Characterisation of the Substrate of
Atrial Fibrillation and Flutter

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fulfilment of the requirements for the degree of

Doctor of Philosophy

August 2008
To my wife Christina and my children Isabelle and Liam
# Table of Contents

Abstract .................................................................................................................. XIII

Declaration ............................................................................................................. XV

Acknowledgements ............................................................................................... XVI

Publications and Communications to Learned Societies ....................................... XVII

Prizes and Awards during Candidature ................................................................. XXI

Abbreviations ......................................................................................................... XXII

## Review of the Literature

1.1 Introduction ......................................................................................................... 1

1.1.1 History of Atrial Fibrillation .......................................................................... 2

1.1.2 Epidemiology of Atrial Fibrillation ................................................................. 3

1.1.3 History of Atrial Flutter .................................................................................. 9

1.1.4 Epidemiology of Atrial Flutter ........................................................................ 11

1.2 The Electrophysiological Basis of Atrial Fibrillation ...................................... 13

1.2.1 The Multiple Heterotopous Centres Theory ............................................... 13

1.2.2 The Multiple Wavelet Hypothesis ................................................................. 13

1.2.3 Localised Sources in the Initiation and Maintenance of Atrial Fibrillation .... 15

1.2.4 The Venous Wave Hypothesis ....................................................................... 19

1.2.5 Rotors and Activation Gradients .................................................................... 21
1.3 Triggers and Substrate in Atrial Arrhythmia

1.3.1 Focal Triggers

1.3.2 Localised Reentry

1.3.3 Anatomical Structures with Site-specific Conduction Properties

1.3.4 Complex Fractionated Atrial Electrograms

1.3.5 Dominant Frequency

1.3.6 The Neural Basis of Atrial Fibrillation

1.3.7 Substrate Associated with Atrial Flutter

1.3.8 Typical and Atypical Atrial Flutter

1.4 Inter-relationships between Atrial Flutter and Atrial Fibrillation

1.4.1 Atrial Flutter begets Atrial Fibrillation

1.4.2 Atrial Fibrillation begets Atrial Flutter

1.5 Rate-related Remodelling

1.5.1 Electrical Remodelling

1.5.2 Structural Remodelling

1.6 Atrial Substrate in Conditions Associated with Atrial Arrhythmia

1.6.1 Heart Failure

1.6.2 Atrial Septal Defects

1.6.3 Hypertension

1.6.4 Valvular Heart Disease

1.6.5 Sub-clinical Atrial Disease in Lone Atrial Fibrillation

1.7 Sinus Node Disease, Remodelling and Atrial Arrhythmias

1.7.1 The Anatomical Sinus Node
1.7.2 The Functional Sinus Node Complex ............................................. 53
1.7.3 Conventional Evaluation of Sinus Node Function ......................... 56
1.7.4 High-density Mapping of the Sinus Node ........................................ 57
1.7.5 Sinus Node Disease ........................................................................ 58
1.7.6 Clinical Conditions Associated with Sinus Node Impairment ........... 59

Right and left atrial electrical substrate of lone atrial fibrillation

2.1 Introduction ............................................................................................... 61
2.2 Methods ..................................................................................................... 62
  2.2.1 Study Population .................................................................................. 62
  2.2.2 Electrophysiological Study and Ablation ............................................. 63
  2.2.3 Electrophysiology Study Protocol ...................................................... 64
  2.2.4 Statistical Analysis ........................................................................... 66
2.3 Results ....................................................................................................... 67
  2.3.1 Baseline Details .................................................................................. 67
  2.3.2 Atrial Refractoriness ...................................................................... 67
  2.3.3 Atrial Conduction Time ..................................................................... 68
  2.3.4 Site-Specific Conduction Abnormalities .......................................... 68
  2.3.5 Sinus Node Function ....................................................................... 69
2.4 Discussion ................................................................................................. 69
  2.4.1 Major findings .................................................................................. 69
  2.4.2 Rate-Related Electrical Remodelling ............................................... 70
  2.4.3 Progression of Atrial Fibrillation ...................................................... 71
  2.4.4 Substrate Predisposing to the Development of Atrial Fibrillation ....... 72
Right atrial electrical substrate of atrial flutter

4.1 Introduction ........................................................................................................ 100
4.2 Methods ............................................................................................................. 101
  4.2.1 Study Population ........................................................................................... 101
  4.2.2 Electrophysiological Study and Ablation ...................................................... 102
  4.2.3 Electrophysiology Study Protocol ................................................................. 102
  4.2.4 Statistical Analysis ........................................................................................ 104
4.3 Results ............................................................................................................... 105
  4.3.1 Baseline Details ............................................................................................ 105
  4.3.2 Atrial Refractoriness ..................................................................................... 105
  4.3.3 Atrial Conduction Time ................................................................................ 106
  4.3.4 Site-Specific Conduction Abnormalities ....................................................... 106
  4.3.5 Sinus Node Function ..................................................................................... 107
4.4 Discussion .......................................................................................................... 107
  4.4.1 Major Findings .............................................................................................. 107
  4.4.2 The Inter-relationship between Atrial Flutter and Atrial Fibrillation ............. 108
  4.4.3 Substrate Predisposing to the Development of Atrial Flutter ....................... 109
  4.4.4 Substrate in Conditions Predisposed to Atrial Arrhythmia ......................... 110
  4.4.5 Implications .................................................................................................. 112
  4.4.6 Limitations ................................................................................................... 112
4.5 Conclusion ........................................................................................................... 113
Right atrial electroanatomical substrate of atrial flutter

5.1 Introduction ........................................................................................................118

5.2 Methods ..............................................................................................................119

5.2.1 Study Population ...............................................................................................119

5.2.2 Electrophysiological Study and Ablation ........................................................... 120

5.2.3 Electroanatomical Study Protocol ......................................................................120

5.2.4 Statistical Analysis ............................................................................................122

5.3 Results ..................................................................................................................123

5.3.1 Baseline Details ................................................................................................. 123

5.3.2 Structural and Voltage Abnormalities .............................................................. 123

5.3.3 Abnormalities in Conduction Velocity .............................................................. 124

5.3.4 Complex Electrograms ......................................................................................124

5.4 Discussion ............................................................................................................125

5.4.1 Major Findings ..................................................................................................125

5.4.2 Substrate in Clinical Conditions Associated with Atrial Arrhythmia .........125

5.4.3 Substrate in Experimental Models of Atrial Flutter ...........................................126

5.4.4 Substrate in Clinical Atrial Flutter ...................................................................127

5.4.5 Implications .......................................................................................................128

5.4.6 Limitations ........................................................................................................128

5.5 Conclusion ............................................................................................................129
High-density mapping of the sinus node to characterise the remodelling resulting from chronic atrial flutter

6.1 Introduction .................................................................................................................. 134

6.2 Methods ....................................................................................................................... 135

6.2.1 Study Population ..................................................................................................... 135

6.2.2 Electrophysiological Study and Ablation ................................................................ 136

6.2.3 Conventional Evaluation of Sinus Node Function .................................................. 137

6.2.4 High-Density Simultaneous Unipolar Mapping of Sinus Node Function .............. 138

6.2.5 Statistical Analysis .................................................................................................. 140

6.3 Results ......................................................................................................................... 141

6.3.1 Baseline Details ...................................................................................................... 141

6.3.2 Sinus Node Dysfunction and Atrial Remodelling .................................................. 141

6.3.3 Extent and Shift of the Atrial Pacemaker Complex .............................................. 142

6.3.4 Preferential Pathway Conduction .......................................................................... 143

6.3.5 Beat-to-beat Variation in Sinus Node Function ...................................................... 143

6.3.6 Crista Terminalis Conduction ................................................................................. 144

6.3.7 Voltage Findings ..................................................................................................... 144

6.4 Discussion ................................................................................................................... 145

6.4.1 Major Findings ......................................................................................................... 145

6.4.2 The Sinus Node: Anatomical and Functional Considerations .................................. 146

6.4.3 Atrial Remodelling and Sinus Node Function ......................................................... 147

6.4.4 Preferential Pathways of Conduction ..................................................................... 149

6.4.5 Implications ............................................................................................................. 151
High-density mapping of atrial fibrillation to determine the optimal recording duration for dominant frequency and automated detection of complex fractionated electrograms

7.1 Introduction .................................................................................................... 166

7.2 Methods ......................................................................................................... 167
7.2.1 Study Population ...................................................................................... 167
7.2.2 Electrophysiological Study ....................................................................... 168
7.2.3 High-Density Bi-atrial Mapping ................................................................. 168
7.2.4 Complex Fractionated Atrial Electrograms .............................................. 169
7.2.5 Dominant Frequency .............................................................................. 170
7.2.6 Statistical Analysis .................................................................................. 171

7.3 Results ............................................................................................................ 171
7.3.1 Baseline details ....................................................................................... 171
7.3.2 CFE-mean ............................................................................................... 172
7.3.3 Dominant Frequency ............................................................................. 173

7.4 Discussion ...................................................................................................... 173
7.4.1 Major Findings ....................................................................................... 173
7.4.2 Time Domain Analysis .......................................................................... 175
7.4.3 Frequency Domain Analysis ................................................................. 176
7.4.4 Differences in Effect of Electrogram Duration between CFE-mean and DF... 177
High-density mapping of atrial fibrillation to determine the relationship between activation frequency, complex fractionated electrograms and the anatomical substrate

8.1 Introduction .......................................................................................................187
8.2 Methods ...........................................................................................................188
  8.2.1 Study Population .......................................................................................... 188
  8.2.2 Electrophysiological Study and Ablation ........................................................ 189
  8.2.3 Study Protocol .............................................................................................. 190
  8.2.4 Complex Fractionated Atrial Electrograms ....................................................... 191
  8.2.5 Activation Frequency ..................................................................................... 192
  8.2.6 Relationship between Activation Frequency and Fractionation .................... 192
  8.2.7 Statistical Analysis ........................................................................................ 193
8.3 Results .................................................................................................................194
  8.3.1 Baseline Details ............................................................................................. 194
  8.3.2 Complex Fractionated Atrial Electrograms ....................................................... 194
  8.3.3 Dominant Frequency ..................................................................................... 195
  8.3.4 Relationship between CFE-mean and Dominant Frequency ......................... 196
8.4 Discussion ............................................................................................................198
  8.4.1 Major findings .............................................................................................. 198
  8.4.2 Spatial Distribution of Complex Fractionated Atrial Electrograms .................. 199
8.4.3 Spatial Distribution of Dominant Frequency .................................................... 199
8.4.4 Relationship between Activation Frequency and Fractionation ..................... 201
8.4.5 Clinical Implications .......................................................................................... 202
8.4.6 Limitations ........................................................................................................ 203
8.5 Conclusion ...........................................................................................................203

Summary

Future Directions

References
Abstract

Atrial fibrillation and atrial flutter are the most common sustained arrhythmias, however their underlying mechanisms are yet to be fully characterised. This thesis evaluates the electrophysiological and electroanatomical substrate of the atria in patients with these arrhythmias.

Experimental studies of atrial fibrillation have demonstrated effective refractory period shortening and conduction slowing as a result of atrial fibrillation giving rise to the concept that “atrial fibrillation begets atrial fibrillation”. However, cardioversion to prevent electrical remodelling does not prevent progression of disease, suggesting a “second factor” drives this process. Chapters 2 and 3 evaluate the atrial substrate in patients with “lone” atrial fibrillation. These studies demonstrate such patients, remote from an arrhythmic event, have prolongation of atrial refractoriness, conduction slowing, impairment of sinus node function, site-specific conduction delay, lower voltage and a greater proportion of complex electrograms compared to reference patients. These abnormalities constitute the “second factor” critical to the development and progression of atrial fibrillation.

Atrial flutter has a close inter-relationship with atrial fibrillation and these rhythms frequently co-exist. Atrial fibrillation often occurs in patients with heart disease known to demonstrate abnormal atrial substrate; whether similar substrate exists in patients with atrial flutter to account for the co-existence of both arrhythmias is unknown. Chapters 4 and 5 evaluate the atrial substrate in patients with atrial flutter, remote from arrhythmia, demonstrating structural abnormalities characterised by loss of myocardial voltage, conduction slowing and impaired sinus node function, without
reduction in atrial refractoriness. These findings implicate a common substrate as the cause of the close inter-relationship between these arrhythmias.

There is a frequent association between atrial arrhythmia and sinus node disease for which several mechanisms have been postulated. In addition, there is a size discrepancy between the anatomical sinus node and the much larger functional sinus node complex. Little is known about normal sinus node function or the effects of remodelling due to arrhythmia. Chapter 6 characterises sinus node activation to determine the nature and extent of the functional sinus node complex in patients with and without chronic atrial flutter. The functional sinus node complex demonstrates dynamic shifts in activation with preferential pathways of conduction to atrial myocardium. Patients with atrial flutter demonstrate lesser voltage, longer conduction times along preferential pathways and a smaller functional sinus node complex. These findings provide insights into the function of the human sinus node in health and disease.

