useful insights into the mechanisms responsible for atrial fibrillation.
6. Tables and Figures

6.1 Tables

Table 1 – Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics n=40</th>
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</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>59 ± 9.2</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>90%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.5%</td>
</tr>
<tr>
<td>Average CHADS2 Score</td>
<td>1.1 ± 0.8</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
<td>29.1 ± 4.2</td>
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<tr>
<td>Long-lasting Persistent AF (%)</td>
<td>67.5%</td>
</tr>
<tr>
<td>Duration of continuous AF pre-ablation (months)</td>
<td>12.9 ± 9.2</td>
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<td>Previous DCR</td>
<td>85%</td>
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<th>Echocardiographic parameters</th>
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<tr>
<td>LVEF</td>
<td>44 ± 15%</td>
</tr>
<tr>
<td>LA area (cm²)</td>
<td>28 ± 5.2</td>
</tr>
<tr>
<td>LA volume indexed (ml/m³)</td>
<td>49 ± 14</td>
</tr>
<tr>
<td>RA area (cm²)</td>
<td>25 ± 6.4</td>
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<table>
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<th>Medications</th>
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<tr>
<td>Beta-blocker</td>
<td>77.5%</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>55%</td>
</tr>
<tr>
<td>Angiotensin II Receptor Blocker</td>
<td>25%</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>22.5%</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>100%</td>
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Table 2 – Global analysis of Electrophysiological Parameters between the RA and LA.

<table>
<thead>
<tr>
<th></th>
<th>Right Atrium</th>
<th>Left Atrium</th>
<th>P value</th>
<th>R value</th>
<th>P value</th>
<th>Correlation</th>
</tr>
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<tr>
<td><strong>Number of points</strong></td>
<td>216 ± 54</td>
<td>220 ± 66</td>
<td>0.76</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td><strong>Bipolar Voltage (mV)</strong></td>
<td>1.77 ± 0.57</td>
<td>1.89 ± 0.77</td>
<td>0.45</td>
<td>0.57</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Unipolar Voltage (mV)</strong></td>
<td>2.28 ± 0.65</td>
<td>2.95 ± 1.14</td>
<td>0.002</td>
<td>0.68</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Low Voltage &lt;0.5mV (%)</strong></td>
<td>15.7 ± 10.3</td>
<td>15.0 ± 15.7</td>
<td>0.84</td>
<td>0.48</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td><strong>Complex Electrograms (%)</strong></td>
<td>20.0 ± 14.2</td>
<td>20.0 ± 15.2</td>
<td>0.99</td>
<td>0.73</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Scar (%)</strong></td>
<td>0.89 ± 2.89</td>
<td>0.79 ± 1.31</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Conduction velocity (m/s)</strong></td>
<td>0.93 ± 0.15</td>
<td>1.01 ± 0.19</td>
<td>0.02</td>
<td>0.49</td>
<td>0.001</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Right atrium</th>
<th>Left atrium</th>
<th><strong>P value</strong></th>
<th><strong>X^2 test (RA vs LA)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scar &lt;0.05mV (% patients)</strong></td>
<td>27.5%</td>
<td>45%</td>
<td>20%</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Low Voltage (% patients)</strong></td>
<td>95%</td>
<td>88%</td>
<td>95%</td>
<td>0.09</td>
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</table>
Table 3: Regional analysis of Tissue voltage and CV between the RA and LA.

<table>
<thead>
<tr>
<th>Region</th>
<th>Right Atrium</th>
<th>Left Atrium</th>
<th>P value</th>
<th>R value</th>
<th>P value Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Voltage (mV)</td>
<td>2.40 ± 0.83</td>
<td>2.10 ± 0.99</td>
<td>0.12</td>
<td>0.31</td>
<td>0.05</td>
</tr>
<tr>
<td>Unipolar Voltage (mV)</td>
<td>3.00 ± 0.90</td>
<td>3.24 ± 1.38</td>
<td>0.54</td>
<td>0.54</td>
<td>0.002</td>
</tr>
<tr>
<td>Conduction velocity ms⁻¹</td>
<td>0.99 ± 0.20</td>
<td>1.04 ± 0.24</td>
<td>0.26</td>
<td>0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Posterior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Voltage</td>
<td>1.18 ± 0.48</td>
<td>1.77 ± 0.77</td>
<td>&lt;0.001</td>
<td>0.42</td>
<td>0.007</td>
</tr>
<tr>
<td>Unipolar Voltage</td>
<td>1.56 ± 0.54</td>
<td>2.92 ± 1.22</td>
<td>&lt;0.001</td>
<td>0.42</td>
<td>0.006</td>
</tr>
<tr>
<td>Conduction velocity ms⁻¹</td>
<td>0.87 ± 0.20</td>
<td>0.95 ± 0.21</td>
<td>0.064</td>
<td>0.29</td>
<td>0.07</td>
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<tr>
<td><strong>Lateral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bipolar Voltage</td>
<td>1.86 ± 0.72</td>
<td>2.15 ± 0.90</td>
<td>0.13</td>
<td>0.47</td>
<td>0.002</td>
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<tr>
<td>Unipolar Voltage</td>
<td>2.36 ± 0.84</td>
<td>3.24 ± 1.30</td>
<td>&lt;0.001</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conduction velocity ms⁻¹</td>
<td>0.96 ± 0.21</td>
<td>0.94 ± 0.21</td>
<td>0.69</td>
<td>0.43</td>
<td>0.006</td>
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<td><strong>Septal</strong></td>
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<tr>
<td>Bipolar Voltage</td>
<td>1.51 ± 0.61</td>
<td>1.58 ± 0.84</td>
<td>0.61</td>
<td>0.62</td>
<td>&lt;0.001</td>
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<tr>
<td>Unipolar Voltage</td>
<td>2.11 ± 0.74</td>
<td>2.48 ± 1.32</td>
<td>0.13</td>
<td>0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conduction velocity ms⁻¹</td>
<td>0.94 ± 0.21</td>
<td>1.07 ± 0.28</td>
<td>0.003</td>
<td>0.05</td>
<td>0.78</td>
</tr>
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</table>
Figure 1: Segmentation of the left and right atrium for regional analysis

**Segmentation of LA and RA for regional analysis**

**Right Atrium**

**Left Atrium**

- Anterior
- Posterior
- Lateral
- Septal

*Figure 1*: The division of the right and left atria into segment for the purpose of regional analysis.
Figure 2: Bi-atrial correlation of electrophysiological parameters

Figure 2A: Correlation of bi-atrial voltage
Figure 2A: Bi-atrial global correlation of bipolar and unipolar tissue voltage. Points represent patients with average global bipolar and unipolar values for that patient plotted.
Figure 2B: Bi-atrial correlation of low voltage, complex electrograms and conduction velocity

Points represent patients with average number of global points reaching defined criteria for complex electrograms (≥ 3 deflections and ≥ 50ms) and low voltage (< 0.5mV bipolar) for that patient plotted. For conduction velocity, points represent the global average conduction velocity for each atria in each patient.
CHAPTER 7: Pulmonary Vein Activity Does Not Predict Long-term Outcome of Catheter Ablation for Persistent Atrial Fibrillation – A Multi-centre Prospective Study.

1. Introduction

PV isolation remains the cornerstone of AF ablation for paroxysmal and persistent atrial fibrillation (AF). However, the outcomes with catheter ablation (CA) for patients with persistent AF are inferior to those with paroxysmal AF\textsuperscript{204, 265-266}. Whilst atrial remodeling is thought to be responsible for the maintenance of AF, to date substrate modification strategies have not improved outcomes beyond PVI alone in randomized multi-centre trials\textsuperscript{168-169, 267-268}. Nonetheless select patients with persistent AF may benefit from novel adjunct ablation strategies beyond PVI\textsuperscript{269-270}. To date, the identification of those patients in whom PV activity is responsible for both the initiation and maintenance of persistent AF and as a result PVI is sufficient, remains elusive. Perhaps the characteristics of PV activity observable during AF can predict procedural outcome in persistent AF\textsuperscript{173}. Retrospective studies have demonstrated an association between PV to LAA gradient and success of the step wise\textsuperscript{174} or electrogram guided\textsuperscript{173} CA approach in persistent AF. However, there remains a notable lack of prospective studies evaluating the role of PV activity and procedural success. This study aimed to determine whether PV activity and PV AF may predict outcome in patients undergoing CA for persistent AF.

2. Methods

2.1 Patient selection

Consecutive patients with persistent AF undergoing first time CA were prospectively enrolled between May 2014 and May 2016 across 3 Australian centres. Patients were excluded if they had undergone prior left atrial ablation or were in sinus rhythm, atrial tachycardia or flutter at the time of procedure. The study was approved by the institutional ethics bodies of each participating centre.
2.2 Pulmonary vein cycle length measurement (Figure 1)

Pulmonary vein cycle length (PVCL) was measured adapting the methodology described by Pascale et al\textsuperscript{174}. In brief, prior to ablation, the multipolar catheter was placed in each PV for 60 seconds. Average PVCL for each vein was determined as the average of 100 consecutive PV cycle lengths. Average PVCL for each patient was the average of each measured PV (PV\textsubscript{4VAverage}). The fastest vein (FV) PVCL was the average PVCL measured in any vein (PV\textsubscript{FVAverage}) for each patient. The shortest cycle length recorded in any PV over 60 seconds was also measured (PV\textsubscript{fast}). Mean left atrial appendage (LAA) CL and posterior wall cycle length (PW\textsubscript{Average}) were measured as the average of 100 consecutive cycles. PVCL intervals were measured offline manually with electronic calipers at 150mm sweep speed, with care taken to measure the leading wavefront from the same electrogram population, despite alterations in activation pattern as has been described previously\textsuperscript{174}. AF in a vein was defined as \(\geq 5\) seconds of continuous electrical activity in at least 2 consecutive PV channels with PVCL <100ms. The definition of AF within a PV was adapted from the definition utilized for complex fractionated atrial electrograms as defined by previous studies\textsuperscript{271-275}. The PVCL was determined as: (1) as the combined average PVCL of all the PVs in a given patient (PV\textsubscript{4VAverage}); (2) the average of the PV with the fastest cycle length (PV\textsubscript{FVAverage}) and (3) the fastest PVCL interval measured in any vein (PV\textsubscript{fast}). The ratio of each of these values relative to the average LAA cycle length, was also determined, to calculate the PV/LAA cycle length gradient has described by Pascale et al\textsuperscript{174}.