Sites of complex fractionated atrial electrograms and highest dominant frequency are implicated in maintaining atrial fibrillation. Chapter 7 determines the minimum recording duration that accurately characterises electrogram complexity and activation frequency. An electrogram duration of ≥5 seconds is required to accurately identify these sites. Chapter 8 evaluates the relationship between sites of fractionation and high frequency activation during atrial fibrillation. Greater fractionation and higher dominant frequency are seen in persistent atrial fibrillation and left atria. Preferential areas of high dominant frequency are observed in paroxysmal but not persistent atrial fibrillation. Areas of complex fractionated atrial electrograms are found adjacent to sites of high dominant frequency.
Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Martin Stiles and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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___________________________________________
Martin Kingsland Stiles
August 2008


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Publications and Communications to Learned Societies

Chapter 1


iii) **Presentation**: Invited to present at the Cardiac Society of Australia and New Zealand 56th Scientific Meeting August 2008, Adelaide, Australia on Complex Electrograms and Dominant Frequency

Chapters 2 and 3


ii) **Presentation**: Presented at the Cardiac Society of Australia and New Zealand 56th Scientific Meeting August 2008, Adelaide, Australia and published in abstract form (Heart Lung Circ 2008;17:S120)

iii) **Presentation**: Presented at the Medical Grand Round, Royal Adelaide Hospital, August 2008. Finalist for the 2008 Nimmo Prize for Full-Time Research
**Chapters 4 and 5**

i) **Manuscript:** Stiles MK, Wong CX, John B, Kuklik P, Brooks AG, Lau DH, Dimitri H, Wilson L, Young GD, Sanders P. Atrial flutter is associated with diffuse atrial abnormalities: Implications for the development of atrial fibrillation. Submitted for publication

ii) **Presentation:** Presented at the Cardiac Society of Australia and New Zealand 56th Scientific Meeting August 2008, Adelaide, Australia and published in abstract form (Heart Lung Circ 2008;17:S114)

**Chapter 6**

i) **Manuscript:** Stiles MK, Brooks AG, Roberts-Thomson KC, Kuklik P, John B, Young GD, Kalman JM, Sanders P. High-density mapping of the sinus node in humans: role of preferential pathways and the effect of remodelling. Submitted for publication

ii) **Presentation:** Presented at the Heart Rhythm Society 28th Annual Scientific Sessions, May 2008, San Francisco, United States of America and published in abstract form (Heart Rhythm 2008;5:S278)

iii) **Presentation:** Presented at the Cardiac Society of Australia and New Zealand 56th Scientific Meeting August 2008, Adelaide, Australia and published in abstract form (Heart Lung Circ 2008;17:S121)
Chapter 7


ii) **Presentation:** Presented at the Heart Rhythm Society 28th Annual Scientific Sessions, May 2007, Denver, United States of America and published in abstract form (Heart Rhythm 2007;4:S348)

iii) **Presentation:** Presented at the Cardiac Society of Australia and New Zealand 55th Scientific Meeting August 2007, Christchurch, New Zealand and published in abstract form (Heart Lung Circ 2007;16:S109)

Chapter 8


ii) **Presentation:** Presented at the American College of Cardiology 57th Annual Scientific Sessions, March 2008, Chicago, United States of America and published in abstract form (J Am Coll Cardiol 2008;51:A6)
iii) **Presentation**: Presented at the Cardiac Society of Australia and New Zealand 56th Scientific Meeting August 2008, Adelaide, Australia and published in abstract form (Heart Lung Circ 2008;17:S120)

iv) **Presentation**: Presented at the Post-graduate Research Expo, School of Medicine, July 2008
Prizes and Awards during Candidature

i) New Zealand Heart Foundation Overseas Training Fellowship, 2005-2006

ii) New Zealand Heart Foundation Travel Grant, Heart Rhythm 06, Boston, United States of America, 2006

iii) Dawes Scholarship, Royal Adelaide Hospital, 2006-2008

iv) Cardiac Society of Australia and New Zealand Annual Scientific Meeting Travelling Scholarship, Canberra, 2006

v) St Jude Medical Australia Pacing and Electrophysiology Young Investigator Award, 2006

vi) Cardiac Society of Australia and New Zealand Travelling Scholarship, European Society of Cardiology Congress, Barcelona, Spain, 2006

vii) Best Moderated Poster in the Drugs/Ablation/Electrical Therapy of Arrhythmias section, World Congress of Cardiology, Barcelona, Spain, 2006

viii) Australian Heart Foundation Travel Grant, Heart Rhythm 07, Denver, United States of America, 2007

ix) University of Adelaide, Postgraduate Travelling Fellowship, 2008

x) Australian Heart Foundation Travel Grant, Heart Rhythm 08, San Francisco, United States of America, 2008

xi) Finalist for the Nimmo Prize for Full-Time Research, Adelaide, 2008
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CFAE</td>
<td>Complex Fractionated Atrial Electrogram</td>
</tr>
<tr>
<td>CFE-mean</td>
<td>An automated measure of electrogram complexity</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CSNRT</td>
<td>Corrected Sinus Node Recovery Time</td>
</tr>
<tr>
<td>DF</td>
<td>Dominant Frequency</td>
</tr>
<tr>
<td>EA</td>
<td>Earliest Activation</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ERP</td>
<td>Effective Refractory Period</td>
</tr>
<tr>
<td>ICC</td>
<td>Intra-Class Correlation</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter-Quartile Range</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>SACT</td>
<td>Sino-Atrial Conduction Time</td>
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<tr>
<td>SBO</td>
<td>Sinus Break-Out</td>
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Standard international NBG pacing codes are used (e.g. VVI, DDD)

Due to the common initials of atrial flutter and atrial fibrillation, these rhythms are not abbreviated in the text. For some tables and figures, the abbreviation “AF” is used for atrial fibrillation. Atrial flutter is abbreviated to “flutter” in some tables and figures.
Chapter 1.
Review of the Literature

1.1 Introduction

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the electrocardiogram, atrial fibrillation is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape and timing, associated with an irregular and often rapid ventricular response when atrioventricular conduction is intact. The ventricular response to atrial fibrillation depends on electrophysiological properties of the atrioventricular node and other conducting tissues, the level of vagal and sympathetic tone, and the action of drugs.

ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (Fuster et al. 2006).

Atrial flutter is characterized by an organized atrial rhythm with a rate typically between 250 and 350 bpm. Electrophysiological studies have shown that this simple ECG definition includes tachycardias using a variety of reentry circuits. The reentry circuits often occupy large areas of the atrium and are referred to as “macro-reentrant.” The classic type of atrial flutter (i.e. typical flutter) is dependent on the cavotricuspid isthmus.

The typical form of atrial flutter is characterized by a sawtooth pattern of regular atrial activation called flutter (f) waves on the ECG, particularly visible in leads II, III, aVF, and V1. If untreated, the atrial rate typically ranges from 240 to 320 beats per minute, with f waves inverted in leads II, III, and aVF and upright in lead V1. The direction of activation in the right atrium may be reversed, resulting in upright f waves in leads II, III, and aVF and inversion in lead V1.

ACC/AHA/Physician Consortium 2008 Clinical Performance Measures for Adults with Nonvalvular Atrial Fibrillation or Atrial Flutter (Estes et al. 2008).

1.1.1 History of Atrial Fibrillation

An irregular pulse, referred to as rebellious palpitations, delirium cordis and pulsus irregularis perpetuus, was a cause of speculation by physicians since early times (Silverman 1994). James Mackenzie (1907), a general practitioner in England, utilising an ink-writing polygraph to record and label jugular venous pulses, initially set about deciphering normal and abnormal cardiac rhythms. His key observation that the jugular "A wave" was lost in a patient who went from a normal to an irregular rhythm provided the first insight into the mechanism of auricular fibrillation, as it was initially called. The first electrocardiographic recordings of atrial fibrillation came shortly after Einthoven invented the string galvanometer in 1901. He published a tracing from a case of pulsus irregularis that showed QRS complexes with normal appearance; these occurred irregularly but had too much background interference to permit the identification of atrial activity (Einthoven 1906). Cushny and Edmunds (1907) demonstrated a connection between irregularity of the pulse and atrial fibrillation.
Hering reporting on the electrocardiograms of patients in 1908, stated that one could see no signs on the electrocardiogram of action of the auricles, and described “F waves” in his recordings (Flegel 1995). These fine waves between ventricular beats were considered to be responsible for the irregular rhythms whose pulse pressure tracings had been published by MacKenzie. In 1909, Rothberger and Winterberg in Vienna, and Lewis in England were the first to establish electrocardiographically that auricular fibrillation was the cause of pulsus irregularis perpetuus (Silverman 1994). Subsequently, Lewis (1910) noted from electrocardiographic studies that the R wave was relatively normal in cases of irregular pulse and argued that ventricular contraction must therefore originate from its usual starting point. He took the fine oscillations between the R waves to be evidence of atrial activity throughout the cardiac cycle. From detailed study of the chest leads, Lewis showed that these oscillations originated from the atria rather than from the atroventricular node as was thought by some (Flegel 1995). Technical advances in ECG recording allowed signal amplification and miniaturisation of the recording system (Ernestene and Levine 1928) which set the stage for the subsequent path to understanding by way of electrophysiological investigation of this frequently encountered clinical arrhythmia.

1.1.2 Epidemiology of Atrial Fibrillation

Atrial fibrillation is the most common chronic cardiac arrhythmia, estimated to affect 2.2 million people in the United States and 4.5 million people in the European Union (Fuster et al. 2006). In Australia, it is a major health problem contributing to a substantial proportion of the estimated 50,000 strokes a year (National Heart
Foundation of Australia 2004; Cadilhac et al. 2007). With ageing of the population and improved survival after the occurrence of myocardial infarction and congestive heart failure, Eugene Braunwald (1997) noted a doubling of admission rates for atrial fibrillation between 1984 and 1994, and described atrial fibrillation as an emerging epidemic. In Australia, the ICD-10 principal diagnosis of “atrial fibrillation and flutter” at discharge from public hospitals increased from 27,245 to 38,296 from 1999 to 2005 (Australian Institute of Health and Welfare 2008). Lifetime risks for development of atrial fibrillation are 1 in 4 for men and women over the age of forty years and are still high (1 in 6) even in the absence of antecedent congestive heart failure or myocardial infarction (Lloyd-Jones et al. 2004).

1.1.2.1 Incidence and Prevalence

The incidence and prevalence of atrial fibrillation varies between studies, most likely related to study design and methods, but perhaps also to true regional variations. Consistently across the studies, the incidence of atrial fibrillation increases with age (Benjamin et al. 1994; Psaty et al. 1997; Miyasaka et al. 2006a). In the Cardiovascular Health Study, the incidence of atrial fibrillation in the 65-74 years age group was 18 per 1000 person-years for men and 10 per 1000 person-years for women. For the age category 75-84 years these numbers more than doubled to 43/1000 and 22/1000, respectively (Psaty et al. 1997). The prevalence of atrial fibrillation is therefore highly age-related and although the age-specific prevalence is higher in men (e.g. for ages 65-69 years: men 5.9%, women 2.8%), the gap narrows with women in the older age categories. Furthermore, as women on average live longer than men, the absolute number of women with atrial fibrillation actually exceeds that of men making this
disease of equal importance to both elderly men and women (Furberg et al. 1994). The number of Australians with atrial fibrillation is estimated at 165,000, with numbers expected to rise substantially due to ageing of the population together with the increasing prevalence of atrial fibrillation with age (Eikelboom and Hankey 2004).

1.1.2.2 Associated Conditions

Key risk factors for the development of atrial fibrillation include increasing age, hypertension, myocardial infarction, congestive heart failure and valvular heart disease (Kannel et al. 1982a; Benjamin et al. 1994; Psaty et al. 1997). Data from the well known Framingham cohort showed that, independent of other documented risk factors, each decade of age increased the probability of developing atrial fibrillation by 2.1-fold in men and 2.2-fold in women. In the same cohort, diabetes (men: 1.4-fold; women 1.6-fold), underlying hypertension (men: 1.5-fold; women: 1.4-fold), past myocardial infarction (1.4-fold in men only), congestive heart failure (men: 4.5-fold; women: 5.9-fold) and valvular disease usually affecting the mitral valve (men: 1.8-fold; women: 3.4-fold) independently increased the likelihood of developing atrial fibrillation (Wolf et al. 1996). More recent data from the Framingham study reports that the development of atrial fibrillation in patients with congestive heart failure is associated with an increase in mortality of 2.7-fold in men and 3.1-fold in women (Wang et al. 2003). The Renfrew-Paisley study from the United Kingdom, found that middle-aged men and women were significantly more likely to develop atrial fibrillation during 25-year follow-up if they had cardiomegaly (13-fold increase), chronic bronchitis (2.2-fold), left ventricular hypertrophy (4.2-fold), myocardial ischaemia (4.5-fold), past history of stroke (3.9-fold) and glucose intolerance (3.1-fold) (Stewart et al. 2001). Other reported causes include
pericarditis, alcohol, thyrotoxicosis, hypertrophic cardiomyopathy, myocarditis, severe infection and disorders of the cardiac conduction system (Aberg 1968; Fuster et al. 2001; Stewart et al. 2001). Nevertheless, despite multiple risk factors for atrial fibrillation, some of those with the condition are remarkable only for the absence of overt cardiovascular disease or precipitating illness; so called “lone” atrial fibrillation (Brand et al. 1985; Kopecky et al. 1987). Such patients younger that 65 years of age do not have the increased risk of thromboembolism seen in atrial fibrillation overall (Kopecky et al. 1987; Rostagno et al. 1995; Stewart et al. 2002). In fact, analysis of the Framingham Study data of patients with lone atrial fibrillation revealed that after a mean follow up of 25.2±9.5 years, cerebrovascular events had only occurred in patients who had developed a least one risk factor for thromboembolism since enrolment (Jahangir et al. 2007). Familial tendencies in lone atrial fibrillation have been described and recently genetic linkage analysis studies have indicated associations with specific chromosomal loci (Lai et al. 2003). Brugada et al. (1997) reported the first monogenic cause for familial atrial fibrillation, implicating a gene on chromosome 10. These studies, together with population studies of first degree relatives (Ellinor et al. 2005), show there is growing evidence that genetic factors are important in the pathogenesis of atrial fibrillation. Nevertheless, familial atrial fibrillation has been shown to be genetically heterogeneous (Darbar et al. 2003; Volders et al. 2007) and, unlike syndromes such as hypertrophic cardiomyopathy and long QT syndrome, the role of genes in the vast majority of people who develop atrial fibrillation probably comes second to the role of environmental factors and co-morbid disease.
1.1.2.3 Consequences of Atrial Fibrillation

Atrial fibrillation is a major cause of morbidity and mortality, increasing risk of death (Benjamin et al. 1998; Vidailet et al. 2002), congestive heart failure (Stewart et al. 2002), and embolic phenomena, including stroke (Wolf et al. 1991; Stewart et al. 2002). Approximately 15% of all strokes are attributable to atrial fibrillation (Wolf et al. 1987) and these are more debilitating than other types of strokes (Jorgensen et al. 1996). Independent of stroke, atrial fibrillation has been linked to cognitive dysfunction although the mechanism by which this results is yet to be determined (Ott et al. 1997; Miyasaka et al. 2007a). Congestive heart failure is not only a risk factor for atrial fibrillation but can also be a consequence of atrial fibrillation. Therefore, whether occurring in tandem or in succession these two conditions often co-exist compounding the adverse consequences of each in a “vicious cycle” (Cha et al. 2004). The incidence of new congestive heart failure for a patient first diagnosed with atrial fibrillation has been observed to be 44 per 1000 person-years. Furthermore, the age- and sex-adjusted mortality risk for patients with atrial fibrillation following congestive heart failure was estimated at 3.4 times that of those without heart failure (Miyasaka et al. 2006b). Atrial fibrillation confers an independent mortality risk, most recently shown in a 21-year community-based study by the Framingham investigators. Patients with newly diagnosed atrial fibrillation had a hazard ratio for dying of 2.08 over a mean of 5.3 years follow-up, when compared with the general population of Minnesota. Furthermore, this was markedly more dramatic (hazard ratio 9.62) in the first 4 months from diagnosis, mainly from cardiovascular causes (Miyasaka et al. 2007b). In Australians over the age of 60 years the relative mortality of patients with atrial fibrillation (adjusted for confounding effects) is 1.92 for all causes and 3.78 for deaths.
from stroke (Lake et al. 1989). Thus, atrial fibrillation is a disease that denotes significant associated morbidity and mortality, with a large impact on both the individual and the community as a whole. Importantly, these associated poor health outcomes must be separated from the co-morbid conditions frequently accompanying atrial fibrillation. “Lone” atrial fibrillation has been defined as the absence of structural heart disease or stroke based on history, physical examination, chest X-ray, routine blood chemistry, and trans-thoracic as well as trans-oesophageal echocardiography. Additional exclusions to this group are coronary artery disease, significant pulmonary disease, hypertension, hyperthyroidism and diabetes (Kopecky et al. 1987; Kumagai et al. 1991; Jaïs et al. 2000). The survival for patients with “lone” atrial fibrillation has been repeatedly shown to be comparable to the general population (Kopecky et al. 1987; Rostagno et al. 1995; Stewart et al. 2002). Although traditional teaching has been that atrial fibrillation progresses from paroxysmal to persistent arrhythmia, a recent Framingham study on the long-term progression and outcomes of patients with lone atrial fibrillation reported that of 71 patients with paroxysmal or persistent atrial fibrillation, just 22 had progression to permanent atrial fibrillation over a mean follow-up of 25.2±9.5 years (Jahangir et al. 2007). Overall survival of the patients with lone atrial fibrillation was similar to the survival of the age- and sex-matched population. Observed survival free of heart failure was slightly worse than expected but the risk for cerebrovascular events was similar to that expected. Importantly, all patients who had a cerebrovascular event had developed ≥1 risk factor for thromboembolism, thereby were no longer strictly “lone” atrial fibrillation. While the association and consequences of atrial fibrillation with all the factors described above may be clear, the mechanisms by which these factors result in arrhythmia is not.
1.1.3 History of Atrial Flutter

The first published description of probable atrial flutter dates back to the nineteenth century when McWilliam (1886) described regular, rapid excitations of the atrium in an animal. Subsequently, Einthoven (1906) made an electrocardiographic recording of atrial flutter. Distinction between atrial flutter and atrial fibrillation by characteristic sawtooth waves in the inferior ECG leads followed (Jolly and Ritchie 1911). This “common” type of atrial flutter was investigated by Lewis (1913) using a combination of epicardial maps and ECG recordings from a canine model induced by rapid atrial pacing. Continual activation of at least some part of the atrium resulted in flutter waves seen in the surface ECG and the activation sequence was orderly, i.e. the wave-front circulated in either a cranio-caudal or a caudo-cranial direction in the right atrium. From this pioneering experimental work it was concluded that atrial flutter was due to intra-atrial circus movement around the venae cavae (Lewis et al. 1921b). Subsequent works that supported that atrial flutter was due to intra-atrial reentry included a crush injury model of this arrhythmia by creating a lesion between the venae cavae (Rosenbleuth and Garcia-Ramos 1947). Based on the epicardial maps, the authors deduced that the reentry loop circled around the atrial crush lesion. Interestingly, they also noted that when the crush lesion was extended from the inferior vena cava to the atrioventricular groove, the arrhythmia disappeared and could not be induced. This important finding suggested the true circuit may have included the cavo-tricuspid isthmus. However, intra-atrial macro-reentry as the mechanism of atrial flutter was not universally accepted. Goto et al. (1967) had shown that aconitine caused abnormal automaticity at rapid rates in the rabbit atria. It was thought that if the atrial site fired fast enough, either flutter (1:1 conduction) or
fibrillation (fibrillatory conduction because the atrial rate was too fast and 1:1 conduction could not be supported) occurred. Building on the work of Rosenbleuth and Garcia-Ramos, Frame et al. (1986) showed that the flutter reentry loop that rotated around the tricuspid annulus could exist through creating a “Y” lesion in the canine right atrium by extending the inter-caval crush lesion to the right atrial free wall. Subsequent experiments in various animal models and clinical studies have not only confirmed that the mechanism of atrial flutter was due to intra-atrial macro-reentry but also allowed the development of curative catheter ablation therapy. Of particular importance are the studies which described techniques of manifest and concealed entrainment, including identification of a site for catheter ablation (Waldo et al. 1977; Inoue et al. 1981; Stevenson et al. 1995). Successful ablation of atrial flutter by radiofrequency energy depended on the identification of a vulnerable, critical zone in the reentrant circuit. Detailed analysis of intra-operative mapping studies of patients with persistent atrial flutter demonstrated that the narrowest part of the circuit had relatively slow conduction and was localised to the low right atrium, between the inferior vena cava and the tricuspid ring (Klein et al. 1986). Furthermore, cryosurgical ablation of this critical region and its surrounding tissue prevented short-term recurrences of the arrhythmia. This was consistent with earlier work which noted that when a crush lesion was extended from the inferior vena cava to the atrioventricular ring, the arrhythmia could no longer be induced (Rosenbleuth and Garcia-Ramos 1947). Subsequent studies using direct current shocks to disrupt the critical zone and eliminate the tachycardia supported the prospect that atrial flutter could be permanently abolished by disruption of the isthmus (Saoudi et al. 1990). However, one drawback of using direct current shock was that the shock itself could
convert atrial flutter. In the early 1990’s, two groups independently found that disruption of the isthmus of the atrial flutter circuit could be carried out safely with radiofrequency catheter ablation (Feld et al. 1992; Cosio et al. 1993). Subsequently, using activation and entrainment mapping with guidance from intra-cardiac echocardiography, points in the right atrium that lay within or outside the circuit were defined. The posterior barriers to conduction were identified as the crista terminalis and the eustachian ridge (Olgin et al. 1995) and it was demonstrated that the tricuspid annulus constitutes an anterior barrier constraining the reentrant wave front of human anti-clockwise atrial flutter (Kalman et al. 1996). Experiments in dogs show that the atrial flutter circuit is critically dependent on a line of functional block extending to the caval veins (Tomita et al. 2001). This has been confirmed in human studies showing the crista terminalis as a line of functional block (Scaglione et al. 2000). Typical atrial flutter therefore is a macro-reentrant circuit in the right atrium with an anatomical barrier anteriorly (the tricuspid valve) and a functional barrier posteriorly (the crista terminalis).

1.1.4  Epidemiology of Atrial Flutter

Less data exists on the epidemiology of atrial flutter than atrial fibrillation, perhaps because it is less common or because it is often included with atrial fibrillation in data analysis, e.g. International Classification of Diseases, Tenth Revision. Certainly atrial flutter shares many clinical risk factors with atrial fibrillation. Using the Marshfield Epidemiological Study Area database of 58,820 residents, Granada et al. (2000) ascertained all new cases of atrial flutter over a 4 year period from 1991. One-hundred
and eighty-one new cases of atrial flutter were diagnosed for an overall incidence of 88/100,000 person-years. Incidence rates ranged from 0.005% in those 50 years old to 0.6% in subjects older than 80. Atrial flutter was 2.5 times more common in men, 3.5 times more common in subjects with heart failure and 1.9 times more likely for subjects with chronic obstructive pulmonary disease. Among those with atrial flutter, 16% were attributable to heart failure and 12% to chronic obstructive lung disease. Three subjects (1.7%) without identifiable predisposing risks were labelled as having “lone atrial flutter”. When these figures are applied to the entire population of the United States, an estimated 200,000 new cases of atrial flutter occur there annually. With regard to mortality, atrial flutter appears more benign than atrial fibrillation, at least initially. Vidaillet et al. (2002) found that for 6 months after diagnosis, mortality was 2.5 times higher among those with atrial flutter (5%) than among controls (2%), but 3.4 times lower than among patients who had atrial fibrillation with or without atrial flutter (17%). After adjusting for baseline characteristics however, early mortality was about seven times higher for patients with atrial fibrillation than for controls. With longer follow-up (mean 3.6 years), overall mortality was similar for patients in all arrhythmia subgroups – 41% for atrial flutter, 45% for atrial fibrillation and 47% in patients with both atrial flutter and atrial fibrillation – as compared with 22% in controls. All three groups of patients with atrial fibrillation or atrial flutter had an approximately two-fold increased risk of mortality compared with controls in models that adjusted for other risk factors. Mortality among patients with atrial fibrillation trended somewhat higher (1.4-fold) than among patients with atrial flutter alone.
1.2 The Electrophysiological Basis of Atrial Fibrillation

1.2.1 The Multiple Heterotopous Centres Theory

Initial theories of the mechanism of atrial fibrillation proposed that each heart fibre becomes independently rhythmic and that each is a focus of its own impulse formation as a result of increased excitability; the multiple heterotopous centres theory. Lewis and Schleiter (1912) reasoned that activity from one or more heterogeneous centres would account for single premature beats, for regular tachycardias and, ultimately, for the completely incoordinate activity seen in auricular fibrillation. However, two unique observations were made by Garrey (1914). Firstly, when a fibrillating chamber was cut into four pieces, each fragment continued to fibrillate; this could not have happened if the fragments were dependent on a single focus. Secondly, although portions of isolated heart muscle were capable of fibrillating, a critical amount of muscle mass was necessary. These observations made the multiple heterotopous centres theory untenable and a competing theory of “circus movement” was proposed in which a circuit of muscle could propagate a wave-front round and round indefinitely, provided the length of muscle exceeded the wave-front length (Lewis et al. 1921b).

1.2.2 The Multiple Wavelet Hypothesis

The circus movement theory was developed further to explain the complexity of experimental findings; these developments included the concept of a single "mother" ring that propagated the arrhythmia and gave rise to "daughter" rings and, finally, to multiple independent rings (Moe 1962). This theory of multiple circus movement, or wavelets, dominated the thinking on the mechanism of atrial fibrillation for many
years. Moe hypothesised that a grossly irregular wave-front becomes fractionated as it divides around islets or strands of refractory tissue and each of the daughter wavelets could then be considered independent offspring; the multiple wavelet hypothesis. However, prior to this, Prinzmetal et al. (1950) had showed that premature systoles, paroxysmal tachycardia, atrial flutter and atrial fibrillation of the left auricle (investigated in over 200 dogs by high speed cinematography, cathode-ray oscillography and multiple-channel electrocardiography) were of unitary origin and suggested that all may occur from one ectopic focus. They categorically stated there is no circus movement and claimed their conception of the auricular arrhythmias simplified the understanding of the mechanism. Subsequent to Moe’s theory however, Allessie et al. (1977) demonstrated reentrant circuits in isolated rabbit atria by using precisely timed premature impulses to produce sustained tachycardia. Of particular interest as an explanation of atrial fibrillation is the ”leading circle” theory in which the initiation of reentry takes place because of non-uniform refractory periods in atrial fibres in close proximity to one another. The initiating impulse conducts in fibres with short refractory periods and is blocked in those with longer ones, forming the conditions for reentry before the impulse has died out. Impulses circulate around a central area that is kept refractory, and thereby blocked, by centripetal wavelets arriving from all sides. The size of the circle is determined by the recovery time of the tissue forming the circuit, because tissue on both sides is kept depolarised by the leading circle. Further evidence to support this hypothesis came about when Cox et al. (1991) demonstrated in an experimental dog model, with supplementary evidence from intra-operative clinical observations in humans, that macro-reentrant circuits within the atrial myocardium were responsible for the entire spectrum of atrial
arrhythmias. Both the experimental study and the clinical study demonstrated that multiple wave fronts, non-uniform conduction, bi-directional block, and macro-reentrant circuits occur during atrial fibrillation. Subsequent work by Allessie’s group on conscious dogs underscored the importance of slowed conduction and shortened refractoriness — a short wavelength, the distance travelled by the depolarisation wave during the refractory period — in determining the onset of atrial fibrillation during rapid electrical stimulation (Rensma et al. 1988). Moe’s original theory of multiple wavelets was lent considerable weight by the clinical observation that chronic atrial fibrillation could be cured in some patients by the placement of multiple surgical lesions (the maze procedure) to compartmentalise the atria into regions presumably too small to sustain such wavelets (Cox et al. 1993). Intra-operative mapping of human atrial fibrillation found pivot points where the wavelets turn around at the end of lines of functional block, illustrating the complexity of atrial activation (Konings et al. 1994).