2.3 Ablation procedure

Trans-oesophageal echocardiography was performed to exclude intra-cardiac thrombus. Anti-arrhythmic medications were ceased one week prior to procedure. Anticoagulation was ceased two days prior to ablation or continued (in the case of vitamin K antagonists) at operator discretion, with intravenous heparin utilised intra-procedurally. Ablation was performed with an irrigated ablation catheter (Biosense Webster Inc. or St Jude Medical) with 3D electroanatomical mapping CARTO3 (Biosense Webster Inc.) or Ensite Velocity (St Jude Medical), with a multipolar catheter utilised to confirm PV isolation. PV isolation with bidirectional block was the procedural endpoint in all cases. Adenosine was administered to assess for dormant PV reconnection with additional ablation delivered at sites of reconnection and adenosine repeated until no further PV reconnection was present. Following
PVI, empirical posterior wall isolation was performed with a LA roof line (30W) and inferior wall line (25W) delivered. If AF organised to an atrial tachycardia then activation and entrainment mapping were performed with targeted ablation.

2.4 Follow up

Unless an implantable device capable of AF detection was present (implantable loop recorder or dual lead pacemaker or implantable cardiac defibrillator), patients underwent 6 monthly 24-hour holter-monitoring. Patients were reviewed at 6 weeks, 3 months then 6 monthly or earlier for symptomatic recurrence. Implantable loop recorder AF detection was determined by standard manufacturer algorithms (Reveal LINQ™, Medtronic, USA or CONFIRM™, St Jude Medical, USA), and manually verified. AF recurrence was defined as any documented atrial fibrillation or atrial tachycardia ≥30 seconds, beyond a 90 day blanking period following ablation, including 3 months post repeat procedure. Patients with symptomatic recurrence were able to undergo repeat ablation at the discretion of their treating physician. Patients required a minimum of 12 months follow up to be included for analysis.

2.5 Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) unless otherwise indicated. After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student’s t test for continuous variables, or the Chi-squared test for categorical variables. The independent samples Mann-Whitney U test was used for non-normally distributed variables. A two-tailed p value of <0.05 was considered significant. Analyses were conducted using SPSS software (version 23, IBM, Chicago, Illinois).

3. Results

3.1 Study Population (Table 1)

130 patients met the inclusion criteria with 7 patients excluded due to insufficient follow up. Table 1 outlines the baseline characteristics of the 123 patients in the study population. The population was predominately male (87%) with hypertension (42%), an average
CHA₂DS₂-VASC score of 1.6 ± 1.1, elevated BMI (30 ± 4.4kg/m²), continuous duration of AF of 15 ± 17 months, moderate left atrial enlargement (LA area 31 ± 8.7cm²) and mildly reduced ejection fraction (48 ± 13%). All patients underwent 4 vein PV isolation and LA posterior wall isolation strategy. Culprit vein isolation alone and SVC isolation was not performed. Pulmonary vein isolation was achieved in 100% of patients, with additional posterior wall isolation achieved in 79%.

3.2 Multi and single procedural success (Tables 2)

Freedom from AF or atrial tachycardia was achieved in 76% (94) patients after 1.2 ± 0.4 procedures, at a mean follow up of 24 ± 8.1 months. Freedom from AF/AT was not associated with co-morbidities, AF burden, ventricular function, atrial dimensions, average CHA₂DS₂-VASC score or anti-arrhythmic drug use. Only termination of AF during ablation was associated with multi-procedural success (20% vs 3.4%, p=0.025).

Single procedure success was achieved in 63% (78) patients. Of those with recurrence (45), 42% (19) underwent repeat ablation. Of those undergoing repeat ablation, three patients (15%) had further recurrence post redo-ablation, with the remaining patients having no further recurrence. Pulmonary vein reconnection was present in 73% (14/19), and posterior wall reconnection in 68% (13/19) of patients at repeat ablation with re-isolation successfully achieved in all cases.

3.3 Pulmonary vein cycle length analysis (Figure 2, Tables 3A and 3B)

The average PVCL across the cohort (PV₄VAverage) was 177 ± 46 ms with the average fastest vein (PV₉VAverage) of 166 ± 25 ms and the average shortest measured cycle length of 101 ± 32 ms. Average AF cycle length (LAA) was 172 ± 24ms, and posterior wall cycle length (PWAverage) was 189 ± 34. Table 2 compares the PVCL characteristics between patients with or without AF/AT recurrence. There was no significant difference in PV₄VAverage (p=0.92, PV₉VAverage (p=0.69), PVfast (p=0.82) between those with and without AF/AT recurrence. The percentage of patients with either a PV₄VAverage/LAA, PV₉VAverage/LAA or PVfast/LAA ratio less than one, was not significantly different between the groups (p=0.71, p=0.58, p=1.0). In
the present study the PVfast/LAA ratio <69% as previously defined by Pascale et al was not predictive of recurrence (recurrence versus multi-procedural success: 55% vs 69%, p=0.16). Similarly, the presence of AF within the PV, was not predictive of recurrence (31% vs 47%, p=0.13). The posterior wall cycle length (PW\text{Average}) did not differ between the groups (p=0.63, Table 3) and correlated strongly with PV4V\text{Average} (R=0.76, p<0.001).

4. Discussion

This study prospectively evaluated the relationship between PV activity and multi procedure success following catheter ablation in patients with persistent AF. The primary finding was that the rapidity of PV electrical activity during AF, whether determined by:

1. the overall average pulmonary vein cycle length (PV4V\text{average});
2. the average of the pulmonary vein with the most rapid activation (PVF\text{average});
3. the shortest measured cycle length (PV\text{Fast}); or
4. the presence of fibrillatory activity within a vein

either absolutely or relative to AF cycle length (LAA cycle length), was not predictive of multi-procedural freedom from AT/AF in patients with persistent AF.

4.1 Pulmonary vein activity and persistent AF

The pulmonary veins are responsible for the majority of triggers for AF however their role in transition to more persistent forms is not well understood\textsuperscript{276}. Patients may experience paroxysms of AF and not progress to persistent AF and in contrast persistent AF may be the first presentation\textsuperscript{276}. Although rapid PV activity is generally the trigger for the initiation of paroxysmal AF\textsuperscript{145}, other factors may be important in the maintenance of persistent AF\textsuperscript{277}. Atrial electrical and structural remodeling has been proposed as the “second factor” responsible for the maintenance of AF. However contrary to a belief that persistent AF is representative of a more diffuse process “beyond the pulmonary veins” PV isolation alone is an effective tool in the majority of persistent AF patients\textsuperscript{168-169}.

Insights into the characteristics of PV activity at the time of CA may be useful in identifying patients most likely to benefit from a PV based ablation approach. In particular, the rapidity of PV electrical activity during AF has been purported as a potential mechanism, however single center studies, evaluating the impact of PVCL during AF upon clinical outcomes have
shown mixed results. Pascale et al reported that the rapid activity in the PVs, as determined by the \( \text{PV}_{\text{fast}}/\text{LAA} \) ratio, was predictive of acute termination of AF and long term multi-procedural outcome, arguing that this relative difference in cycle lengths generated a “gradient” serving to “refuel” the substrate maintaining AF. O’Donnell et al demonstrated that PVs responsible for initiating AF displayed a shorter cycle length during AF, suggesting a role in maintaining AF in addition to initiation however these findings were confined to paroxysmal AF. Lim et al, utilized high density body surface mapping of persistent AF and identified the PV’s and surrounding antrum as the predominant location of re-entrant and focal drivers.

The present study examined the role of pulmonary vein cycle length and fibrillation within the PV and its impact on catheter ablation outcomes in a systematic prospective fashion. We found no relationship between markers of PV activity either absolutely or as a ratio to LAA cycle length in identifying patients more likely to benefit from CA. These findings are in contrast to the earlier study by Pascale et al and may in part be explained by several important differences: ablation strategy (PVI and posterior wall isolation vs PVI plus stepwise ablation), study population size (123 versus 94) and the intensity and duration of follow-up. In addition we analyzed 100 consecutive cycles for each of the veins as opposed to identifying the single shortest interval of PVCL in the earlier study. As such the rapidity of electrical activity within the PVs was not demonstrated to be a useful marker to identify patients most likely to benefit from a PV based ablation approach.

### 4.2 Rapid PV electrical activity – Driver of AF or marker of remodeling?

Rather than being attributable to the rate of PV activity, the success of catheter ablation in some patients with persistent AF and not in others may in part be due to individual differences in the role of factors beyond pulmonary vein isolation. Greater contributions of the autonomic ganglia, the presence of non PV triggers, and atrial fibrosis to the maintenance of AF may in part explain the limited success of PVI in some patients. In canine studies, Onkka et al identified sympathetic nerve fibres in the vagal nerve capable of accelerating heart rate when stimulated, whilst Wu et al identified the ligament of Marshall in addition to the PVs as sources of rapid activations in sustained AF in the canine model. Natale and coworkers identified non PV triggers as responsible for recurrent AF in the presence of enduring PVI. Atrial tissue fibrosis as determined by cardiac MRI is predictive.
of arrhythmia outcome in patients undergoing catheter ablation\textsuperscript{282} with a randomized study ongoing to assess the role of scar isolation. Bai et al reported improved success of PVI plus proven posterior wall isolation (65\% vs 20\% at 12 months, p<0.001)\textsuperscript{285} for catheter ablation for persistent AF suggesting the posterior wall may be important in AF maintenance.

4.3 Limitations

The ablation strategy included posterior wall isolation with the present study commenced before the publication of STAR AF \textsuperscript{2169}. Although not specifically evaluated in STAR AF 2, this remains a commonly performed ablation strategy in persistent AF. The findings from the current study were determined in patients who underwent PVI plus posterior wall isolation at the time of first procedure and the clinical efficacy of culprit PVI and PVI alone was not examined. A randomized comparison of PVI vs PVI plus posterior wall isolation is the subject of further studies. Although higher than in other similar studies, the lack of continuous monitoring in all patients may have under-reported the true incidence of AF recurrence. Repeat procedures to determine the presence of PV reconnection were only performed for arrhythmia recurrence and as such the presence of enduring PVI in those without recurrence is not known. PV recordings for 60 seconds may have limited the capacity to detect infrequent intermittent rapid activity. Although amiodarone was discontinued one week prior to ablation a residual effect upon PVCL cannot be excluded given its long half-life. The relationship between coronary sinus and PVCL was not formally assessed and may provide further insights into the relationship between atrial substrate and PV activity. Due to the very nature of fibrillatory activity, annotation of the leading wavefront may vary between observers and could, in part, be overcome by dominant frequency analysis.

5. Conclusion

Pulmonary vein activity including PV fibrillation both in isolation and relative to left atrial AF cycle length, was not predictive of outcome in patients with persistent AF undergoing catheter ablation. As such PV activity does not identify patients most likely to benefit from a PV based ablation strategy.
6. Tables and figures

6.1 Tables

Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
</tr>
<tr>
<td>Age (years) 62 ± 9.1</td>
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<tr>
<td>Gender (% male) 87%</td>
</tr>
<tr>
<td>Hypertension (%) 42%</td>
</tr>
<tr>
<td>Diabetes (%) 15%</td>
</tr>
<tr>
<td>Average CHA2DS2-VASC Score 1.6 ± 1.1</td>
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<tr>
<td>Obstructive sleep apnoea (%) 16%</td>
</tr>
<tr>
<td>BMI (kg/m2) 30 ± 4.3</td>
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<tr>
<td>Longstanding persistent AF 62%</td>
</tr>
<tr>
<td>Time since AF diagnosis (months) 59 ± 70</td>
</tr>
<tr>
<td>Time from diagnosis to persistent AF (months) 44 ± 70</td>
</tr>
<tr>
<td>Duration of continuous AF pre-procedure (months) 16 ± 17</td>
</tr>
<tr>
<td>Duration of follow up (months) 24 ± 8.1</td>
</tr>
<tr>
<td><strong>Echocardiographic parameters</strong></td>
</tr>
<tr>
<td>LA area (cm²) 31 ± 8.7</td>
</tr>
<tr>
<td>LA diameter (mm) 48 ± 8.0</td>
</tr>
<tr>
<td>Average LVEF (%) 49 ± 13%</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td>Beta-blocker 52% (64)</td>
</tr>
<tr>
<td>Failed AADs 57% (70)</td>
</tr>
<tr>
<td>Sotalol 22% (27)</td>
</tr>
<tr>
<td>Flecanide 15% (18)</td>
</tr>
<tr>
<td>Amiodarone 20% (25)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB 60% (74)</td>
</tr>
<tr>
<td>Anticoagulation 92% (113)</td>
</tr>
<tr>
<td>Continuous monitoring 29% (36)</td>
</tr>
<tr>
<td><strong>Procedural characteristics</strong></td>
</tr>
<tr>
<td>Pulmonary Vein Isolation (%) 100%</td>
</tr>
<tr>
<td>Posterior wall isolation achieved (%) 79% (97)</td>
</tr>
<tr>
<td>Cavo-tricuspid isthmus ablation (%) 9.8% (12)</td>
</tr>
<tr>
<td>AF termination during procedure* 16% (20)</td>
</tr>
<tr>
<td>Electrical cardioversion during procedure 84% (103)</td>
</tr>
<tr>
<td>Ablation time (mins) 175 ± 46</td>
</tr>
<tr>
<td>Fluoroscopy time (mins) 15.4 ± 4.5</td>
</tr>
<tr>
<td>Radiation dose (mGy) 121 ± 130</td>
</tr>
<tr>
<td>Dose area product (mGy/cm²) 18469 ± 12718</td>
</tr>
<tr>
<td>Re-do ablation (%) 15% (18)</td>
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<tr>
<td>Average number of procedures (%) 1.2</td>
</tr>
<tr>
<td><strong>Pulmonary vein activity</strong></td>
</tr>
<tr>
<td>PV₄VAverage (ms) 177 ± 25</td>
</tr>
<tr>
<td>PV₅VAverage (ms) 166 ± 25</td>
</tr>
<tr>
<td>PVfast (ms) 101 ± 32</td>
</tr>
<tr>
<td>LAA CL (ms) 172 ± 24</td>
</tr>
<tr>
<td>Posterior WallAverage (ms) 189 ± 34</td>
</tr>
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</table>
* Includes organisation of AF into sustained atrial flutter or tachycardia and then subsequently terminated with further ablation during the same procedure.

Table 2 - Comparison of baseline and procedural characteristics between patients with and without multi-procedure success and AF/AT recurrence

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Multi-procedural success</th>
<th>P-value</th>
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<tbody>
<tr>
<td>n=123</td>
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<tr>
<td>Age (years)</td>
<td>60 ± 7.8</td>
<td>62 ± 9.5</td>
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<tr>
<td>Hypertension (%)</td>
<td>50% (15)</td>
<td>54% (37)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>14% (4)</td>
<td>16% (15)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>94 ± 15</td>
<td>94 ± 17</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 2.9</td>
<td>30 ± 4.6</td>
</tr>
<tr>
<td>OSA* (%)</td>
<td>21% (6)</td>
<td>15% (14)</td>
</tr>
<tr>
<td>Average CHA²DS²VASC score</td>
<td>1.7 ± 1.0</td>
<td>1.6 ± 1.1</td>
</tr>
<tr>
<td>Duration of follow up</td>
<td>26 ± 8.1</td>
<td>23 ± 8.1</td>
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<tr>
<td>Average number of procedures (%)</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Continuous monitoring (%)</td>
<td>41% (12)</td>
<td>26% (24)</td>
</tr>
<tr>
<td>Heart failure (LVEF &lt;50%) (%)</td>
<td>37% (11)</td>
<td>33% (31)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>48 ± 13%</td>
<td>49 ± 13%</td>
</tr>
<tr>
<td>Time since AF diagnosis (months)</td>
<td>61 ± 73</td>
<td>53 ± 57</td>
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<tr>
<td>Time from diagnosis to persistent AF (months)</td>
<td>45 ± 74</td>
<td>40 ± 58</td>
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<tr>
<td>Continuous AF duration (months)</td>
<td>17 ± 19</td>
<td>15 ± 16</td>
</tr>
<tr>
<td>Longstanding persistent AF (%)</td>
<td>52% (15)</td>
<td>50% (47)</td>
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<tr>
<td>Anti-arrhythmic drug (%)</td>
<td>55% (16)</td>
<td>57% (54)</td>
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<td>Sotalol</td>
<td>17% (5)</td>
<td>23% (22)</td>
</tr>
<tr>
<td>Flecanide</td>
<td>24% (7)</td>
<td>12% (11)</td>
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<tr>
<td>Amiodarone</td>
<td>14% (4)</td>
<td>22% (22)</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>52% (15)</td>
<td>52% (49)</td>
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<tr>
<td>Anti-arrhythmic drug at follow up (%)</td>
<td>55% (16)</td>
<td>37% (35)</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>49 ± 9.1</td>
<td>46 ± 7.9</td>
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<tr>
<td>LA area (cm²)</td>
<td>30 ± 4.7</td>
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<tr>
<td>Index procedural characteristics</td>
<td>83% (24)</td>
<td>88% (73/83)</td>
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<tr>
<td>Posterior wall isolated</td>
<td>3.4% (1)</td>
<td>20% (19)</td>
</tr>
</tbody>
</table>

* OSA formally diagnosed at time of procedure
** as determined by overall average PVCL (PV4Average)
*** including ablation beyond PVI excluding CTI
Table 3 Pulmonary vein electrical activity and procedural success

Table 3A Pulmonary vein electrical activity stratified by multi-procedural success

<table>
<thead>
<tr>
<th>PVCL measured parameter</th>
<th>Multi-procedural success</th>
<th>P value</th>
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<tr>
<td></td>
<td>Yes (n=94)</td>
<td>No (n=29)</td>
</tr>
<tr>
<td>N=123</td>
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<tr>
<td>PV4V average (ms)</td>
<td>178 ± 28</td>
<td>177 ± 24</td>
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<tr>
<td>PVFV average (ms)</td>
<td>164 ± 26</td>
<td>166 ± 24</td>
</tr>
<tr>
<td>PVfast (ms)</td>
<td>102 ± 26</td>
<td>101±35</td>
</tr>
<tr>
<td>LAA CL (ms)</td>
<td>170 ± 27</td>
<td>173 ± 23</td>
</tr>
<tr>
<td>PW average</td>
<td>188 ± 30</td>
<td>189 ± 50</td>
</tr>
<tr>
<td>PV4V average / LAA</td>
<td>1.05 ± 0.11</td>
<td>1.06 ± 0.21</td>
</tr>
<tr>
<td>PVFV average / LAA</td>
<td>0.97 ± 0.11</td>
<td>0.97 ± 0.12</td>
</tr>
<tr>
<td>PVfast / LAA</td>
<td>0.61 ± 0.14</td>
<td>0.58 ± 0.18</td>
</tr>
<tr>
<td>PV4V average / LAA &lt; 1 (%)</td>
<td>34% (10)</td>
<td>38% (36)</td>
</tr>
<tr>
<td>PVFV average / LAA &lt; 1 (%)</td>
<td>62% (18)</td>
<td>69% (65)</td>
</tr>
<tr>
<td>PVfast / LAA &lt; 1 (%)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>PVfast / LAA &lt; 69% (%)</td>
<td>55% (16)</td>
<td>69% (65)</td>
</tr>
<tr>
<td>AF in pulmonary vein</td>
<td>31% (9)</td>
<td>47% (44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>Single-procedural success</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=78)</td>
<td>No (n=45)</td>
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<tr>
<td>N=123</td>
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<tr>
<td>PV4V average (ms)</td>
<td>178 ± 25</td>
<td>176 ± 26</td>
</tr>
<tr>
<td>PVFV average (ms)</td>
<td>164 ± 26</td>
<td>167 ± 24</td>
</tr>
<tr>
<td>PVfast (ms)</td>
<td>102 ± 35</td>
<td>100 ± 27</td>
</tr>
<tr>
<td>LAA CL (ms)</td>
<td>173 ± 23</td>
<td>171 ± 25</td>
</tr>
<tr>
<td>PW average</td>
<td>188 ± 48</td>
<td>186 ± 28</td>
</tr>
<tr>
<td>PV4V average / LAA</td>
<td>1.07 ± 0.22</td>
<td>1.03 ± 0.11</td>
</tr>
<tr>
<td>PVFV average / LAA</td>
<td>0.97 ± 0.12</td>
<td>0.96 ± 0.11</td>
</tr>
<tr>
<td>PVfast / LAA</td>
<td>0.58 ± 0.18</td>
<td>0.59 ± 0.15</td>
</tr>
<tr>
<td>PV4V average / LAA &lt; 1 (%)</td>
<td>37% (29)</td>
<td>38% (17)</td>
</tr>
<tr>
<td>PVFV average / LAA &lt; 1 (%)</td>
<td>67% (52)</td>
<td>69% (31)</td>
</tr>
<tr>
<td>PVfast / LAA &lt; 1 (%)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>PVfast / LAA &lt; 69% (%)</td>
<td>68% (53)</td>
<td>62% (28)</td>
</tr>
<tr>
<td>AF in pulmonary vein</td>
<td>47% (44)</td>
<td>31% (9)</td>
</tr>
</tbody>
</table>
6.2 Figures