1.2.3 Localised Sources in the Initiation and Maintenance of Atrial Fibrillation

At the time that surgical treatments of atrial fibrillation were being advanced, the first direct evidence that the pattern of circulating wavelets during atrial fibrillation in humans is not entirely random was published (Gerstenfeld et al. 1992). The hypothesis that local atrial activation should be influenced by the constant anatomy and the receding tail of refractoriness from the previous activation was proven by demonstrating that a tendency for wave fronts to follow paths of previous excitation (often termed "linking") was transiently present for the majority of patients with atrial fibrillation. Further evidence that atrial fibrillation is not random comes from more
recent studies showing repetitive periodic activity demonstrating temporal and spatial stability in the left atrium, particularly the pulmonary veins and posterior regions (Skanes et al. 1998; Mansour et al. 2001). Analysis of the activation frequency at these sites is highly suggestive of localised reentry or “rotors” which have been proposed as drivers of the fibrillatory process (Jalife et al. 1998; 2002). Mansour (2001) reported that wave-fronts propagated from left to right in 80% of sheep atria and that right-to-left propagation occurred in a significantly smaller percentage of cases. The cycle length of left atrial sources determined the dominant peak in the frequency spectra in atrial fibrillation and ablation of inter-atrial connections reduces right atrial signal frequency but not left. Human studies have also suggested localised reentry as a driving mechanism of atrial fibrillation and are discussed further in Section 1.3.2. After the leading circle wavelet theory had held sway for decades, Scherf (1947) revived the focus theory by applying aconitine focally to the atrium, and in this way could induce atrial fibrillation. More recently, research has similarly focussed on identifying local triggers for atrial fibrillation. It has been observed that atrial fibrillation can ensue from the degeneration of other atrial tachycardias such as atrial flutter or accessory pathway mediated rhythms, and in fact ablation of such pathways can reduce the incidence of atrial fibrillation (Haïssaguerre et al. 1992). Focal atrial tachycardia is thought to arise from abnormal automaticity of cardiac cells and shows a predilection for sites in close proximity to anatomical structures such as the crista terminalis (Chen et al. 1994; Kalman et al. 1998), the atrial septum (Chen et al. 2000; Marrouche et al. 2002), the coronary sinus (Volkmer et al. 2002; Badhwar et al. 2005; Kistler et al. 2005), the atrioventricular annuli (Morton et al. 2001; Matsuoka et al. 2002; Kistler et al. 2003b; Hachiya et al. 2005) and the pulmonary veins (Kistler et al. 2003a; Hachiya et
Cells around the tricuspid annulus with nodal characteristics have been found (McGuire et al. 1996). Although histologically similar to atrial cells they resembled nodal cells in their cellular electrophysiology, response to adenosine, and connexin expression which suggests that nodal-like cells capable of sustaining ectopic activity exist in these structures where focal tachycardia has been found to originate. Perhaps the most important source of ectopy for the initiation of atrial fibrillation is that arising from the pulmonary veins (Haïssaguerre et al. 2000a). In a landmark study 94% of the 69 ectopic foci found to initiate atrial fibrillation in 45 patients with drug-refractory episodes were within the pulmonary veins (Haïssaguerre et al. 1998). Furthermore, in the same study, radiofrequency ablation of these same foci kept 62% of these subjects free of atrial fibrillation at a mean of eight months follow up. A further study targeting the pulmonary veins by a slightly different technique of wide circumferential ablation with good long term success lends further weight to the role of the pulmonary veins in the genesis and maintenance of atrial fibrillation (Pappone et al. 2000). Anatomical investigation of the pulmonary veins reveals sleeves of atrial myocardium extending into the proximal veins a variable distance (Nathan and Eliakim 1966; Moubarak et al. 2000), the length of which is greatest in the superior veins (Saito et al. 2000). Myocardial bundles can be seen to cover the complete pulmonary vein circumference in 54% of veins examined 1cm from the ostium (Weiss et al. 2002). Fibres of muscle in these ostial regions are variably arranged with one or more layers of longitudinal, circular, oblique or spiral fibre orientation interwoven with non-conducting connective tissue, perhaps explaining the observation of the non-uniform breakthrough pattern of pulmonary vein activity into left atrial tissue (Haïssaguerre et al. 2000b). Zones of activation delay have been observed in canine pulmonary veins.
and correlated with abrupt changes in fascicle orientation, perhaps facilitating reentry and arrhythmias (Hocini et al. 2002). Reports of pulmonary vein aneurysm being implicated as a trigger for atrial fibrillation (Yamane et al. 2000) lend further weight to the importance of vein structure in the electrical output to the left atrium. There is also evidence to support the existence of important differences in membrane channel distribution between the pulmonary veins and the left atrium (Melnyk et al. 2005) as well as greater variation in myocyte size and fibrosis in the pulmonary veins of patients with atrial fibrillation (Tagawa et al. 2001). The stage may then be set for reentry to occur within or around the pulmonary veins when triggered by short-coupled “automatic” discharges (Shah et al. 2001). Study of human embryos with immunohistochemical staining of the conduction system has shown specialised conduction tissue at areas known to demonstrate abnormal automaticity in the adult (Blom et al. 1999). Electron microscopy of autopsy specimens has suggested the presence of P cells, transitional cells and Purkinje cells in the pulmonary veins (Perez-Lugones et al. 2003). Very recently, histological investigation of pulmonary vein sleeves has identified “interstitial cells of Cajal”; cells known to act as pacemakers in the gut which undoubtedly have the potential to act as a pacemaker through their expression of ion channels with I_f properties (Morel et al. 2008). Clearly, these “triggers” found in the pulmonary veins and other sites are important in the initiation of atrial fibrillation, as backed up by evidence to show re-initiation of atrial fibrillation following cardioversion may be a result of local discharge from these areas (Lau et al. 1999; Haïssaguerre et al. 2000c). Why these areas should be predisposed to initiating atrial fibrillation and how their independent discharge should bring about wavelet reentry has been the subject of intense investigation.
1.2.4 The Venous Wave Hypothesis

Building on work gone before, Haïssaguerre et al. (2004b) proposed the venous wave hypothesis. This was an alternative hypothesis to the classical multiple wavelet mechanism proposed by Moe that in at least some patients with paroxysmal atrial fibrillation the pulmonary vein is the source of fibrillatory activity that maintains the atria in fibrillation. Studies have shown that the pulmonary veins are capable of automaticity and triggered activity under conditions of rapid atrial pacing or congestive heart failure (Chen et al. 2001; Okuyama et al. 2003). The pulmonary veins of patients with atrial fibrillation have been shown to have distinctive electrophysiological properties when compared to those of patients without arrhythmia, and also to the atria to which they are attached (Jaïs et al. 2002). The specific architecture of the muscular sleeves within the pulmonary veins of dogs may facilitate reentry (Hocini et al. 2002), and indeed reentry has been observed within human pulmonary veins at multi-electrode basket studies (Kumagai et al. 2004). Pulmonary veins identified as initiators of arrhythmia demonstrate periods of short cycle length during ongoing atrial fibrillation (O'Donnell et al. 2002). Isolation of such pulmonary veins renders the atria less inducible to atrial fibrillation and therefore suggests a dynamic interplay occurring between the atria and pulmonary veins (Oral et al. 2002). Chen et al. (1999) reported longer refractory periods at the proximal portions of the pulmonary veins and this distal-to-proximal gradient has been confirmed by others (Kumagai et al. 2004). This may be somewhat protective against more distal rapid activation being conducted to the atria, however this difference was attenuated with isoprenaline emphasising the dynamic role of the autonomic system in the electrophysiology of the pulmonary veins (Chen et al. 1999). Rapid pacing of isolated pulmonary veins following ablation can
induce local sustained reentry and features of decremental conduction within the paced vein (Takahashi et al. 2003). Arora et al. (2003), performing optical mapping studies of normal canine pulmonary veins, demonstrated that these structures possess both anisotropic conduction and repolarisation heterogeneity. With extrastimulus testing they observed regions of uni-directional conduction block and slowed conduction that initiated leading circle reentry which became sustained with isoprenaline. Pulmonary vein isolation has been shown to produce a progressive prolongation of the atrial fibrillation cycle length, varying in extent from vein to vein and between individuals, culminating in arrhythmia termination in most patients after a significant cumulative increase in the cycle length (Haïssaguerre et al. 2004a). The distinctive electrophysiological properties of the pulmonary veins of patients with atrial fibrillation have been shown to be emphasised by amiodarone therapy and may be responsible for heterogeneous alteration of pulmonary vein electrophysiology (Rostock et al. 2005). Recently, Rostock et al. (2008) have demonstrated differential rate-adaptation of the electrophysiological properties of the pulmonary veins in patients without a history of atrial fibrillation. They observed that the effective refractory period (ERP) of the pulmonary veins was higher than the ERP in the atria at baseline, and that the shortening of ERP in response to 15 minutes of atrial fibrillation was greater in the pulmonary veins than in the atria. This suggests that the changes within the pulmonary veins promote the maintenance of atrial fibrillation to a greater degree than the atria. Thus, there potentially exists within the pulmonary veins alone the electrophysiological milieu necessary for both the initiation and maintenance of atrial fibrillation. This hypothesis is further supported by evidence of continued fibrillatory activity seen in disconnected pulmonary veins (Willems et al. 2003) and the
common observation of slow dissociated pulmonary vein activity. The venous wave hypothesis therefore suggests that pulmonary veins have heterogeneous electrophysiological properties capable of sustaining reentry and that these structures are implicated not only as a trigger of atrial fibrillation in patients with the appropriate substrate, but also as a source of “venous waves/drivers” that are capable of maintaining the atria in fibrillation.

1.2.5 Rotors and Activation Gradients

Localised regions of high-frequency activity demonstrating spatio-temporal periodicity have been suggested to act as drivers of atrial fibrillation (Skanes et al. 1998; Jalife et al. 2002; Everett et al. 2006; Lin et al. 2006). Jalife et al. (1998) proposed the theory of “mother rotors” as drivers of atrial fibrillation, with fibrillatory activity of nearby myocardium unable to maintain 1:1 conduction with the rapid site. Evidence for organisation of atrial fibrillation has come from animal optical mapping studies which have used spectral analysis to demonstrate repetitive high frequency activity during atrial fibrillation, consistent with the hypothesis of “driving” rotors (Kalifa et al. 2006). Similar findings have also been reported in humans (Wu et al. 2002; Lazar et al. 2004; Sahadevan et al. 2004; Sanders et al. 2005a; Haïssaguerre et al. 2006b). Gradients of activation from the pulmonary veins to the remaining atrium of patients with paroxysmal atrial fibrillation have been reported (Sanders et al. 2006). However, such specific patterns of activation gradient are less conclusive in persistent atrial fibrillation. Retrospective analysis of ablation of paroxysmal atrial fibrillation shows that atrial fibrillation cycle length prolongation and eventual termination occurs at
sites of high frequency activation (Sanders et al. 2005a); this has not been shown for persistent atrial fibrillation. Further discussion of the identification of high frequency activation sites and their role in the atrial substrate is discussed in Section 1.3.5.

1.2.6 Summary

Since the first descriptions of atrial fibrillation, our understanding of the nature of this rhythm has expanded and the explanations for its occurrence evolved. From the initial Multiple Heterotopous Centres Theory, to the Multiple Wavelet Hypothesis, the more recent Venous Wave Hypothesis, and the proposed concept of Rotors driving atrial fibrillation, it is apparent that complex and varied mechanisms are at play in the initiation and maintenance of this rhythm. It is probable that both focal activity and reentry are responsible for the maintenance of atrial fibrillation. However, these mechanisms may not have to be present in the same person at the same time (Wu et al. 2004). Changes in electrophysiological characteristics of the myocardium could convert multiple wavelet reentry atrial fibrillation into focal discharge atrial fibrillation and vice-versa. Alternatively, a partnership between focal discharge and reentrant mechanisms might be necessary for maintenance of atrial fibrillation. Much is still to be learnt about the electrophysiological basis of atrial fibrillation.

1.3 Triggers and Substrate in Atrial Arrhythmia

The concept of triggers, initiators and perpetuators advanced by Allessie et al. (2001) requires that for atrial fibrillation to exist it must be initiated by some trigger and then maintained by favourable electroanatomical properties, or substrate.
1.3.1 Focal Triggers

Abnormal impulse initiation may be divided into automaticity and triggered activity. Automaticity is the property of cardiac cells to undergo spontaneous diastolic depolarisation and initiate an electrical impulse in the absence of external electrical stimulation (Peters et al. 2000). This is a known property of a variety of cardiac tissues including the sinus node and subsidiary pacemaker sites and is thought to be due to gradual inward net current (\(\text{I}_i\)) (Brown et al. 1979). Triggered activity is a term used to describe impulse initiation dependent on after-depolarisations. After-depolarisations are oscillations in membrane potential that follow the upstroke of an action potential (Cranefield 1977). Delayed after-depolarisations occur following the repolarisation of an action potential. This can cause triggered activity if the after-depolarisation reaches threshold for a subsequent action potential. The most widely recognised cause of delayed after-depolarisation triggered activity is digitalis (Ferrier and Moe 1973). In contrast, early after-depolarisations occur prior to the repolarisation of an action potential. These tend to delay the repolarisation phase and are important in the mechanism of the congenital long QT syndromes. Mutated genes such as SCN5A, KVLQT1 and HERG prolong action potential duration and allow early after-depolarisations (Roden et al. 1996). Evidence supporting focal sources in promoting atrial fibrillation comes from studies characterising atrial tachycardia late after ablation for atrial fibrillation. Haïssaguerre et al. (2005b) reported on 55 atrial tachycardias of which 20 were characterised as focal in origin, 27 as macro-reentrant and the remaining 8 (localised to the atrial septum) displayed mixed mechanistic characteristics. Gerstenfeld et al. (2005) reported a small series of 5 patients in whom a focal atrial tachycardia was present following segmental pulmonary vein isolation.
Arentz et al. (2007) performed a sophisticated basket-mapping study of the pulmonary veins to characterise spontaneous activity initiating atrial fibrillation and found that the first ectopic activity of all events was of focal origin. Nevertheless, some tachycardias from the distal pulmonary veins of short cycle length demonstrated continuous activity throughout a significant proportion of the tachycardia cycle length favouring some reentrant mechanism occurring subsequently. Despite the highly sophisticated mapping techniques employed there remains some methodological problems in assessing the mechanism of tachycardia in pulmonary veins; entrainment mapping is difficult at high rates, pacing manoeuvres may terminate tachycardia, capture of the pulmonary vein without capture of adjacent structures is an issue, and rapid pacing of itself induces fractionated electrograms (Willems and Rostock 2007). Markowitz et al. (2007) have demonstrated that adenosine can assist in the differentiation between focal and reentrant tachycardia, and furthermore micro-reentrant circuits can also be distinguished from automatic focal atrial tachycardia by this means. This also suggests that some focal sources previously thought to be due to automaticity or triggered activity may in fact be due to localised reentry.

1.3.2 Localised Reentry

The requirements for reentry are:

(i) uni-directional conduction block,

(ii) a core of inexcitable tissue around which the wave-front propagates, and

(iii) the maintenance of excitable tissue ahead of the propagating wave-front (the “excitable gap”) (Peters et al. 2000).
The excitable gap is facilitated by slowing of conduction and/or shortening of the refractory period. The wavelength (in metres) is the product of the conduction velocity (in metres/second) and the refractory period (in seconds). This is critical to the development of atrial reentry; a shorter wavelength requires less atrial mass to sustain reentry. Or to put it another way, a given atrial mass can sustain more reentrant circuits if the wavelengths are shorter. It is important to realise that the above requirements may be anatomical or functional. The core of inexcitable tissue may be non-myocardial tissue (such as a valve) or an area of functional block (such as the crista terminalis) (Yamashita et al. 1992; Tai et al. 1998). The excitable gap will depend on the refractory period of the circuit, itself highly influenced by drugs, hormonal and autonomic factors. Sanders et al. (2005b) demonstrated local reentry by performing endocardial mapping with a multi-spline catheter during focal atrial tachycardia. Features such as entrainment and a large proportion of cycle length observable within the mapped area were able to be established. Haisaguerre et al. (2005b) have reported similar observations during atrial fibrillation organised by prior ablation. Indeed, localised reentry can be mapped to sites where the greatest impact of ablation on the atrial fibrillation cycle length has been shown to occur; the pulmonary veins, the fossa ovalis, the coronary sinus and the base of the left atrial appendage. Although these may be iatrogenic from the prior ablation procedure, the fact that they share common sites with critical regions maintaining atrial fibrillation is evidence that these areas of localised reentry are integral to the initiation and maintenance of arrhythmia. This group subsequently were able to demonstrate features of small circuits consistent with local reentry by simultaneous mapping with a multi-spline catheter during the
latter stages of the initial ablation procedure for atrial fibrillation when periods of relative organisation of electrograms can be seen (Haïssaguerre et al. 2006a).

1.3.3 Anatomical Structures with Site-specific Conduction Properties

Integral to the theories of the electrophysiological basis of atrial fibrillation is the concept of heterogeneous conduction properties. There are regions within the atria where predictable alterations in these properties are seen.

1.3.3.1 Right Atrium

The crista terminalis has unique conduction properties; specifically the gap junctions are located at the poles of muscle cells resulting in a higher degree of “end-to-end” connections than other myocardial tissue (Saffitz et al. 1997). This confers a high degree of anisotropy to this structure, resulting in conduction velocities 10 times greater in the longitudinal than the transverse direction (Saffitz et al. 1994). This feature of preferential conduction has been studied for some time (Spach et al. 1981) and had led some investigators to conclude that specialised conduction exists within the atria, despite no histological evidence of Purkinje-equivalent fibres (Liebman 1985). Numerous studies have explored the functional conduction properties of the crista terminalis (Olgin et al. 1995; 1996; Tai et al. 1998; 2004). In addition, site-specific conduction delays in the low right atrial myocardium and the presence of non-uniform anisotropic characteristics of the posterior triangle of Koch have been suggested as critical substrate for induction of atrial fibrillation (Papageorgiou et al. 1996). This area of the atrium has been shown to have complex electrophysiological properties and
multiple inputs to the atrioventricular node (McGuire et al. 1993) which may account for its unique conduction characteristics.