Figure 1: Pulmonary vein cycle length measurement

**Pulmonary vein cycle length measurement**

**Panel A** demonstrates measurement of pulmonary vein cycle length. Cycle length was measured from leading earliest activation of each wavefront, irrespective of changes in activation pattern as shown. Panel B illustrates atrial fibrillation occurring in the pulmonary vein, with continuous activity in PV15-16 and PV17-18 and PVCL intervals of <100ms between wavefronts. Panel C illustrates a patient with slow PV activity with PV4Vaverage cycle length of 222ms. Panel D illustrates a patient with rapid PV activity with PV4Vaverage of 137ms. All electrograms displayed at 200mm/s sweep speed. Exploded figure below showed the annotation of PV wavefronts in AF, with the leading edge outlined in red.
Exploded figure of Figure 1 Panel B

Pulmonary vein AF
Figure 2: Pulmonary vein electrical activity and multi-procedural success

Figure 2: A graphical representation of PV electrical activity and the multi-procedural outcome. The presence of AF within a pulmonary vein (Figure 2a), Absolute PVCL values (Figure 2B) and the average ratio of each absolute parameter and the average LAA cycle length (Figure 2C) and were not predictive of multi-procedural success.
CHAPTER 8: Determining the Optimal Dose of Adenosine for Unmasking Dormant Pulmonary Vein Conduction Following Atrial Fibrillation Ablation: Electrophysiological and Hemodynamic Assessment. DORMANT-AF study

1. Introduction
Durable pulmonary vein isolation remains the cornerstone of AF ablation\textsuperscript{145,169}. There has been much interest in the role of adenosine in identifying dormant PV/LA conduction following acute pulmonary vein isolation (PVI), and its implications for long-term clinical outcome\textsuperscript{286-287}. However recent single-centre and large multicentre trials have reported conflicting results\textsuperscript{288-290}. The confusion surrounding the role of adenosine may be in part explained by variation in adenosine dosing strategies and dosing endpoints among published studies\textsuperscript{160, 190, 192, 291-292}. Given the unique pharmacokinetics of adenosine, in particular an ultra-short half-life, dosing is likely to have a significant impact on its usefulness. Nonetheless, a systematic characterisation of the electrophysiological and haemodynamic effects of adenosine has not been previously explored. We sought to undertake a comprehensive prospective dose finding study to determine: (1) the dose response relationship of adenosine and pulmonary vein reconnection and (2) the relationship between electrophysiological and haemodynamic indicators of adenosine activity and PV reconnection and (3) establish practical dosing guidelines for the use of adenosine in PVI.

2. Methods
2.1 Patient selection
This multicentre study enrolled consecutive patients undergoing index AF ablation from July 2015 to February 2016. Exclusion criteria consisted of: (1) refusal to consent to study; (2) a history or severe or poorly controlled airway disease; (3) pre-existing complete heart block, (4) known hypersensitivity to adenosine; (5) severe valvular stenosis or (6) untreated or un-evaluated coronary artery disease. The study protocol and design were approved by the local ethics committee at each of the centres involved in the trial.
2.2 Catheter ablation procedure

Oral anticoagulation was discontinued 24-48hrs pre-procedure with the exception of vitamin K antagonists, which were continued. Anti-arrhythmic medication was discontinued 5 half lives pre-procedure with the exception of amiodarone. All procedures were performed under general anaesthesia with the assistance of a 3D mapping system (NAVX, St Jude Medical). After exclusion of intra-cardiac thrombosis, a deca and quad polar catheter were positioned in the coronary sinus and HIS position respectively. Tran-oesophageal echocardiographic guided double trans-septal punctures were performed (SL1 8 and 8.5F sheaths). Unfractionated heparin was administered to achieve an activated clotting time of >350 seconds. Mapping of the left atrium and pulmonary veins (PVs) was performed with a 20 pole spiral catheter, and ablation with a 4mm irrigated-tipped catheter (Flexibility D/F, St Jude Medical). Bidirectional PVI was the endpoint in all procedures and was achieved with wide antral circumferential ablation (WACA) with addition ablation within the WACA to achieve isolation if required. Additional ablation lines or substrate modification were performed at operator discretion.

2.3 Adenosine dosing protocol

Electrophysiologic and haemodynamic response to three different doses of adenosine (12, 18 and 24mg) was assessed. Adenosine challenge was performed during CS pacing at 600ms following acute PVI. If the superior and inferior veins isolated en bloc, then the superior and inferior veins were tested simultaneously with adenosine The ablation catheter was always used in concert with the multipolar catheter in the opposing vein to assess dormant conduction during adenosine challenge if:

1. the upper and lower veins isolated en bloc and as such were electrically connected to each other and
2. no ablation was performed on the inter-venous ridge.

Otherwise, the veins were individually assessed with multipolar catheter in each upper and lower vein with each vein tested separately with all three doses. The multipolar catheter and ablation catheter, where utilized, were positioned at the pulmonary venous ostium as determined by 3D mapping and local PV electrograms. Each dose of adenosine was diluted with normal saline to 10mL volume and administered in a random order as determined by a computer algorithm (random.org random sequence generator). The primary operator, anaesthetist and technician were blinded to the dose order, which was administered
sequentially following the intervening complete recovery of conduction and blood pressure (approximately 2-4 minutes). Each dose was administered in a standardised manner via a cubital 18-20 gauge intravenous canula in the forearm as a rapid bolus injection (recorded as ‘time zero’ in the log), immediately followed by a 10mL rapid saline flush. In the event of adenosine mediated PV reconnection, all 3 doses were completed then further ablation performed and the veins retested with each adenosine dose in the original manner. Ablation was completed with the endpoint of no further dormant conduction.

2.4 Pulmonary vein reconnection
Adenosine mediated PV dormant conduction was defined as the transient appearance of associated PV signals in the multipolar and or ablation catheter occurring within 2 minutes following adenosine administration. Spontaneous reconnection was defined as the occurrence of PV/LA reconnection in the absence of adenosine activity.

2.5 Hemodynamic measurements
All patients had general anaesthesia and continuous blood pressure monitoring via a radial arterial pressure line. Hemodynamic support was standardised with a metaraminol or phenylephrine infusion aiming for baseline SBP > 100mmHg prior to adenosine administration, additional boluses could be administered at the anaesthetist’s discretion. The following hemodynamic parameters were recorded:

1. Baseline blood pressure (BP): BP recorded immediately prior to administration of each adenosine dose.
2. Nadir BP: the lowest BP recording after administration of each adenosine dose following the return of 1:1 atrio-ventricular conduction (to avoid the confounding effect on systemic BP of low cardiac output in the setting of adenosine induced transient AVB).
3. Time to nadir BP: the time from time zero to the nadir BP

2.6 Electrophysiologic measurements
Electrograms were continuously recorded utilising EP WorkMate (St Jude Medical) or CardioLab (General Electric). All intervals were measured offline using inbuilt horizontal electronic callipers. For each adenosine dose, the following measurements were recorded:
1. Time zero time point at which the adenosine dose was administered.
2. Baseline PR interval just prior to time zero.
3. Interval from time zero to the p wave onset of the first beat with PR prolongation >20ms from baseline. This approximates the time from administration to initial onset of adenosine activity.
4. Interval from time zero to the onset of the first non-conducted p wave. This approximated the time from adenosine administration to full adenosine activity.
5. Interval from the onset of the first non-conducted p waves to the onset of the first conducted p wave. This approximates the duration of maximal adenosine activity.
6. The interval from the onset of the first beat with PR prolongation >20ms to the onset of the first p wave with baseline PR interval (i.e. PR interval recovery). This approximates the total time of adenosine activity.

2.7 Statistical analysis
Data are expressed as mean ± standard deviation (SD) unless otherwise indicated. After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student’s t test for continuous variables, or the Chi-squared test for categorical variables. A two-tailed p value of <0.05 was considered significant. Correlation was determined by using the Pearson Product-Moment correlation coefficient and a linear regression model. Analyses were conducted using SPSS software (version 23, IBM, Chicago, Illinois).

3. Results

3.1 Study Population (Table 1 and 2)
55 consecutive patients undergoing AF ablation at 2 centres were screened. Five were excluded, three due to the presence of significant airway disease, 1 patient with significant baseline hypotension and one patient refused to consent. 50 patients were subsequently included in the analysis. Their baseline demographic and procedural details are listed in Table 1. Patients were predominately male (66%), hypertensive (52%) with paroxysmal AF (72%) and an average CHADS2 score 1.3 ±1.0. Average LVEF was normal (58.9 ± 6.7%) with mild LA enlargement (LA area: 24.6 ± 6.9cm², LA diameter 4.2 ± 0.8cm). Nine (18%)
patients had 3-vein anatomy with a left common PV in all cases, the remainder having 4 pulmonary veins. Pulmonary vein isolation was achieved in all (100%) patients, with 12 patients (24%) receiving further substrate modification involving posterior LA isolation. Overall, 339 adenosine doses (113 at each dose) were administered assessing 191 individual PVs with 585 individual vein challenges.

3.2 Pulmonary vein reconnection (Figure 1)
Pulmonary vein reconnection occurred in 28% (14 patients) and 16.5% (32) of pulmonary veins assessed. This represented 35 individual doses, and 63 individual vein challenges. All cases (100%) of PV reconnection were associated with transient AVB with at least one non-conducted atrial paced beat (100% vs. 83%, p=0.007). There were no instances of dormant conduction in the absence of AV block. In those veins demonstrating dormant conduction (16%), no dormant conduction was evident in those veins at adenosine doses insufficient to produce AV block. The presence of dormant PV conduction predicted the subsequent occurrence of spontaneous PV reconnection (Table 2). In this study, all cases of spontaneous PV reconnection following adenosine mediated reconnection persisted in the setting of adenosine mediated reconnection. Such cases were interpreted as having both adenosine mediated and spontaneous reconnection (33%) and accounted for much of the predictive relationship demonstrated in this study (see table). Spontaneous PV reconnection occurred in 11% of PVs in the absence of adenosine mediated reconnection (p=0.004, OR=4.22, 95%CI: 1.51-11.83) Additional RF was applied at the site of PV reconnection and adenosine at all 3 doses repeated to confirm electrical isolation. There were no instances of spontaneous reconnection following the application of further ablation for adenosine-mediated reconnection.

There were significantly longer procedure times (dormant conduction vs no dormant conduction: 190 ± 30 vs 160 ± 36 mins, p=0.01) and longer RF times (48 ± 9.8 vs 42 ± 8.5 mins, p=0.024) in patients with dormant conduction compared to those without dormant conduction.

3.3 Electrophysiological Parameters (Table 4)
The electrophysiological markers of adenosine activity at each adenosine dose (339 in total, 113 challenges at each dose) were assessed and are summarised in Table 3. There was no difference in time from administration to the onset of adenosine activity (time to PR
prolongation or AV block) between the doses. AVB was more likely to occur at 24mg compared to 12mg of adenosine (92% vs. 82%, p=0.019) but no more likely than 18mg (91%, p=0.62). Similarly, the duration of adenosine cardiac activity (the time from PR prolongation to PR recovery) differed significantly between the 24mg and 12mg doses (35.4 ± 10.7s vs. 28.6 ± 11.2secs, p<0.001), but not between the 24 and 18mg doses (33.1 ± 11.8secs, p=0.15). There was a significant increase in the duration of AVB with 12mg (12.0 ± 8.9secs) vs. 18mg (16.1 ± 9.1s, p=0.001) vs. 24mg of adenosine (19.0 ± 9.3s, p<0.001).

Given the requirement for adenosine induced AVB to unmask dormant PV conduction, the dose per kg (both actual and ideal body weight) of adenosine was correlated with the duration of AVB (Figure 2). A significant linear relationship between dose/kg and duration of AVB was demonstrated (R=0.51, p<0.001). Doses above 0.3mg/kg were 100% sensitive in achieving AV block.

3.4 Hemodynamic Parameters (Table 5)

Baseline blood pressure was comparable prior to each dose and there was no difference on time to blood pressure nadir between the doses. Both the absolute magnitude and percentage of average mean blood pressure drop was significantly greater in the 24mg and 18mg compared to the 12mg doses (ΔMBP; 12 vs. 24mg: -22 ± 10 vs. -27 ± 12mmHg, p<0.001; 12 vs. 18mg, -26 ± 13mmHg vs. -41) with a ceiling effect between the 18 and 24mg doses (p=0.21, p=0.34). There was no difference in blood pressure response between doses responsible for dormant PV conduction and those that did not (p=0.71).

3.5 Body Weight and Adenosine dose (Figure 3)

To assess the impact of body weight upon measured electrophysiological and haemodynamic parameters the study population was stratified according to body weight, adenosine doses in patients weighing ≥90kg (n=144) demonstrated a significantly attenuated response. There was a significant reduction in the occurrence of AV block (92% vs. 82%, p=0.009), duration of AVB (12.98 ± 8.76 vs. 17.56 ± 9.71s, p<0.001) and duration of adenosine cardiac activity (28.4 ± 9.9 vs. 35.10 ± 11.8s, p<0.001) across all adenosine doses compared with patients <90kg (n=195). In addition, the time to onset of adenosine activity (PR prolongation, p=0.007 and AV block onset, p=0.011) was also reduced (see Table 4). Significant differences in the duration of AVB and duration of adenosine cardiac activity were demonstrable at each individual dose (12mg: p=0.0052, p=0.0046; 18mg: p=0.0073,
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p=0.0041; 24mg: p=0.041, p=0.0095). Similarly, an attenuated hemodynamic response to doses in patients ≥90kg was also noted (ΔMBP: ≥90kg vs. <90kg: -21 ± 8.3 vs. -29 ± 13mmHg, p<0.001).

Patients were further stratified into four groups (<70kg, 70-90kg, 91-110kg and >110kg). There were no significant differences between the 70-90kg and 91-110kg groups with respect to both electrophysiological and hemodynamic parameters (70-90kg vs. 91-110kg: AVB: 91% vs. 91%, p=1.0; duration of AVB: 14.0 vs. 14.6s, p=0.60; mean percentage drop in MBP: 33.7% vs. -35.6%, p=0.22). Hence patients in these groups were combined and the doses were compared between three groups (<70kg, 70-110kg and >110kg). There was a significant reduction in the incidence of AVB in patients >110kg (65% vs. 91% in 70-110kg group; p<0.001; and 97% in weight <70kg, p<0.001), and in the duration of AVB when present (>110kg 10.1seconds vs. 14.3s in 70-110kg group, p=0.006; vs. <70kg: 10.1s vs. 23.8s, p<0.001). Hemodynamic effects (average percentage drop in MBP from baseline) were attenuated in patients >110kg (24.5% vs. 34.9% in 70-110kg, p<0.001; vs. 43.8% in <70kg, p<0.001). Notably, the ceiling effect with respect electrophysiological and hemodynamic parameters observed with doses above 18mg described above, was not demonstrable when patients >110kg were considered in isolation. The distribution of weights across the study population, with the highest number in the 70-110kg group (66%), likely explains the apparent ‘ceiling’ effect of doses, when the cohort was analyzed as a whole. Practical guidance for adenosine dose selection, incorporating weight variability, is provided in figure 4.

4. Discussion
The present study provides a: (1) systematic evaluation of the effect of varying adenosine doses on the ability to unmask dormant pulmonary vein conduction following acute pulmonary vein isolation; (2) characterize the relationship between the electrophysiological and hemodynamic effects of adenosine and dormant PV conduction. The major findings from the present study are:

1. Adenosine mediated dormant pulmonary vein conduction was only demonstrated at doses sufficient to demonstrate AVB with at least one non-conducted atrial paced beat;

2. Other than the requirement to achieve AVB, there is no demonstrable relationship between dormant conduction and varying doses of adenosine;
3. The presence of dormant PV conduction following acute pulmonary vein isolation is predictive of spontaneous PV reconnection (11% vs. 3% of doses, \( p=0.014; \) OR=4.34, 95%CI: 1.21-14.53);
4. In patients < 110kg, there was no advantage in adenosine doses beyond 18mg with a ceiling effect upon electrophysiological and hemodynamic markers of adenosine activity demonstrated.
5. In patients > 110kg there was relative resistance to adenosine with AV block not achieved in 35%.

The practical implications are that if adenosine is being utilized to determine dormant PV conduction following PVI it must be administered in a dose sufficient to cause AVB with at least one non-conducted atrial paced beat. On the basis of the present study the following dose based on weight are recommended:
- Patients < 70kg - adenosine minimum 12mg
- Patients 70-110kg - adenosine minimum 18mg
- Patients >110kg – adenosine 24mg or higher aiming for dose >0.3mg/kg.
- Repeat adenosine at higher dose if AVB not achieved

4.1 The Mechanism of Adenosine in AF ablation
The present study demonstrates the importance of sufficient adenosine to achieve AVB as required to illicit dormant PV conduction. Datino and colleagues elegantly characterized the mechanism of adenosine in unmasking dormant conduction in the canine model. Adenosine hyperpolarizes vulnerable atrial myocytes via potassium channels (\( I_{\text{KADO}} \)), which restores voltage-dependent sodium channels (\( I_{\text{Na}} \)), facilitating electrical conduction and results in transient PV/LA reconnection. However, conduction slowing and AV block is the result of adenosine mediated effects on \( I_{\text{KADO}} \) channels and an inhibition of L-type calcium channels (\( I_{\text{CaL}} \)). Provided AVB was achieved, there was no observable benefit to higher doses in the identification of dormant conduction.

4.2 Clinical Implications
Dosing regimens in trials evaluating adenosine mediated dormant conduction, including the two largest randomized trials, have varied considerably. However the potential impact of adenosine dosing upon the clinical outcomes has not been explored. Macle and
colleagues performed a multi-center randomized controlled trial involving 534 patients with paroxysmal AF with dormant conduction present in 284 (53%). Patients randomized to further ablation had a significant improvement in freedom from AF (69%) compared to those randomized to no further ablation (42%). Importantly Macle et al utilized adenosine at a minimum dose of 12mg which was then titrated to achieve at least one blocked p wave or a sinus pause of > 3 second. In contrast, Kobori et al recruited 2,113 AF patients (33% with non-paroxysmal AF) and randomized 1112 patients to adenosine-triphosphate (ATP) guided pulmonary vein isolation (with further ablation if dormant conduction identified) or no ATP. There was no significant difference in freedom from AF at 12 months between the groups. A standard dose of 0.4mg/kg of ATP as a single rapid bolus was administered with no requirement for conduction slowing or AV block, and the incidence of AV block was not reported. The pharmacological characteristics of ATP and adenosine have been reviewed by Belhassen and colleagues. Doses of 15-40mg of ATP were associated with transient sinus bradycardia or first or second-degree AVB, but not complete AV block. A rapidly infused dose of ATP at 0.3mg/kg in 48 healthy subjects demonstrated sinus bradycardia or conduction slowing in only 48% of patients. In contrast doses of adenosine administered at doses of 0.18mg/kg in 17 subjects were able to achieve AVB in all cases. ATP is completely metabolized to adenosine, which is responsible for the electrophysiological effect of ATP, which may explain its different pharmacological profile to adenosine, and a greater dependence on rate of infusion. Belhassen concluded that ATP possessed half the potency of adenosine at equivalent doses. A dose of 0.4mg/kg of ATP, as utilized by Kobori and colleagues is likely equivalent to 0.2mg/kg of adenosine, at which AV block may not be reliably achieved. Hence, it is possible that a proportion of patients in the ATP guided PVI arm may have had dormant conduction undetected due to an inadequate ATP dose. This may have affected the ability of further ablation to improve outcome as a proportion of patients receiving no additional ablation may have had undetected dormant conduction. Our findings suggest that the varying dosing regimens may in part explain the contradictory results of these large multi-center trials.