1.3.3.2 Inter-atrial Connections

The inter-atrial connections are regions where the electrical wave-front traverses from right to left during sinus rhythm. The most important and well studied of these is Bachmann’s bundle which is located superiorly on the anterior surface of the inter-atrial septum. This connection has been demonstrated in animal experiments to have differing conduction properties than other atrial myocardium (velocity of conduction is faster and ERP is higher), representing a potential substrate for reentry to occur (Platonov 2007). In humans, left atrial mapping studies have demonstrated Bachmann’s bundle as well as posterior and inferior connections in the vicinity of the coronary sinus (De Ponti et al. 2002; Markides et al. 2003; Betts et al. 2004; Lemery et al. 2007). Most of these studies have been conducted in patients with atrial fibrillation during sinus rhythm and demonstrate Bachmann’s bundle as critical, however for atrial ectopic beats occurring from the posterior left atrium it is easy to propose how the inferior connections may contribute to initiation of arrhythmia. In addition, fibro-fatty degeneration of Bachmann’s bundle has been reported as common among patients with a history of atrial fibrillation (Becker 2004). Recently, a study of 84 post-mortem hearts has confirmed inter-atrial muscular connections present anteriorly at Bachmann’s bundle, posteriorly between right pulmonary veins and inferiorly between the coronary sinus and right inferior pulmonary vein (Platonov et al. 2008). Several investigators have used the knowledge of the anatomy of inter-atrial connections to guide placement of an atrial pacemaker lead with the aim of shortening atrial
activation and thereby reducing atrial fibrillation (Bailin et al. 2001; Padeletti et al. 2001; Hermida et al. 2004; de Voogt et al. 2007). The results of these studies are mixed, perhaps due to varying positions of the pacing lead and accompanying anti-arrhythmic pacing algorithms, as well as heterogeneity within the atrial fibrillation population itself. Nevertheless, it remains a promising area of research for patients with sick sinus syndrome, a group in whom atrial fibrillation is common.

1.3.3.3 Left Atrium

In the left atrium, several structures (besides the pulmonary veins; see Sections 1.2.3 and 1.2.4) have been investigated for their site-specific properties. The left lateral ridge (the infolding of myocardium between the left pulmonary vein antra and the appendage) is an area of interest due to the close proximity of the vein of Marshall and the ganglionic plexus epicardially (Cabrera et al. 2008). It is also a challenging area for ablation, due to its narrow superior aspect making catheter stability difficult. The septopulmonary bundle is of recent interest as a left atrial “crista-equivalent”. Markides et al. (2003) demonstrated by non-contact mapping a vertical line of functional block in the posterior left atrium corresponding to a region of abrupt change in fibre orientation seen in 10 post-mortem hearts. High-resolution mapping in a sheep model has demonstrated wave-break occurring at the regions along the septopulmonary bundle that showed sharp changes in fibre direction and abrupt increases in myocardial thickness (Klos et al. 2008). Waves propagating from the pulmonary veins into the posterior left atrium triggered reentry and atrial fibrillation by breaking at boundaries along this bundle. Roberts-Thomson et al. (2008) have described a vertical line of functional conduction delay in a consistent anatomical
location in the posterior left atrium of patients with structural heart disease, most markedly with atrial dilatation. This line facilitates circuitous wave-front propagation, suggesting a potential role in arrhythmogenesis.

1.3.4 Complex Fractionated Atrial Electrograms

One of the characteristic features of the underlying substrate of atrial fibrillation is the presence of complex fractionated atrial electrograms (CFAE). CFAE observed during intra-operative mapping of human atrial fibrillation are found mostly in areas of slow conduction and/or at pivot points where the wavelets turn around at the end of arcs of functional block (Konings et al. 1994). Results from this pivotal publication by the laboratory of Allessie and colleagues were confirmed by later studies in which the morphology of electrograms during atrial fibrillation reflected the occurrence of various specific patterns of conduction (Konings et al. 1997). The authors postulated that electrogram morphology might be used to identify regions with structural conduction disturbances involved in the perpetuation of atrial fibrillation. Prior to this, Cosio et al. (1986) had identified complex electrograms as important in the determination of abnormal conduction in atrial flutter. Jaïs et al. (1996) initially described regional bi-atrial disparities in endocardial fractionation in paroxysmal atrial fibrillation and found that complex electrical activity was more frequently found in the septal and posterior regions of both atria, with more regular activity seen in the trabeculated atria. These findings led Nademanee et al. (2004) to hypothesise that if CFAE were to be selectively eliminated by catheter ablation, wavelet reentry should stop, thereby preventing atrial fibrillation perpetuation. The earlier observations that
led to the multiple wavelet theory as the underlying mechanism for atrial fibrillation (random reentry with meandering wavelets) is at odds with the observation of site-specific reentry. Possible explanations include the linking phenomenon (Gerstenfeld et al. 1992), which may explain maintenance of the direction of wavelet propagation during atrial fibrillation, and the existence of adverse electrical remodelling with repeated episodes of atrial fibrillation (Wijffels et al. 1995). By targeting sites of CFAE for ablation, Nademanee et al. (2004) reported 70% of a balanced paroxysmal and persistent cohort were arrhythmia-free off medication one year following a single ablation procedure. Furthermore, with a mean of 1.24 ablation procedures and a small minority still on anti-arrhythmic drugs, 91% were free of atrial fibrillation. The inter-atrial septum was the most common site for CFAE in this study; other common sites were the pulmonary veins, left atrial roof and proximal coronary sinus. It is important to note that while many previous studies have used an epicardial approach where areas such as the septum, pulmonary veins and coronary sinus os are not accessible (Cox et al. 1991; Gerstenfeld et al. 1992), these were precisely the sites found to contain CFAE at endocardial mapping. CFAE may be seen more frequently at sites of known site-specific conduction abnormalities (Roberts-Thomson et al. 2008). In addition, an association between CFAE and atrial fibrillation cycle length was demonstrated by Rostock et al. (2006) who observed a shortening in cycle length preceding the development of maximum fractionation at 91% of mapped sites, suggesting a functional nature to these electrograms. More recently, Nademanee et al. (2008) have published long-term outcomes for high-risk patients ablated by this technique. For a mean of 1.68 procedures per patient, 81% of these challenging cases were in sinus rhythm at an average of 2.3 years follow up. Just 13% of those free of
atrial fibrillation required anti-arrhythmic agents to maintain sinus rhythm. However, these results have not been reproduced by operators seeking to emulate this success. Although most investigators have incorporated CFAE-targeted ablation into a multifaceted ablation approach (Takahashi et al. 2007; Porter et al. 2008; Verma et al. 2008), Oral et al. performed solely CFAE-targeted ablation in 100 patients with chronic atrial fibrillation and reported modest success of 33% maintenance of sinus rhythm without drugs at 14 months mean follow-up. Perhaps one reason for the lack of reproducible outcomes by this method is that operators have been reliant on subjective analysis of CFAE classification as guided by the published definitions. Definitions for CFAE are plentiful and varied, and include:

(i) electrograms with an FF interval <100ms or continuous activity (Jaïs et al. 1996),

(ii) fractionated electrograms composed of ≥2 deflections, perturbation of the baseline with continuous deflection of a prolonged activation complex, or atrial electrograms with a cycle length ≤120ms (Nademanee et al. 2004),

(iii) fractionated potentials with ≥3 deflections from the isoelectric line or continuous activity as their criteria for CFAE (Rostock et al. 2006), and

(iv) electrograms with a cycle length ≤120ms or shorter than the coronary sinus, or those that were fractionated or displayed continuous electrical activity (Oral et al. 2007).

It is perhaps the variability of these descriptions that accounts for some of the inconsistent results reported across different centres using CFAE-targeted ablation. Takahashi et al. (2008) attempted to define the characteristics of electrograms which
identified successful ablation by measuring the effect of ablation on change in atrial fibrillation cycle length. They found that electrograms with a temporal activation gradient of >70ms or continuous activity indicated favourable sites for effective ablation. Algorithms for quantification of electrogram fractionation have become commercially available and the use of such algorithms to complement established ablation strategies should aim to target critical sites maintaining fibrillation, while sparing bystander atrium. The first publication using an automated fractionation detection tool to describe ablation outcomes has taken advantage of the reproducible nature of automated algorithms allowing it to guide ablation in a consistent fashion across three centres to demonstrate an incremental success rate over historical controls (Verma et al. 2008). While there is mounting evidence to suggest that mapping CFAE by automatic techniques identifies critical ablation sites, the effectiveness of CFAE-targeted ablation is yet to be widely demonstrated. Nevertheless, a consistent approach to characterise fractionation is the first step towards establishing a reproducible method on which trials designed to address the efficacy of CFAE-guided ablation may rely.

1.3.5 Dominant Frequency

Analysis of electrograms within the time domain has led to identification of features such as automatic activity and complex fractionation, however due to the apparently chaotic nature of electrical activity during atrial fibrillation it is difficult to see underlying patterns of depolarisation that may be important in the substrate maintaining atrial fibrillation. This has led to the analysis of electrograms in the
frequency domain by fast fourier transform. Using this technique, information about local activation may be distilled from an electrogram otherwise too complex or noisy to be appreciated in the time domain. The atrial electrograms obtained during fibrillation are often such electrograms and hence fast fourier transform “unlocks” that information for analysis. The fast fourier transform attempts to reduce a complex electrogram to its constituent sine wave components and plots the frequency of these waves against the amplitude of the wave power to represent the electrogram in the frequency domain. The frequency value demonstrating peak power in this spectrum is termed the dominant frequency (DF). A strong correlation has been shown experimentally between DF and atrial rotor frequency observed by optical mapping (Sarmast et al. 2003). Sites demonstrating high DF have been proposed as “drivers” of atrial fibrillation (Jalife et al. 1998; Berenfeld et al. 2000; Sanders et al. 2005a). Evidence for organisation of atrial fibrillation from optical mapping in animal studies has used spectral analysis to demonstrate repetitive high frequency activity with temporal and spatial periodicity during atrial fibrillation (Skanes et al. 1998; Kalifa et al. 2006). Similar findings by alternative, lower-resolution techniques have been reported in humans (Wu et al. 2002; Lazar et al. 2004; Sahadevan et al. 2004; Sanders et al. 2005a). Higher DF has been reported in the left atrium of patients with paroxysmal atrial fibrillation (Lazar et al. 2004; Lin et al. 2006). Furthermore, the maximal DF has been reported in the pulmonary veins in patients with paroxysmal but not persistent atrial fibrillation (Sanders et al. 2006). Persistent atrial fibrillation has a less conclusive pattern of DF distribution. Although some publications have shown a higher mean DF in the left atria, particularly around the pulmonary veins (Wu et al. 2002), others have shown that this distinction disappears for longstanding atrial fibrillation where other
sites are observed to predominate (Lazar et al. 2004; Atienza et al. 2006; Sanders et al. 2006; Stiles et al. online early). Isolation of the pulmonary veins abolishes this left-to-right gradient in paroxysmal atrial fibrillation and, for the subset of patients with persistent atrial fibrillation in whom a left-to-right gradient exists, success of pulmonary vein isolation alone exceeds that of persistent atrial fibrillation without such gradient (Lazar et al. 2006). Retrospective analysis of ablation of paroxysmal atrial fibrillation shows that atrial fibrillation cycle length prolongation and eventual termination occurs at sites of high DF (Sanders et al. 2005a). This has not been shown for persistent atrial fibrillation where DF is distributed more evenly throughout atrial regions, prompting a more aggressive multi-region approach to be advocated when ablating longstanding persistent atrial fibrillation (Haïssaguerre et al. 2005a). The precise role of DF analysis to guide ablation clinically, like that of CFAE and ganglionated plexi, is yet to be established.

1.3.6 The Neural Basis of Atrial Fibrillation

An additional dimension to the substrate of atrial fibrillation is that of the influence of the autonomic nervous system. It has long been observed that electrical stimulation of the autonomic nerves to the heart could induce atrial fibrillation (Lewis et al. 1921a; Hoff and Geddes 1955). Atrial fibrillation has been proposed to be a consequence of disordered autonomic tone (Coumel 1994). Neural influences on the atria mediated via the autonomic ganglia found in the epicardial fat pads have been hypothesised to play an important role in converting ectopic activity into atrial fibrillation (Scherlag et al. 2005a). This is based on the findings that during stimulation of canine atrial ganglia
fewer ectopic beats were required to initiate atrial fibrillation and, conversely, that blockade of neural elements by lignocaine inhibits inducibility to atrial fibrillation by ectopic beats. Applying this knowledge clinically, Scherlag et al. (2005b) added ablation of the left atrial ganglionated plexi to the usual strategy of pulmonary vein antrum isolation in 33 of 60 patients with paroxysmal or persistent atrial fibrillation. Those receiving atrial denervation had less recurrence of atrial fibrillation at short-term follow up (median 5 months). Techniques by which to identify ganglionated plexi for subsequent ablation have since been published. Using high-frequency electrical stimulation, an autonomic ganglion is identified by profound ventricular rate slowing and subsequent ablation of the same area renders the stimulation response negative on re-testing (Lemery et al. 2006). Pappone et al. (2004) have published a 99% success rate at 12 months follow up for patients who demonstrated complete vagal denervation at their ablation procedure. Additionally, failure to achieve vagal denervation was predictive for recurrence of atrial fibrillation. Takahashi et al. (2006) characterised the change in atrial fibrillation cycle length occurring with vagally-mediated atrioventricular block during pulmonary vein isolation and found a greater decrease in the cycle length of pulmonary vein activity than in the coronary sinus, suggesting that vagal excitation enhances the driving role of pulmonary veins. Recently, animal data linking the action of ganglionated plexi to complex fractionated electrograms (Lin et al. 2007) and frequency gradient (Lu et al. 2008) have been published. Convincing outcome data on the use of this technique to assist ablation is yet to be published, but this remains a promising area of research.
1.3.7 Substrate Associated with Atrial Flutter