4.3 Dormant PV conduction and Spontaneous Reconnection

In our study the occurrence of dormant PV conduction as performed immediately after achieving acute PVI, was predictive of subsequent spontaneous reconnection. However, 3% of veins with no dormant conduction at any dose subsequently developed spontaneous
reconnection over a 30 minute waiting time. This is reflective of differing physiological processes associated with reconnection in each situation. Arjuna et al evaluated 15 patients with cardiac MRI immediately following PVI and demonstrated that the ablation line consisted of both delayed enhancement, consistent with necrosis, and high T2 signal intensity, indicative of edema. Those with subsequent PV reconnection showed a higher proportion of high T2 signal relative to delayed enhancement, compared to those without PV reconnection. This suggests that the mechanism of spontaneous PV reconnection may depend on the resolution of edema between neighboring regions of necrosis. In contrast, adenosine acts via $I_{KAdo}$ in surviving functional myocytes to facilitate dormant conduction. The presence of dormant conduction following acute PVI may reflect both the absence of necrosis and edema. This finding is supported by Jiang et al who found that in patients with both adenosine mediated and spontaneous PV reconnection, such reconnection appeared to occur via the same gap. Das and colleagues recently demonstrated that further ablation at sites of acute reconnection may negate their culpability for sites of subsequent late reconnection. However the pathologic mechanisms responsible for spontaneous and adenosine mediated PV reconnection may differ significantly as acute testing with adenosine does not replace a suitable waiting period for spontaneous recovery.

### 4.4 Dose Relationship to Electrophysiological and Hemodynamic Parameters

In the present study the electrophysiological and hemodynamic effects of adenosine displayed a plateau beyond doses above 18mg in patients less than 110kg (figure 4). This was evident with respect to the occurrence of AVB, the duration of adenosine cardiac activity and the magnitude of blood pressure drop from baseline. This finding is important given the sole determinant for adenosine dose is that dose which reliably achieves AVB to demonstrate dormant PV conduction where it exists. Thus the routine administration of adenosine doses above 18mg may generally not be required in patients less than 110kgs. In contrast there was a relative resistance to adenosine in patients > 110kg with over a third of patients failing to achieve AVB. This finding is not unexpected given the near linear relationship between circulating blood volume and weight, however its impact upon electrophysiological and hemodynamic parameters has not been previously appreciated. It is also of clinical relevance given recent work highlighting the impact of obesity upon AF prevalence and worsened outcomes post AF ablation, and the increasing likelihood of obese patients presenting for AF ablation. Given the typical use of absolute weight for most dosing regimes, this was
utilized for our analysis, however, a similar relationship was also demonstrated when data was stratified according to ideal body weight or body mass index.

4.5 Limitations
Several limitations need to be noted in this study. Firstly, this study focused specifically on adenosine and did not test ATP. Although other studies suggest that the potency of ATP at identical doses is lower than adenosine, given we did not specifically test ATP and its subtly differing pharmacokinetic profile to adenosine, conclusions from this study regarding the dose response relationship of ATP should be made with caution. Secondly, patients failing to manifest AV block at maximal dose (24mg) may have demonstrated AVB at higher doses – however this would have required adenosine doses beyond current dosing guidelines and as such this was not performed. Thirdly, testing of the veins with adenosine immediately following isolation may have resulted in under-identification of dormant conduction. Lastly, in those patients with adenosine-mediated reconnection, whether the increased RF time was due to the achievement of initial PVI or due to additional RF applied to extinguish adenosine-mediated reconnection, was indistinguishable. The increased RF time noted should be interpreted in this context.

5. Conclusions
In patients undergoing adenosine testing for dormant PV conduction following PVI, an adenosine dose sufficient to cause AVB is required to unmask dormant PV conduction. AVB in response to adenosine is significantly reduced in patients weighing more than 110kgs. Patient weight and variable adenosine dosing may in part explain the conflicting results of studies evaluating the role of adenosine to improve freedom from AF following PVI.
6. Tables and Figures

6.1 Tables

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics (n=50)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>66%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18%</td>
</tr>
<tr>
<td>IHD</td>
<td>20%</td>
</tr>
<tr>
<td>Heart Failure (LVEF&lt;50%)</td>
<td>12%</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2%</td>
</tr>
<tr>
<td>% Persistent</td>
<td>28%</td>
</tr>
<tr>
<td>Previous DCR</td>
<td>34%</td>
</tr>
<tr>
<td>SR at procedure</td>
<td>72%</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>5.24 ± 5.9</td>
</tr>
<tr>
<td>LVEF</td>
<td>58.9 ± 6.7%</td>
</tr>
<tr>
<td>LA area cm²</td>
<td>24.6 ± 6.9</td>
</tr>
<tr>
<td>LAVI ml/m²</td>
<td>41.7 ± 12.7</td>
</tr>
<tr>
<td>Antiarrhythmic meds</td>
<td>90%</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>70%</td>
</tr>
<tr>
<td>Average BMI</td>
<td>28.3 ± 5.2</td>
</tr>
<tr>
<td>Average Weight</td>
<td>86.1 ± 19.0</td>
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### Table 2: Procedural characteristics

<table>
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<tr>
<th>Procedural Characteristics</th>
<th>Value</th>
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<tr>
<td>Pulmonary vein isolation</td>
<td>100%</td>
</tr>
<tr>
<td>Posterior wall isolation</td>
<td>18%</td>
</tr>
<tr>
<td>Cavo-tricuspid Isthmus</td>
<td>36%</td>
</tr>
<tr>
<td>Other ablation (slow pathway, focal atrial tachycardia ablation)</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Fluoroscopy time</strong></td>
<td><strong>13.6 ± 4.0 mins</strong></td>
</tr>
<tr>
<td><strong>RF time</strong></td>
<td><strong>43.5 ± 9.0 mins</strong></td>
</tr>
<tr>
<td><strong>Procedure time</strong></td>
<td><strong>164 ± 43 mins</strong></td>
</tr>
<tr>
<td><strong>Radiation dose</strong></td>
<td><strong>65.6 ± 34.8 mGy</strong></td>
</tr>
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</table>
Table 3 – Adenosine mediated and spontaneous reconnection

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<tr>
<th>Adenosine Reconnection</th>
<th>Spontaneous Reconnection</th>
<th>Totals</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (33%)*</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>No</td>
<td>18 (11%)*</td>
<td>152 (89%)</td>
</tr>
<tr>
<td>Totals</td>
<td>25</td>
<td>166</td>
</tr>
</tbody>
</table>
Table 4 – Electrophysiological Parameters

<table>
<thead>
<tr>
<th>N=50 patients</th>
<th>N=339 doses</th>
<th>12mg n=113</th>
<th>18mg n=113</th>
<th>24mg n=113</th>
<th>p value (12 vs. 18)</th>
<th>p value (18 vs. 24)</th>
<th>p value (12 vs. 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline PR</strong> (ms)</td>
<td></td>
<td>179 ± 56.7</td>
<td>183 ± 59.0</td>
<td>182 ± 59.2</td>
<td>0.62</td>
<td>0.96</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Time to PR lengthening (s)</strong></td>
<td></td>
<td>16.2 ± 4.9</td>
<td>15.7 ± 4.8</td>
<td>14.9 ± 5.4</td>
<td>0.49</td>
<td>0.22</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Time to AV block (s)</strong></td>
<td></td>
<td>17.0 ± 4.9</td>
<td>16.6 ± 4.2</td>
<td>16.7 ± 5.4</td>
<td>0.54</td>
<td>0.89</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Any AV block (% doses)</strong></td>
<td></td>
<td>81.5%</td>
<td>90.5%</td>
<td>92.4%</td>
<td>0.059</td>
<td>0.62</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Duration of AV block (s)</strong></td>
<td></td>
<td>12.0 ± 8.9</td>
<td>16.1 ± 9.1</td>
<td>19.0 ± 9.3</td>
<td><strong>0.001</strong></td>
<td><strong>0.025</strong></td>
<td>&lt;0.001</td>
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<tr>
<td><strong>PR prolong. to recovery time (s)</strong></td>
<td></td>
<td>28.6 ± 11.2</td>
<td>33.1 ± 11.8</td>
<td>35.4 ± 10.7</td>
<td><strong>0.007</strong></td>
<td>0.145</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N=50 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=339 doses</td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>12mg (n=113)</th>
<th>18mg (n=113)</th>
<th>24mg (n=113)</th>
<th>p value (12 vs. 18)</th>
<th>p value (18 vs. 24)</th>
<th>p value (12 vs. 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SBP (mmHg)</td>
<td>112 ± 16.7</td>
<td>114 ± 17.8</td>
<td>113 ± 17.5</td>
<td>0.34</td>
<td>0.51</td>
<td>0.78</td>
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<tr>
<td>Baseline MBP (mmHg)</td>
<td>69.3 ± 13.1</td>
<td>69.9 ± 13.1</td>
<td>66.7 ± 11.1</td>
<td>0.73</td>
<td>0.54</td>
<td>0.79</td>
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<tr>
<td>Nadir SBP (mmHg)</td>
<td>79.7 ± 13.2</td>
<td>73.6 ± 13.0</td>
<td>70.6 ± 11.8</td>
<td>&lt;0.001</td>
<td>0.075</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nadir MBP (mmHg)</td>
<td>47.7 ± 9.5</td>
<td>43.2 ± 9.2</td>
<td>41.5 ± 9.2</td>
<td>&lt;0.001</td>
<td>0.15</td>
<td>&lt;0.001</td>
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<tr>
<td>Time to nadir (s)</td>
<td>47.2 ± 9.0</td>
<td>47.4 ± 9.6</td>
<td>48.0 ± 9.0</td>
<td>0.87</td>
<td>0.60</td>
<td>0.48</td>
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<tr>
<td>% drop (SBP)</td>
<td>28.8 ± 10.3</td>
<td>35.3 ± 11.2</td>
<td>37.0 ± 10.1</td>
<td>&lt;0.001</td>
<td>0.21</td>
<td>&lt;0.001</td>
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<tr>
<td>% drop (MBP)</td>
<td>30.5 ± 11.4</td>
<td>37.3 ± 12.8</td>
<td>38.9 ± 12.3</td>
<td>&lt;0.001</td>
<td>0.34</td>
<td>&lt;0.001</td>
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<tr>
<td>Time to BP recovery (s)</td>
<td>73.7 ± 17.4</td>
<td>75.9 ± 16.2</td>
<td>82.8 ± 16.9</td>
<td>0.47</td>
<td>0.017</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

Table 5 – Hemodynamic Parameters
6.2 Figures

Figure 1: Comparisons of doses (A) and occurrence of AV block (B) between veins with and without PV reconnection.

Figure 1A

Total doses administered: 339 doses

- Dormant conduction identified: 35 doses
  - 12mg: 11 doses (31.5%)
  - 18mg: 13 doses (37%)
  - 24mg: 11 doses (31.5%)

- No dormant conduction identified: 304 doses
  - 12mg: 102 doses (33.5%)
  - 18mg: 100 doses (33%)
  - 24mg: 102 doses (33.5%)

Figure 1B

_occurrence of AV block_

\[\star = p<0.01\]

**Occurrence of AV block**

- Dormant conduction
- No dormant conduction

\[\star = p<0.01\]
Figure 2: Comparison of adenosine dose per kg and duration of AV block at each dose.
Figure 3: Body weight and AV block

**Figure 3A**

<table>
<thead>
<tr>
<th>Body Weight Range</th>
<th>Patients, n=50 (%)</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70kg</td>
<td>22%</td>
<td>69</td>
</tr>
<tr>
<td>70-110kg</td>
<td>66%</td>
<td>231</td>
</tr>
<tr>
<td>&gt;110kg</td>
<td>12%</td>
<td>39</td>
</tr>
</tbody>
</table>

Occurrence of AVB (%)

- <70kg: 22%
- 70-110kg: 66%
- >110kg: 12%

Duration of AVB (s)

- <70kg: * 69
- 70-110kg: + 231
- >110kg: 39

**Figure 3B**

- Occurrence of AV block (%): * = p<0.001
- Duration of AV block (s): * = p<0.001, + = p<0.01
Figure 3C

Average % drop in MBP

![Graph showing comparison of percentage drop in MBP between different weight groups.]

Figure 3: A comparison of occurrence of AV block (A), average duration of AV block (B), and average mean percentage drop in MBP (C) between each weight group (<70kg, 70-110kg and >110kg). MBP = mean blood pressure.
Figure 4: Dosing guidance for adenosine use in AF ablation

**Figure 4A**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>&lt; 70kg, n=69</th>
<th>70 - 110 kg, n=231</th>
<th>&gt; 110 kg, n=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>12mg</td>
<td>91.3%</td>
<td>84.4%</td>
<td>53.8%</td>
</tr>
<tr>
<td>18mg</td>
<td>100%</td>
<td>93.5%</td>
<td>61.5%</td>
</tr>
<tr>
<td>24mg</td>
<td>100%</td>
<td>93.5%</td>
<td>69.2%</td>
</tr>
</tbody>
</table>

\[\star p<0.01\]

\[\dagger p<0.05\]
Figure 4B

Figure 4: Practical dosing guidance for adenosine use in AF ablation. The likelihood (A) and duration (B) of AV block at each adenosine dose tested. AVB = atrio-ventricular block

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>&lt;70kg, n=69</th>
<th>70 - 110 kg, n=231</th>
<th>&gt;110 kg, n=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>12mg</td>
<td>19.8</td>
<td>10.8</td>
<td>7.2</td>
</tr>
<tr>
<td>18mg</td>
<td>24.5</td>
<td>14.6</td>
<td>9.9</td>
</tr>
<tr>
<td>24mg</td>
<td>27.2</td>
<td>14.6</td>
<td>13.8</td>
</tr>
</tbody>
</table>
CHAPTER 9: Conclusion and Future Directions

1. Overview

Atrial fibrillation and heart failure are growing epidemics around the world. This thesis has explored several aspects of the interplay between these conditions, with an important emphasis on the evolving role of catheter ablation in this clinical space. In total, seven original research projects, including a fully completed and published prospective multi-center randomized controlled clinical trial were performed, to comprehensively evaluate the relationship between heart failure, atrial fibrillation and the role of catheter ablation (Chapters 2 to 4), including a detailed description of remodeling attributable to heart failure. Two prospective descriptive studies (Chapters 7 and 8) evaluated key aspects of catheter ablation (pulmonary vein electrical activity and intra-procedural adenosine use) from unique perspectives, adding important insights in each area. In total, this body of work makes and important contribution to the existing literature in the area of catheter ablation and heart failure, with the potentially practice changing implications.

2. Summary of findings

Chapter 1 provided a comprehensive review of the literature with respect to atrial and ventricular remodeling in the setting of both atrial fibrillation and heart failure, with a particular focus upon structural remodeling, and its impact upon ventricular function. The under-appreciated impact of heart failure aetiology upon catheter ablation outcomes was specifically evaluated in Chapter 2. That study analyzed a combined dataset of patients with heart failure presenting for catheter ablation across three high volume centers to determine the impact of pre-existing or known causes of heart failure upon outcomes. For the first time, the absence of known heart disease was shown to predict greater improvement in ventricular function, freedom from atrial fibrillation, functional capacity and even mortality.

Chapter 3 was a randomized controlled clinical trial comparing catheter ablation to medical therapy in patients with persistent atrial fibrillation and cardiomyopathy that was otherwise unexplained, and often termed idiopathic or dilated cardiomyopathy. This is the largest published randomized trial of catheter ablation versus medical rate control in heart failure performed to date, the first to specifically evaluate patients with no other explanation for heart failure, the first to rigorously follow up post ablation outcomes with implantable loop
recorders and the first to specifically explore the role of MRI detected ventricular fibrosis on clinical outcome. The finding of dramatic improvements in LVEF, along with reductions in ventricular and atrial dimensions and biomarkers, demonstrated the under-appreciated impact of AF on heart failure in this patient population, with those without MRI detected myocardial fibrosis achieving the best results.

The Chapter 4 expanded on the findings of Chapter 3 by exploring the effect of the restoration of sinus rhythm and improvement of ventricular function upon myocardial fibrosis. In a novel finding, in concert with improvements in ejection fraction, and ventricular dimensions, T1 myocardial times decreased consistent with a regression of diffuse fibrosis. The dramatic improvements in ventricular function seen in the CAMERA-MRI population coupled with serial MRI imaging provided a unique opportunity to explore the reversibility of myocardial fibrosis, which has never been previously explored in this setting.

In contrast to exploring the impact of AF upon ventricular function, Chapter 5 explored the impact of heart failure upon the atria. Whilst the remodeling associated with AF itself, particularly in persistent phenotypes is well described, the additive impact of heart failure in concurrent AF and systolic dysfunction had not been previously explored. The finding that systolic dysfunction exerted an adverse remodeling effect over and above that of AF itself, was novel and provides important insights into the challenges associated with achieving equivalent long term procedural outcomes compared to those without heart failure.

The findings of Chapter 6, that persistent AF phenotypes exhibit bi-atrial electrophysiological changes, emphasised the bi-atrial nature of remodeling processes, and the crucial importance of managing systemic influences upon AF including heart failure and other risk factors. It also validated assessment of the right atrium as a surrogate for the left atrium with respect to invasive substrate analysis.

Pulmonary vein isolation remains the cornerstone of AF ablation, even in the setting of persistent AF, where other substrate modification strategies have yet to be validated in prospective randomized studies. Whilst the role of pulmonary vein ectopy in triggering AF in both paroxysmal AF is well described, its role in maintaining AF in persistent phenotypes is unclear. Chapter 7 was a prospective observational study evaluating the predictive potential of pulmonary vein electrical activity in predicting long-term freedom from AF following
catheter ablation. This study found no relationship between PV activity during AF and clinical outcome. This may suggest that atrial substrate beyond the pulmonary veins may be crucial in maintaining AF, suggesting that extra-pulmonary substrate modification may be a necessary component of a long term success in persistent AF ablation.

Being the only robustly validated endpoint of catheter ablation, procuring durable pulmonary vein isolation remains a crucial objective of catheter ablation. Identifying dormant conduction with the use of adenosine has held some promise in aiding the achievement of this objective but the results of large multi-center trials have been mixed. The systematic dose finding study described in Chapter 8 clarified important unanswered questions regarding the relationship between dormant conduction and electrophysiological (such as AV block) and haemodynamic (blood pressure lowering) effects of adenosine. The novel findings that AV block is required to unmask dormant conduction and that a dose/weight relationship existed with regards to adenosine dosing, add significantly to the literature in this space.

3. Significance of these findings
In interpreting the findings of this body of work, several important points are worthy of more detailed enunciation, with a focus on their clinical significance and relevance to contemporary practice.

3.1 Arrhythmia mediated cardiomyopathy
A crucial and novel finding of this work is, in essence, the description of a novel ‘clinical syndrome’ of arrhythmia-mediated cardiomyopathy whereby ventricular irregularity and the loss of atrial contractile dysfunction can precipitate reduced systolic function in the absence of rapid ventricular rates. Whilst systolic dysfunction due to clearly elevated ventricular rates is well described, persisting systolic impairment even after maximal pharmacological rate control is an important clinical finding. It is important to stress however, that although ‘rapid’ ventricular rates may be absent in patients achieving guideline criteria for adequate rate control, the restoration of sinus rhythm still offers substantially greater rate control than even rate-controlled AF, highlighting an additional benefit of sinus rhythm. The use of catheter ablation as a tool to re-establish sinus rhythm, in patients who had largely failed pharmacological rhythm control, was paramount in demonstrating this ‘clinical syndrome’.