Experimental models of atrial flutter have shown abnormal electrical substrate to be present. Morton et al. (2002) demonstrated in a sheep model that prolonged atrial flutter resulted in abrupt-onset reduction in refractoriness and slower-onset reduction in conduction velocity. Much work on atrial flutter has been performed in the sterile pericarditis dog model which has been shown to dependably produce atrial flutter in a time course similar to the post-bypass arrhythmias seen clinically. The inducibility of atrial flutter in this model is independent of differences in ERP, conduction time or threshold (Page et al. 1986). More recently, the role of inflammation in atrial flutter has been highlighted in a study in which the usually reliable induction of atrial flutter in this model was abolished by pre-treatment with prednisone (Goldstein et al. 2008). Interestingly, this observation of no atrial flutter with steroid was accompanied by lower ERP compared to the 11 untreated pericarditis dogs, strongly suggesting that this aspect of electrical remodelling is neither integral to the initiation nor maintenance of atrial flutter. Histological and gross inspection of the atria revealed marked structural changes of inflammation in the untreated group, all of whom (bar one with atrial fibrillation) developed atrial flutter. Therefore, suppression of inflammation by corticosteroid is able to prevent subsequent arrhythmia in dogs given sterile pericarditis which has intriguing implications for patients following cardiac surgery. Patients with chronic atrial flutter have been observed to have electrical remodelling by way of shortened monophasic action potential durations with impaired rate adaptation compared to control patients (Franz et al. 1997). Sparks et al. (2000) studied patients with paroxysmal atrial flutter and observed a reduction in ERP immediately after 5-10 minutes of induced atrial flutter, followed by a return to
baseline ERP over a period of minutes. In patients with chronic atrial flutter however, ERP remained low out to 30 minutes and was seen to recover only when re-tested at 3 weeks. These patients also demonstrated an improvement in corrected sinus node recovery time (CSNRT) over the 3 week period suggesting sinus node dysfunction as a direct result of chronic atrial flutter. Further evidence for remodelling of sinus node function with atrial flutter is reported by Daoud et al. (2002) who studied patients with chronic atrial flutter following ablation and observed impaired sinus node function which recovered over a 3 month period. Differences in the underlying substrate seen in atrial flutter between young and old have been published, with younger patients tending toward slowest conduction in the lateral isthmus while older patients demonstrate a low voltage zone and slowest conduction in the medial isthmus (Huang et al. 2008). The substrate predisposing to atrial flutter may differ from that seen in atrial fibrillation alone. Patients with typical atrial flutter in addition to paroxysmal atrial fibrillation have been shown to have more frequent recurrence of arrhythmia following pulmonary vein cryoisolation with accompanying isthmus line (Moreira et al. 2007). This suggests non-pulmonary vein sites are more important to the maintenance of atrial fibrillation in patients with co-existent atrial flutter. This may reflect the observation that an increase in the dispersion of refractoriness predicts the inducibility of atrial fibrillation in patients undergoing ablation for atrial flutter (Ramanna et al. 2005).
1.3.8 Typical and Atypical Atrial Flutter

Electrophysiological studies have shown that the simple ECG definition of an organised atrial rhythm with a rate typically between 250 and 350 beats per minute includes many atrial tachycardias using a variety of reentry circuits. The reentry circuits often occupy large areas of the atrium and are referred to as “macro-reentrant” (Blomstrom-Lundqvist et al. 2003). Most early work on atrial flutter focussed on the more common typical anti-clockwise flutter; i.e. atrial flutter characterised by negative flutter waves in the inferior ECG leads and a circuit moving in an anti-clockwise direction when viewed from the left anterior oblique radiographic view. This classic type of atrial flutter is dependent on the cavotricuspid isthmus. Other forms of atrial flutter have been described, including clockwise flutter and true atypical flutter. Clockwise atrial flutter uses the same circuit with the same endocardial barriers as its anti-clockwise counterpart and is best considered a form of typical atrial flutter (Kalman et al. 1997). It is amenable to the same ablation treatment as anti-clockwise atrial flutter; i.e. cavotricuspid isthmus ablation. Clockwise isthmus-dependent atrial flutter shows the opposite ECG pattern to the anti-clockwise form – positive flutter waves in the inferior leads and wide, negative flutter waves in lead V1, transitioning to positive waves in lead V6. Olgin et al. (1997) showed that even in patients with clinical anti-clockwise atrial flutter, clockwise atrial flutter is frequently induced before ablation and is dependent on the site of induction; pacing from the smooth right atrium induces anti-clockwise atrial flutter, whereas pacing from the trabeculated right atrium induces clockwise atrial flutter. Atrial flutter caused by macro-reentry circuits that do not use the cavotricuspid isthmus are less common. Most are related to an atrial scar that creates conduction block and a central obstacle for reentry (Blomstrom-Lundqvist et
al. 2003). Prior cardiac surgery involving the atrium (such as repair of congenital heart disease, mitral valve surgery or the atrial maze procedure) is a common cause (Nakagawa et al. 2001; Triedman et al. 2001), as is (more latterly) ablation for atrial fibrillation. True atypical atrial flutters usually show heterogeneous ECG morphologies, shorter cycle lengths than typical atrial flutter, and frequent transitions from and to atrial fibrillation (Kalman et al. 1997). Ablation of these macro-reentrant loops is particularly challenging as each circuit is unique to each patient. Furthermore, patients with substantial atrial scarring may not demonstrate the ECG features of typical flutter when cavotricuspid isthmus-dependent flutter is indeed present, and conversely an atypical flutter circuit may manifest on the surface ECG as common-type atrial flutter (Chugh et al. 2006).

### 1.4 Inter-relationships between Atrial Flutter and Atrial Fibrillation

Atrial flutter has a close inter-relationship with atrial fibrillation; the two rhythms frequently co-exist (Halligan et al. 2004) and share many of the same aetiological factors (Vidaillet et al. 2002). The inter-relationship is further distorted, in that for some epidemiological reports the two conditions are reported together (Australian Institute of Health and Welfare 2008). The substrate of atrial fibrillation however has been more extensively investigated than that of atrial flutter and whether these two arrhythmias share this substrate is unknown.
1.4.1 Atrial Flutter begets Atrial Fibrillation

The incidence of atrial fibrillation episodes prior to atrial flutter ablation is, perhaps not surprisingly, a strong predictor for the occurrence of atrial fibrillation after the procedure (Da Costa et al. 2002; Hsieh et al. 2002; Ramanna et al. 2005). However, ablation of atrial flutter has been observed to significantly reduce the occurrence of atrial fibrillation at 496±335 days post-ablation from 55% to 33% (Schmieder et al. 2003). Despite this reduction a significant proportion, perhaps even the majority with long-term follow-up, eventually develop atrial fibrillation (Chinitz et al. 2007; Meissner et al. 2007; Moreira et al. 2008). Paydak et al. (1998) reported that 20±9 months after atrial flutter ablation, 25% of patients have atrial fibrillation; Hsieh et al. (2002) published a series of 333 patients in which 31% of patients had occurrence of atrial fibrillation at 29±17 months follow up; and Ellis et al. (2007) described new atrial fibrillation in 82% at 39±11 months follow up. Independent factors predictive of atrial fibrillation within 6 months following ablation for atrial flutter are left ventricular ejection fraction and, for those without prior atrial fibrillation, degree of mitral regurgitation (Paydak et al. 1998; Da Costa et al. 2002). Yang et al. (2003) reported mechanisms of transition from flutter to fibrillation observed in the laboratory during atrial flutter ablation procedures as lower or upper loop reentry, and focal ectopic activity (including pulmonary vein discharge). After 4 weeks of experimental atrial flutter, conversion to atrial fibrillation has been demonstrated to be dependent on critically timed extra-stimuli, as demonstrated by Morton et al. (2002) in a sheep model. It is being increasingly recognised that macro-reentry may be a significant contributor to the maintenance of long-standing persistent atrial fibrillation (Haïssaguerre et al. 2005b). Indeed, ablation of conduction gaps in the crista terminalis
can result in atrial fibrillation organising to atrial flutter (Liu et al. 2002). In the subgroup of patients with atrial fibrillation in whom the administration of a class 1C anti-arrhythmic agent converts them to atrial flutter, it has been shown that atrial flutter ablation, together with continuation of the drug, results in satisfactory control of both arrhythmias (Schumacher et al. 1999).

1.4.2 Atrial Fibrillation begets Atrial Flutter

Key to the understanding of the close inter-relationship of atrial flutter and atrial fibrillation is the recognition that typical atrial flutter almost always develops from antecedent atrial fibrillation of variable duration. The classic model of reentry seen in clinical practice is that of atrioventricular reentry tachycardia. In this reentry circuit, a critically timed extra-stimulus encounters block in one limb of the circuit which is then able to subsequently conduct in the opposite direction, thereby setting up a circuit. In atrial flutter this pre-existing circuit may not exist, therefore more than a simple ectopic is required for its initiation. The line of functional inter-caval block needs to be created by a burst of rapid atrial rhythm for stable atrial flutter to ensue (Shimizu et al. 1991). Some patients have a fixed inter-caval line of block and others have been shown to have at least some degree of functional block (Olgin et al. 1995), therefore atrial flutter may develop without preceding atrial fibrillation only in those with fixed block. Waldo and Cooper (1996) observed triggers in post-bypass patients that led to transitional atrial fibrillation and then atrial flutter. Roithinger et al. (1997) observed regular right atrial activation during atrial fibrillation which slowed and organised into atrial flutter. If the pre-requisite inter-caval functional block is not achieved however,
either the atrial fibrillation will spontaneously revert to sinus rhythm or it will persist as fibrillation rather than become atrial flutter. In short, there is no atrial flutter if the line of functional block between the venae cavae does not form. It would therefore seem that atrial fibrillation of variable duration (very brief to prolonged episodes) precedes the onset of atrial flutter. The best evidence of this association is perhaps the study by Ortiz et al. (1994) in the sterile pericarditis model on the association between the length of inter-caval block and atrial rhythm. During all episodes of stable pacing-induced atrial flutter, a line of functional block with a mean length of 24mm was localised on the right atrial free wall. When the previously stable line of functional block decreased to a mean of 16mm the line of functional block was not long enough to maintain stable atrial flutter and conversion to atrial fibrillation resulted. When sustained atrial fibrillation evolved to stable atrial flutter, there was reformation of a long line of functional block, long enough (≥ prior length) to create a stable reentrant circuit. Thus, the atrial rhythm was shown to depend directly on the length of functional block between the inferior and superior venae cavae. Testing the hypothesis that atrial fibrillation facilitates development of the line of functional conduction block along the crista terminalis required to sustain atrial flutter, the effect of trigger elimination by performing pulmonary vein isolation without cavitricuspid isthmus ablation was studied by Wazni et al. (2003). In 59 patients with both atrial fibrillation and atrial flutter, 32 of these patients developed episodes of atrial flutter acutely. However, only 3 had sustained atrial flutter after 8 weeks suggesting that, without the antecedent atrial fibrillation, atrial flutter was unable to be initiated. This concept of treating fibrillation to cure flutter still requires further evaluation before becoming mainstream therapy. Thus, it can be seen that atrial flutter and atrial fibrillation are
closely inter-related and that the features previously shown in the underlying atrial substrate of atrial fibrillation are likely to be also present in atrial flutter, even in those in whom no clinical history of atrial fibrillation is noted. Critical to our management of patients with both atrial flutter and atrial fibrillation is an understanding of the interactions and shared characteristics of these rhythms.

1.5 Rate-related Remodelling

1.5.1 Electrical Remodelling

Wijffels et al. (1995) observed that in normal goats, induction of atrial fibrillation was relatively difficult and lasted for just a few seconds. With repetitive induction of arrhythmia however, the cycle length of the atrial fibrillation shortened and episodes became sustained. This led to the notion that “atrial fibrillation begets atrial fibrillation” by means of shortening in atrial ERP after periods of atrial fibrillation. Further experimental studies have confirmed this finding in dogs (Morillo et al. 1995; Elvan et al. 1996; Goette et al. 1996) with the additional observations that atrial fibrillation caused an increase in the heterogeneity of refractoriness (Fareh et al. 1998) and maladaptation of refractoriness to rate (Lee et al. 1999). While initial studies did not observe conduction abnormalities, subsequent canine studies by Gaspo et al. (1997) demonstrated that progressively longer episodes of atrial fibrillation also resulted in conduction slowing. Attenuation of conduction velocity was maximal at 6 weeks, and lagged behind that of maximum reduction in ERP at 7 days, suggesting that these abnormalities are mediated by different mechanisms. Morton et al. (2002) demonstrated a reduction in atrial refractoriness in a sheep model with sustained
atrial flutter. Again a reduction in conduction velocity was seen to develop over a slower time course. Thus, the mechanism by which electrical remodelling of the atria lends toward the perpetuation of arrhythmia in response to atrial fibrillation is by a shortening of the reentrant “wavelength”. Human studies of patients with recent atrial arrhythmia have also been shown to have shorter ERP than control groups, as well as conduction delay and sinus node dysfunction (Cosio et al. 1983; Kumagai et al. 1991). Yu et al. (1999) demonstrated shorter ERP with impaired rate adaptation and depressed conduction following cardioversion for longstanding atrial fibrillation, with the ERP gradually increasing after 4 days of sinus rhythm. Garratt et al. (1999) evaluated the effect of repeated episodes of atrial fibrillation on atrial electrical remodelling. While marked remodelling was observed with five days of atrial fibrillation, two days of sinus rhythm was adequate to reverse all abnormalities. Despite repetitive episodes of atrial fibrillation, there were no additive changes observed in atrial electrical remodelling. Sparks et al. (2000) documented the changes in atrial ERP following ablation for chronic atrial flutter and observed a recovery in ERP over a 3 week period. In the same study, 10 minutes of induced atrial flutter in a group of patients presenting in sinus rhythm for their flutter ablation reduced ERP but this recovered within 15 minutes. To investigate the possibility that early and repeated cardioversion of atrial fibrillation could avoid the cycle of adverse electrical remodelling, Fynn et al. (2002) evaluated this strategy in the clinical setting. Despite an aggressive protocol to achieve and maintain sinus rhythm, frequent cardioversion failed to prevent the progression to more atrial fibrillation. This occurred despite a well documented increase in atrial ERP at successive cardioversions indicating that reversal of electrical remodelling was in fact taking place. Indeed, their findings suggest that in
patients with a history of atrial fibrillation, sinus rhythm does not beget sinus rhythm. In addition to the effects on ERP and conduction, several investigators have observed remodelling of the sinus node that develops soon after the initiation of arrhythmia and reverses after restoration of sinus rhythm. Kumagai et al. (1991) reported significantly longer sino-atrial conduction time (SACT) and CSNRT in patients recently cardioverted from chronic lone atrial fibrillation compared to controls. Elvan et al. (1996) demonstrated in dogs that atrial fibrillation was responsible for impaired sinus node function which partially reversed when sinus rhythm was restored. Other investigators have confirmed the prolongation of CSNRT in patients following cardioversion for atrial fibrillation compared to control patients (Tse et al. 1999) and furthermore this finding may be associated with a trend to recurrence of atrial fibrillation (Manios et al. 2001). This phenomenon of sinus node remodelling does not appear unique to atrial fibrillation but has also been demonstrated with atrial flutter (Sparks et al. 2000; Daoud et al. 2002). Hocini et al. (2003) demonstrated in 20 patients with a documented >3 second pause post-termination of atrial fibrillation that isolation of the pulmonary veins and linear atrial ablation improved sinus node function as measured by ambulatory heart rate parameters and CSNRT at 2 years. 19 of these patients avoided the implantation of a pacemaker, including 1 with ongoing infrequent episodes of atrial fibrillation.