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This study, for the first time, characterizes this syndrome in a prospective randomized fashion in comparison to ongoing atrial fibrillation.

3.2 MRI detected fibrosis and arrhythmia mediated cardiomyopathy
A novel aspect of this research has been the utilization of cardiac MRI imaging to understand both the pathophysiology and the clinical course of arrhythmia-mediated cardiomyopathy both with and without the restoration of sinus rhythm.

3.2.1 Fibrosis and patient selection
The absence of fibrosis on baseline cardiac MRI was highly predictive of normalization of systolic function and was associated with substantially greater improvements in ejection fraction from baseline compared to those with evidence of fibrosis. An inverse negative correlation between the magnitude of ejection fraction improvement and the percentage of late gadolinium enhancement was also demonstrated.

The physiological interplay between both conditions means that in selected patients, heart failure can be significantly or even entirely driven by atrial fibrillation. In addition to a significant overlap in pathophysiological mechanisms, the overlap in clinical symptoms, such as exertional dyspnoea and fatigue frequently lead to a co-diagnosis of both condition upon initial presentation. This ‘chicken or egg’ scenario is common and presents a clinical conundrum for the treating physician.

In the accompanying editorial comment published with the completed manuscript of Chapter 3, Wazni et al highlight the point that rate controlled AF is often only retrospectively attributed as the cause of cardiomyopathy after noting an improvement in ejection fraction following catheter ablation. The authors also comment that this study “now gives us a practical tool by which to better stratify these patients”. Cardiac MRI is a safe, readily available, non-invasive approach to characterizing this patient population, with a real potential to improve the clinical management of these patients.

3.2.2 Regression of ventricular fibrosis
Diffuse fibrosis is present in a number of disease states including hypertrophic cardiomyopathy\textsuperscript{302}, hypertension\textsuperscript{100}, diabetes\textsuperscript{303}, atrial fibrillation\textsuperscript{225} and heart failure\textsuperscript{134}, and
its detection by T1 mapping using cardiac MRI has been validated histologically\textsuperscript{133}. Chapter 4 describes a reduction in diffuse fibrosis in a sub-group of patients in the CAMERA-MRI study who underwent T1 mapping at baseline and follow-up. This is the first study to demonstrate that myocardial T1 times can improve following the restoration of sinus rhythm accompanied with substantial improvements in ejection fraction. Although this finding remains to be validated histologically, it is nonetheless consistent with the reversal of ventricular remodeling (such as an improvement in cardiac dimensions) seen in these patients. The regression of fibrosis may partly explain the apparent improved long term prognosis with respect to freedom from AF and systolic dysfunction as demonstrated by the findings in Chapter 2. This adds to the argument that catheter ablation in this patient group is a highly effective treatment and should be considered early in the management tree for a patient meeting these inclusion criteria.

Nonetheless, important caveats remain. Firstly, the failure to ‘normalise’ myocardial T1 times may be a product of short duration of follow up in this study, but may also be indicative of an underlying predisposition to adverse remodeling in this patient group. It should be noted that systolic dysfunction is not a universal consequence of persistent AF, and the factors both physiological and genetic identifying at risk individuals remains to be determined. Should T1 times remain persistently elevated in patients with recovered arrhythmia mediated cardiomyopathy, as has been shown in the setting of tachycardia related cardiomyopathy due to focal atrial tachycardia\textsuperscript{304}, then myocardial T1 time may be a useful prognostic marker of patients with persistent atrial fibrillation likely to develop LV dysfunction, and select those most likely to benefit from early treatment. Secondly, persisting diffuse fibrosis may also suggest that other medical therapy such as anti-heart failure medications may need to be continued indefinitely. The possibility remains these patients may display an underlying pre-disposition to LV dysfunction even in the absence of AF, which may have accelerated the manifestation of systolic impairment in an otherwise at risk individual. These interesting clinical relevant questions should be the subject of further studies.

3.3 Catheter ablation and procedural success

Another important aspect of this research is demonstrating the efficacy of catheter ablation in this patient population. A key feature in determining outcome was the novel use of
implantable loop recorders to continuously monitor patients for AF recurrence and, more importantly, monitor overall burden of AF following ablation. Given the pathophysiology of AF induced cardiomyopathy, where long term ventricular irregularity, loss of atrial contractile function and relatively higher rates lead to a reduction in systolic function and adverse ventricular and atrial remodeling, a reduction in burden, rather than simply symptomatic recurrence of AF, or a symptomatic recurrence of >30 seconds, is likely of greater clinical utility. The improvement in ejection fraction seen in the majority of patients in the CAMERA-MRI study, even in those with recurrence (>30 seconds AF/atrial tachycardia), highlights the limitation of this definition of “procedural success” in this setting. By comparison, all patients undergoing catheter ablation underwent a significant reduction in AF burden (range 100% to 76% reduction) from baseline to six months. A more reasonable model for judging procedural success in this patient population would be to adopt the approach utilized in ventricular ectopic induced cardiomyopathy, whereby ectopic burden reduction in conjunction with an improvement in ejection fraction is well-recognized measure of procedural success.

3.4 Heart failure, atrial fibrillation and atrial remodeling

Chapters five, six and seven, are aimed at exploring the understanding of the structural and electrical substrate in persistent atrial fibrillation in patients both with and without systolic dysfunction. The findings of Chapter 5 for the first time demonstrate that systolic impairment itself has an independent influence upon the atrial substrate over and above the impact of AF itself. The significance of this finding is that in the clinical situation of an arrhythmia mediated cardiomyopathy, where both atrial fibrillation is accompanying systolic dysfunction can be treated, the potential exists for this adverse substrate to be reversed, potentially improving the long term outcome following catheter ablation. The findings reported in Chapter 2 were consistent with this, as seen by positive association of recovery of systolic function and the long-term freedom from AF. However, demonstrating that recovery of systolic function is associated with a regression in atrial substrate upon repeat invasive analysis, should be the subject of further study.

The association of atrial remodeling with pulmonary vein cycle length, was another novel finding of this work. Chapter five described a positive correlation between markers of adverse remodeling in the pulmonary venous antrum, and increasing pulmonary vein cycle

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length. However, the potential for this novel marker of atrial remodeling to be used as predictor of long term success in catheter ablation of persistent AF, was not borne out in a large prospective study (Chapter seven). This result stood in contrast to previous retrospective analyses, and likely highlights the limitations in extrapolating clinical outcome data from non-prospective studies, which has been a common theme in the area of persistent AF ablation.

4. Future directions

Whilst acknowledging its potential utility, current heart failure and atrial fibrillation guidelines have no specific recommendations for the role of catheter ablation in the setting of systolic impairment. However, recent advances in this field, including the work presented in this thesis, and the soon to be reported results of a large multi-centre international randomised study, have the real potential to change practice guidelines in this area. Outcomes from the Catheter Ablation versus Standard Conventional Treatment in Left Ventricular Dysfunction and Atrial Fibrillation (the CASTLE-AF Study NCT00643188) were recently reported at the European Society of Cardiology Annual Scientific Congress in Barcelona 2017, although at the time of submission of this thesis this trial remained unpublished. Indeed, the trial reported in this work in Chapter 3 was published online by the Journal of the American College of Cardiology simultaneously with the release of the findings of CASTLE-AF, given the importance of both studies to the field. That study screened 3,013 patients across 31 centres in 9 countries, and randomised 397 patients with atrial fibrillation and LVEF \(\leq 35\%\) (of any aetiology) to either catheter ablation (n=200) or medical therapy (n=197). Patients were followed up for 5 years with a primary endpoint as composite of overall mortality and heart failure related hospital admissions. All patients had implantable dual lead cardiac defibrillators facilitating continuous monitoring for AF recurrence. By five years, AF burden was 25% in the catheter ablation group compared to over 60% in the medical rate control group. The primary endpoint was reached by significantly fewer patients in the catheter ablation group compared to the conventional treatment group (HR=0.62 (95% CI: 0.34, 0.87, p=0.006) with a risk reduction of 38%. Furthermore, on secondary analysis cardiovascular mortality, heart failure hospitalisation and cardiac related hospital admissions all individually reached significance (RR=51%, p=0.008; RR=44%, p=0.004; RR=28%, p=0.050 respectively). This is the first large multi-centre randomised controlled trial to
demonstrate improvements in hard clinical endpoints such as mortality and hospitalisation with catheter ablation. As such, once published, this trial has the potential to transform the role of catheter ablation in this field.

However, despite this impressive result, the breadth of the inclusion criteria of patients included in this trial, particularly the inclusion of patients with varying AF burdens (paroxysmal and persistent) and heart failure aetiologies (ischaemic and non-ischaemic cardiomyopathy), does limit its ability to provide insight into selecting those patients with systolic dysfunction likely to achieve the best results following catheter ablation. In this regard, the research presented in this body of work helps to provide the treating physician with some guidance. In particular, identifying those patients for whom AF is likely to be significantly contributing to or entirely responsible for the systolic dysfunction, including utilising cardiac MRI as an additional stratification tool, provides practical and pragmatic steps to select those patients likely to achieve the best long-term results with catheter ablation. The combination of these results, suggests that patients with AF and an otherwise unexplained cardiomyopathy may indeed experience a benefit in mortality and morbidity in addition to improvements in ejection fraction and symptoms. Although more work needs to be done to identify the optimal ablation strategy in these patients, the role of catheter ablation in the setting of heart failure is rapidly establishing itself as an important anti-heart failure treatment in selected patients with the potential for long-term improvements in patient outcomes. In the accompanying editorial to the published CAMERA-MRI trial, Wazni et al commented that “the positive results of this study should encourage the rethinking of current guidelines, especially in heart failure patients in whom the maintenance of durable sinus rhythm with minimal use of anti-arrhythmic drugs achieved through catheter ablation may be a matter of life and death”306.

To conclude, this body of work has comprehensively evaluated the role catheter ablation in the setting of systolic dysfunction, including examining the existing literature, conducting a multi-centre international retrospective analysis, and the performance of several prospective studies, including a completed and published randomised controlled clinical trial. It has also explored several novel aspects of catheter ablation including the role of pulmonary vein electrical activity and intra-procedural adenosine. As evidenced by the peer-reviewed publications emanating from this work, this thesis makes a substantial contribution to the existing literature in this field.
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