1.5.2 Structural Remodelling

While the above electrical changes observed due to atrial arrhythmia are a relatively recent finding, Davies and Pomerance (1972) were the first to suggest structural
change due to atrial fibrillation itself. After post-mortem examination of 100 patients with atrial fibrillation, they described loss of atrial myocardium in the region of the sinus node and nodal artery stenosis in patients with long-term atrial fibrillation, as compared to the lack of such features in patients in whom arrhythmia had only been present within the last 2 weeks of their life. Additional data from tissue of patients taken at cardiac bypass operations reported degenerative changes in the atria of patients with arrhythmias (Mary-Rabine et al. 1983). Further characterisation of atrial tissue from patients undergoing cardiac surgery has revealed apoptotic death of myocytes in those with atrial fibrillation, suggesting some degree of irreversible remodelling (Aimé-Sempé et al. 1999). Other changes at the cellular level have been observed in the distribution of connexin sub-types in patients with atrial fibrillation (Kostin et al. 2002). In patients with sinus rhythm, gap junction proteins are localised to the intercalated discs, whereas in patients with atrial fibrillation there is lateralisation of these proteins and a preferential expression of connexin 40 over connexin 43. Ausma et al. (2003) have observed that ultrastructural changes evolve over a much longer time frame than the electrical remodelling of the atria in response to rate, and alterations in ultrastructure are not completely resolved as late as four months after return to sinus rhythm from prolonged atrial fibrillation. These slowly resolving alterations have been characterised as an increase in myolysis and the fraction of extracellular matrix per myocyte, as well as changes in the expression of structural proteins. It is these structural changes associated with atrial fibrillation occurring over a slower time-course than that of electrical remodelling which have been proposed as the critical factors in the “domestication” of atrial fibrillation (Allessie et al. 2002).
1.6 Atrial Substrate in Conditions Associated with Atrial Arrhythmia

As discussed in Sections 1.1.2 and 1.1.4, several clinical conditions have been shown to have an association with atrial fibrillation and atrial flutter. Study of the atrial substrate in conditions predisposing to atrial arrhythmia may give insights into the factors promoting rhythm disturbance.

1.6.1 Heart Failure

In patients with symptomatic heart failure, the prevalence of atrial fibrillation ranges from 10 to 30 percent, with the highest incidence among those with the most severe heart failure (Stevenson and Stevenson 1999). The electrophysiological substrate of the atria present in heart failure has been studied extensively. Boyden et al. (1984) demonstrated large amounts of interstitial fibrosis, cellular hypertrophy and degeneration, and thickened basement membranes in the atria of a feline model of cardiomyopathy. Power et al. (1998) showed in a ventricular pacing-induced sheep model of heart failure, that larger left atria were increasingly susceptible to atrial fibrillation. Li et al. (1999) published findings from a canine model of heart failure that showed an increase in the heterogeneity of conduction associated with histological changes of marked interstitial fibrosis, and furthermore that these changes are mediated via significant alterations in cellular electrophysiology (Li et al. 2000). Clinical studies of heart failure have demonstrated that electrophysiological and structural remodelling is present even in a cohort without known atrial fibrillation (Sanders et al. 2003). Studies of the right atrium showed that voltage reduction and areas of electrical silence were more apparent in the heart failure group when compared to a control
group, and that atrial refractoriness was increased in the diseased atria. Conduction delay was recorded not only in global measures and regional analysis, but also specifically at the crista terminalis in the heart failure group who were more susceptible to atrial fibrillation.

1.6.2 Atrial Septal Defects

Patients with haemodynamically-significant atrial septal defects are characterised by chronic right atrial volume overload and are at increased risk of atrial arrhythmia; furthermore this risk persists despite correction of the underlying anatomical defect (Murphy et al. 1990). Morton et al. (2003), in studying 13 patients with atrial septal defects, demonstrated an increase in right atrial refractoriness, conduction delay at the crista terminalis and sinus node dysfunction compared to a control group. Importantly, re-study in 4 of these patients at >6 months following correction of the defect showed that site-specific conduction delay persisted while there was no significant change in the electrical parameters, perhaps explaining why risk of arrhythmia has been shown to persist.

1.6.3 Hypertension

Hypertension is the most common contributor to the burden of atrial fibrillation in the developed world, simply due to its high prevalence in Western society (Kannel et al. 1982a). Increases in left atrial dimension and left ventricular mass as well as prolongation of the maximum duration and dispersion of the P wave, and reduced A-wave velocity are predictors for the onset of atrial fibrillation in the hypertensive
population (Ciaroni et al. 2000). Kistler et al. (2006) demonstrated in an ovine model of hypertension that widespread conduction abnormalities and shortening of atrial wavelength were present when compared to controls. The increase in atrial fibrillation that they observed occurred despite no significant change in refractoriness. Atrial myocyte hypertrophy and myolysis were seen in all hypertensive sheep and focal scarring in many. Mitochondrial and nuclear enlargement was seen under electron microscopy in hypertensive sheep but not in any controls.

1.6.4 Valvular Heart Disease

Mitral regurgitation is associated both with atrial fibrillation and congestive heart failure; furthermore onset of arrhythmia often heralds haemodynamic decompensation (Grigioni et al. 2002). Animal models of mitral incompetence have shown that while conduction is unchanged after chronic atrial volume overload, a uniform increase in atrial refractoriness is observed suggesting that electrical remodelling is not the means by which atrial fibrillation is inclined to develop in this disease (Verheule et al. 2003). Similarly, mitral stenosis predisposes to atrial fibrillation. Boyden et al. (1982) studied 23 dogs with spontaneous mitral valve fibrosis and left atrial enlargement. Although these animals demonstrated no difference in action potential duration it was noted that there were reduced numbers of muscle cell layers and an unusually large amount of connective tissue between greatly hypertrophied cells. Atrial fibrillation is a disease with which rheumatic mitral stenosis is not only frequently associated, but is in fact a potentially disastrous complication of, leading to a 17-fold increase in the risk of thromboembolism (Wolf et al. 1978). Fan et
al. (2002) performed electrophysiological evaluation of the right atrium in 31 patients at the time of mitral commissurotomy for rheumatic mitral stenosis. Following cardioversion of atrial fibrillation, these patients demonstrated shorter ERP, sinus node dysfunction and no difference in atrial conduction compared to those patients who presented for the procedure in sinus rhythm. Soylu et al. (2004) evaluated right atrial ERP before and after mitral commissurotomy in 25 patients with mitral stenosis in sinus rhythm. This study observed an acute increase in ERP immediately after relief of mitral stenosis. However, neither of these studies included a normal control group to determine the effects of mitral stenosis independent of the effects of the arrhythmia itself or provided left atrial data. Recently, John et al. (online early) have described in detail the electrophysiological substrate of both the right and left atria of a group with severe mitral stenosis undergoing mitral valvuloplasty. This study demonstrated widespread and severe atrial remodelling when compared to a control group with left sided accessory pathways, despite not having previously had atrial fibrillation. This suggests that it was the structural remodelling, in this case characterised by voltage reduction, conduction slowing and sinus node dysfunction, which predisposed this group to their increased susceptibility to atrial fibrillation during ERP testing. Indeed, the ERP testing revealed an increase in atrial refractoriness which runs counter to the electrical remodelling seen following episodes of atrial fibrillation (Wijffels et al. 1995) and is more in keeping with the “atrial remodelling of a different sort” first reported by Li et al. (1999) in another condition predisposed to atrial fibrillation.
1.6.5 Sub-clinical Atrial Disease in Lone Atrial Fibrillation

Frustaci et al. (1997) reported abnormal atrial histology including inflammatory infiltrates and patchy fibrosis in all of 12 patients studied with paroxysmal lone atrial fibrillation, and in none of 11 control patients. Excess fibrosis has been characterised as an increased concentration of collagen type I in patients with lone atrial fibrillation compared to controls and this increase has been observed to be attenuated in those patients receiving angiotensin converting enzyme inhibitors (Boldt et al. 2006). Further evidence that inflammation plays a role in atrial fibrillation comes from the observation that C-reactive protein is elevated in patients with lone atrial fibrillation (Chung et al. 2001). Diastolic dysfunction diagnosed by transeptal haemodynamic evaluation of left atria has been demonstrated to be present in patients with lone atrial fibrillation (Jaïs et al. 2000). In addition, there is some evidence to suggest that patients with lone atrial fibrillation have microvascular dysfunction in the coronary circulation (Skalidis et al. 2008). Thus, it is feasible that patients without overt structural heart disease may have fibrosis, inflammation, structural change and vascular dysfunction that contribute to the underlying atrial substrate. In addition, when considering the atrial substrate encountered in diseases known to be associated with the subsequent development of atrial arrhythmia some unifying features can be seen to emerge. Atrial refractoriness is either unchanged or increased, while structural abnormalities, conduction delay and sinus node dysfunction become increasingly apparent. Cellular and ultrastructural alteration underpins these gross and functional changes and the end result of such abnormal substrate is an increase in the likelihood of initiation and maintenance of atrial arrhythmia.
1.7 Sinus Node Disease, Remodelling and Atrial Arrhythmias

“The sinus node is the essence of life” – Bruno Kisch, co-founder and president of the American College of Cardiology, 1951-1953.

Remodelling of the sinus node is known to develop soon after the initiation of arrhythmia and reverse after restoration of sinus rhythm (see Section 1.5.1). Irrespective of the mechanism by which sinus node remodelling occurs due to rapid atrial rates, an increase in the time window due to sinus bradycardia can facilitate the development of atrial fibrillation by increasing atrial ectopy and the dispersion of refractoriness (Luck and Engel 1979). Therefore, the frequent co-existence of atrial arrhythmia and sinus node disease may be due to a slow sinus rate increasing vulnerability to atrial fibrillation, a common disease substrate, and/or arrhythmia directly impairing sinus node function; all 3 possibilities have evidence to support them (Rubenstein et al. 1972; Moss and Davis 1974; Gomes et al. 1981).

1.7.1 The Anatomical Sinus Node

The anatomical sinus node is located at the junction of the superior vena cava with the right atrium (James 1977; Anderson et al. 1979). The sinus node consists of specialised nodal cells lying immediately sub-epicardially at the superior pole of the sulcus terminalis of the right atrium which, under autonomic influence, spontaneously depolarise at a variable rate to match heart rate to physiological demand. The endocardial aspect of the sulcus terminalis is marked by the crista terminalis; the structure demarcating the embryonic junction of the anterior trabeculated appendage and the posterior smooth-walled venous component. In a study of 47 adult hearts, the
histological sinus node has been shown to be crescent-shaped with the long axis parallel to the crista terminalis and has a mean length of 13.5mm (range 8-21.5mm) (Sanchez-Quintana et al. 2005). Histological sectioning of the atria by a range of investigators has failed to identify islands of nodal cells separate from the sinus node itself. Indeed, all such studies have demonstrated that the sinus node has a defined and consistent anatomical location (James 1977; Anderson et al. 1979; Boineau et al. 1980; Sanchez-Quintana et al. 2005). No insulating tract is seen and nodal tissue radiates for short distances into the surrounding working myocardium. In comparison to contractile cardiac myocytes, nodal cells are smaller cells that are packed within a dense matrix of connective tissue. The lack of intercalated discs and poorly developed sarcoplasmic reticulum are proposed reasons for slow intra-nodal conduction (James et al. 1966). Recent immunohistochemical studies on the sinus node have revealed regional differences in connexin expression. Kwong et al. (1998) showed that the canine sinus node was composed of mainly connexin 43-negative cells, with the majority expressing connexin 40. The one-third of cells expressing connexin 43 however, abutted working atrial myocardium and it is hypothesised that these cells form bridges for the propagation of the action potential from the centre of the sinus node to the atrial muscle.

1.7.2 The Functional Sinus Node Complex

Shifts in the origin of the sinus node impulse along the sulcus terminalis under autonomic influences were first observed by Lewis et al. (1910) and by Meek and Eyster (1914) early last century. The advent of medium-density epicardial mapping
using multi-polar epicardial plaques confirmed the initial observations, with the functional sinus node demonstrating complex activity under autonomic control (Bouman et al. 1968; Geesbrecht and Randall 1971; Goldberg 1975; Goldberg et al. 1981). Boineau and colleagues (1978; 1980) performed medium-density mapping of the right atrial epicardium with simultaneous endocardial mapping in a subset, together with some histological analysis, under conditions of sympathetic and parasympathetic stimulation and following overdrive pacing. They observed that the sinus P wave may arise from a ‘pacemaker complex’, distributed over an extensive extra-nodal area spanning the superior vena cava - right atrial junction to the inferior vena cava. These studies of the canine functional sinus node complex have identified that the area of the origin of cardiac depolarisation exceeds that of the anatomical sinus node area by 3 to 4-fold. A strong correlation between heart rate and functional sinus origin was observed with vagal stimulation and isoprenaline infusion resulting in inferior and supero-anterior shifts, respectively. This study reported several seminal observations; (i) at least three anatomically fixed (in contrast to diffusely wandering) areas of sinus node origin were present, each of which became dominant within a specific range of heart rates, (ii) after intramural disconnection of the origins they maintained their normal function in their respective heart rate ranges, and (iii) origin points were mapped to the same anatomical location using both epicardial and endocardial mapping, which suggested a lack of intramural preferential conduction. However, in conflict with their proposition was the histological absence of specialised nodal cells at the extra-nodal sinus origins. On the weight of evidence, Boineau et al. (1980) concluded that the multi-centric nature of functional sinus origin was mediated through a complex system of separate atrial pacemakers with differential sensitivities
to autonomic control. Boineau et al. (1988) extended their studies to humans to elegantly describe the functional sinus node origin(s) using 156 bipole epicardial plaques in 14 patients undergoing open-heart surgery for the ablation of accessory pathways. They reported uni-focal nodal and extra-nodal sinus origins in addition to multi-centric origins over two to four widely distributed pacemaker sites. The similarity in anatomical origin of escape beats after overdrive pacing compared to that in sinus rhythm supported the role of extra-nodal sites in healthy sinus function. The functional sinus pacemaker complex in humans was estimated to exist over a zone centred about the long axis of the sulcus terminalis encompassing a 7.5 by 1.5cm area, with a cranial and caudal border consisting of the superior and inferior venae cavae, respectively.

Alternative hypotheses for extra-nodal sinus origins proposed by Boineau et al. (1988) include; (i) the existence of specialised conduction tracts from the anatomically fixed nodal source to remote exit sites, and (ii) a coordinated exchange of dominance amongst competing pacemakers via autonomic modulation. For the former explanation, the presence of nodal radiations into adjacent atrial myocardium through electrically isolating connective tissue supports this theory, however no insulated rapidly conducting tissue analogous to that found in the ventricles has been conclusively demonstrated (Anderson et al. 1981a). Supporting the latter hypothesis, autonomically mediated shifts in activation sites appear linked to changes in heart rate, however the mechanism by which a stable rate is maintained without faster pacemakers dominating is yet to be shown. These considerations led to a hybrid model being proposed where neural and hormonal factors influence both the site of pacemaker activation and the point of exit from the sinus node (Schuessler et al. 1996). Additional canine right atrial studies have shown that transmembrane
potentials from sinus node pacemaker cells do not show a temporal or spatial relationship with atrial extracellular potentials (Bromberg et al. 1995). This suggests relative electrical isolation of the sinus node from surrounding working atrial myocardium with the earliest extracellular potentials representing the exit points from the node. Further evidence of a multi-centric and widely distributed functional pacemaker complex comes from clinical studies that have aimed to modify sinus activity in patients with inappropriate sinus tachycardia. Inappropriate sinus tachycardia is a non-paroxysmal tachyarrhythmia characterised by an increased resting heart rate and/or an exaggerated heart rate response to minimal exertion or a change in body posture (Still et al. 2005). In contrast to a single uni-focal lesion, procedures for the treatment of inappropriate sinus tachycardia require extensive ablation along the entire length of the crista terminalis to achieve functional inhibition of the sinus node (Kalman et al. 1995; Lee et al. 1995).

1.7.3 Conventional Evaluation of Sinus Node Function

Conventional tests of sinus node automaticity and sino-atrial coupling are based on indirect surrogate measures and as such, are thought to contain limited clinical value (Tonkin and Heddle 1984). Sinus node automaticity has traditionally been assessed by the duration of the first return cycle after cessation of sinus overdrive pacing (Mandel et al. 1971; Narula et al. 1972). The CSNRT adjusts for the preceding sinus cycle length before overdrive pacing, however neither the raw measure nor CSNRT provide a pure assessment of sinus node automaticity and both are confounded by extrinsic influences. Consequently, there is poor inter-laboratory agreement for ‘normal’ ranges
of CSNRT (Kulbertus et al. 1975; Breithardt et al. 1977; Alboni et al. 1982) and the positive predictive accuracy in patients with suspected sinus node dysfunction is as low as 30% (Yee and Strauss 1987). Methods to evaluate sino-atrial conduction have included indirect measures (Strauss et al. 1973; Narula et al. 1978) and the direct method by the recording of a sinus node electrogram (Hariman et al. 1980). However, as with measures of automaticity, the positive predictive value of these tests for identification of clinical sinus node disease has been too low to warrant routine clinical use. Nevertheless, due to their widespread use within the body of literature on sinus node disease, these measures retain a degree of utility for research on the mechanism of sinus node dysfunction.

1.7.4 High-density Mapping of the Sinus Node

Initial mapping studies of the functional sinus node complex utilised multi-electrode plaques placed epicardially or endocardially at surgery (Boineau et al. 1978). The subsequent development of 3-dimensional endocardial mapping systems has allowed less invasive assessment of sinus node activity, although high-density has been achieved using analysis of many sequential beats rather than single-beat mapping (Sanders et al. 2004b). The advent of non-contact mapping has facilitated high-density simultaneous endocardial mapping of cardiac depolarisation. The morphology of unipolar electrograms provides measurable information of the depolarisation wave-front direction, speed and width of the approaching or retreating wave. In an animal model, virtual unipolar electrograms from non-contact mapping were able to differentiate between endocardial and sub-endocardial pacing origins thus providing
information on the intramural depth of impulse origin (Kroll et al. 2003). The morphology characteristics of virtual electrograms have been shown to match with high reliability those of conventional contact unipolar electrograms (Schilling et al. 1998; Kadish et al. 1999; Schilling et al. 2000; Thiagalingam et al. 2004a; Earley et al. 2006). Higa et al. (2004) have shown insights into the additional information provided via the utilisation of high density unipolar mapping during atrial tachycardia. Non-contact mapping showed that in many cases the traditionally mapped origin – the site from which centrifugal activation occurs to spread activation to the remaining atria – was indeed a break-out point. Detailed inspection of the unipolar electrograms demonstrated an earlier site of origin (“QS” morphology) with a preferential pathway of conduction to the break-out point. These investigators were able to confirm the existence of an alternate origin with a preferential conduction pathway by curative ablation of the tachycardia at both the origin and also along the preferential pathway. Whether similar pathways exist in the non-diseased atrium, including within the sinus node, is yet to be reported.

1.7.5 Sinus Node Disease

Sinus node disease is thought to result from disordered impulse generation within the sinus node or impaired conduction of the impulse to the surrounding atrial tissue (Ferrer 1968). While differentiation between these two potential aetiologies has been difficult owing to the absence of an appropriate experimental model, Sanders et al. (2004a) have performed point-by-point atrial mapping studies in patients with sinus node disease and found evidence of a diffuse atrial myopathy. Compared to age-
matched controls, patients with sinus node disease demonstrated an increase in atrial refractoriness, atrial conduction time and P wave duration. Interestingly, the sinus node complex in disease was more often uni-centric and localised to the low crista terminalis with evidence of regional conduction slowing and scar. These data suggest that impulse conduction rather than impulse generation are responsible for the manifestations of sinus node disease.

1.7.6 Clinical Conditions Associated with Sinus Node Impairment

An association with sinus node dysfunction is seen for many disease states. This not only includes the direct relationship between atrial arrhythmia and sinus node remodelling, but also conditions (e.g. heart failure) that demonstrate an association with both atrial arrhythmia and impairment of sinus node function. Elvan et al. (1996) demonstrated significant prolongation of CSNRT and the intrinsic sinus cycle length after two to six weeks of atrial fibrillation in dogs. In humans, short durations of rapid atrial pacing resulted in similar sinus node inhibition (Hadian et al. 2002) and CSNRT was significantly longer in patients cardioverted from chronic lone atrial fibrillation compared to controls (Kumagai et al. 1991; Tse et al. 1999; Manios et al. 2001). Manios et al. (2001) also reported that sinus node inhibition improved within 24 hours after cardioversion. Sinus node dysfunction as measured by traditional parameters has been reported after reversion to sinus rhythm from atrial flutter (Sparks et al. 2000; Daoud et al. 2002). A decrement in sinus node function has been reported during clinically induced atrial stretch. In a prospective randomised comparison, Sparks et al. (1999) reported that long-term (3 months) VVI pacing resulted in increased atrial
refractoriness, a prolongation of P wave duration and longer CSNRT in comparison to DDD pacing. They further highlighted that the changes observed in the VVI pacing group were reversed with three months of DDD pacing. Similar increases in P wave duration and CSNRT have been reported in patients with atrial stretch due to significant atrial septal defects (Morton et al. 2003) and congestive heart failure (Sanders et al. 2004b). For the latter, Sanders et al. reported a more caudal localisation of sinus origin and greater structural remodelling of the crista terminalis in heart failure patients when compared to age-matched controls. Structural remodelling was represented by a loss of voltage, demonstration of conduction delay at the crista terminalis and circuitous propagation of the sinus impulse. These findings raise the possibility that dysfunction of the sinus node may have been a consequence of structural change associated with atrial stretch.
Chapter 2.
Right and left atrial electrical substrate of lone atrial fibrillation

2.1 Introduction

Atrial fibrillation arises as a result of a complex interaction of triggers, perpetuators and substrate (Allessie et al. 2001). Experimental studies of atrial fibrillation have demonstrated shortening of the ERP and slowing of conduction as a result of atrial fibrillation and have suggested that these factors combine to promote continuing atrial fibrillation, giving rise to the concept that “atrial fibrillation begets atrial fibrillation” (Morillo et al. 1995; Wijffels et al. 1995; Goette et al. 1996; Gaspo et al. 1997; Fareh et al. 1998). Clinical studies have shown reversal of electrical remodelling over time after termination of arrhythmia (Yu et al. 1999; Hobbs et al. 2000). However, strategies of prompt termination of atrial fibrillation to avoid this cycle of adverse remodelling have failed to show benefit (Fynn et al. 2002). In fact, the natural history of paroxysmal atrial fibrillation is one of increasing frequency and duration of episodes (Kopecky et al. 1987). These observations have led to the search for a “second factor” integral to the development and progression of atrial fibrillation (Garratt et al. 1999).

We hypothesised that patients with paroxysmal “lone” atrial fibrillation have an abnormal atrial substrate that determines disease progression. In order to evaluate the substrate predisposing to atrial fibrillation, free of the electrical remodelling effects of the arrhythmia itself, we evaluated the electrophysiological characteristics of atria in patients with paroxysmal “lone” atrial fibrillation, remote in time from the arrhythmia.
2.2 Methods

2.2.1 Study Population

This study comprised 13 patients undergoing first-time ablation for paroxysmal atrial fibrillation and a reference group of 13 patients with structurally normal hearts undergoing radiofrequency ablation for atrioventricular reentry tachycardia with left-sided accessory pathways and no history of atrial fibrillation. Patients for the study group were excluded if they had atrial fibrillation during the week prior to ablation (established by continuous monitoring) or any of the criteria that would prohibit the diagnosis of “lone” atrial fibrillation, previously defined as the absence of structural heart disease or stroke based on history, physical examination, chest X-ray, routine blood chemistry, and trans-thoracic as well as trans-oesophageal echocardiography (Kopecky et al. 1987; Kumagai et al. 1991; Jais et al. 2000). Coronary artery disease was excluded by clinical, ECG or stress test criteria. Pulmonary disease, hypertension, hyperthyroidism and diabetes were eliminated by appropriate tests. Paroxysmal atrial fibrillation was defined according to the Expert Consensus Statement as recurrent atrial fibrillation that terminates spontaneously within 7 days (Calkins et al. 2007). Thus, of 109 patients with highly symptomatic atrial fibrillation presenting for ablation screened, 13 patients were suitable to be included in this study.

All anti-arrhythmic medication was ceased ≥5 half-lives prior to the study. No patient had received amiodarone. All patients provided written informed consent to the study protocol which was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.
2.2.2 Electrophysiological Study and Ablation

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. In patients with atrial fibrillation the study protocol was performed before ablation, while in the reference group this was done after accessory pathway ablation. The left atrium was accessed using a single transeptal puncture following which repeated bolus unfractionated heparin was utilised to maintain the activated clotting time between 300-350 seconds.

Following the study protocol, patients with atrial fibrillation underwent circumferential pulmonary vein ablation with an end-point of isolation confirmed by circumferential mapping (Lasso, Biosense-Webster) with either elimination or dissociation of pulmonary venous potentials. Ablation of the pulmonary veins was performed using a delivered power of 30W with irrigation rates of 30mL/min (Thermocool, Biosense Webster). Additional substrate modification was performed in patients with an episode of atrial fibrillation ≥48 hours or with a left atrial size ≥57mm (longest diameter). This took the form of linear ablation along the left atrial roof with an end-point of linear double potentials and conduction block demonstrated by an activation detour during pacing of the left atrial appendage. Cavotricuspid isthmus ablation with an endpoint of bi-directional isthmus block was performed only in patients with a history of typical flutter or if mapping confirmed typical flutter during the procedure. Linear ablation was performed with a delivered power of 30-35W with irrigation rates of 30-60mL/min.
2.2.3  Electrophysiology Study Protocol

The following catheters were positioned for the study protocol: (i) a 10-pole catheter (2-5-2mm inter-electrode spacing, Daig Electrophysiology) within the coronary sinus with the proximal bipole at the coronary sinus ostium as determined in the best septal left anterior oblique position; (ii) a 20-pole “crista” catheter (1-3-1mm inter-electrode spacing, Biosense-Webster) placed along the crista terminalis with the distal tip superiorly such that the second bipole lay at the junction of the superior vena cava and right atrium, stabilised by a long sheath (CSTA, Daig Electrophysiology) to ensure close apposition to this structure; (iii) a 20-pole catheter (2-5-2mm inter-electrode spacing, Daig Electrophysiology) placed along the lateral right atrium; and (iv) a roving 10-pole catheter (2-5-2mm inter-electrode spacing, Biosense-Webster) was positioned within the left atrium via trans-septal puncture (Figure 2-1). This catheter was stabilised with the use of a long sheath (Preface, Biosense-Webster or SL0, Daig Electrophysiology) and sequentially positioned as follows at the: (i) left atrial roof; (ii) inferior left atrium; (iii) mid-posterior left atrium; (iv) left atrial appendage and (v) high right atrial septum, as previously described (John et al. online early). Electrophysiological evaluation was performed as detailed below.

2.2.3.1  Effective Refractoriness

Atrial ERP was evaluated at twice diastolic threshold at cycle lengths of 600 and 450ms using an 8-beat drive followed by an extra-stimulus, starting with a coupling interval of 150ms increasing in 10ms increments. ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site the ERP was measured 3 times at each cycle length and averaged. If ERP varied by >10ms an additional 2 measurements were
made and the total number averaged. ERP was measured from the following sites: (i) distal coronary sinus; (ii) proximal coronary sinus; (iii) low-lateral right atrium; (iv) high-lateral right atrium; (v) high-septal right atrium; (vi) left atrial appendage; (vii) mid-posterior left atrium; (viii) inferior left atrium; (ix) junction of the left superior pulmonary vein with the left atrial roof; and (x) junction of the right superior pulmonary vein with the left atrial roof. Atrial fibrillation induced by ERP testing lasting >5 minutes was considered sustained; when this occurred, no further data was acquired.

2.2.3.2  Atrial Conduction

Atrial conduction time was assessed along linearly placed catheters by pacing the distal bipole (1,2) and determining the conduction time to a proximal bipole (9,10) at the left atrial roof, inferior left atrium, coronary sinus and lateral right atrium. Conduction time at each site was averaged over 10 beats during stable capture at 600 and 450ms cycle lengths.

P wave duration was determined as a marker of global conduction by the average of 10 beats on ECG lead II.

2.2.3.3  Site-specific Conduction Abnormalities at the Crista Terminalis

The number of bipoles on the crista terminalis catheter with discrete double potentials separated by an isoelectric interval or complex fractionated activity of ≥50ms duration, and the maximum electrogram duration were determined during sinus rhythm, constant pacing and for the shortest-coupled captured extra-stimulus from the
proximal coronary sinus, low-lateral right atrium, inferior left atrium and left atrial appendage.

2.2.3.4 Sinus Node Function

Sinus node function was evaluated as follows: (i) Baseline sinus cycle length was determined over 10 consecutive sinus cycles; (ii) SACT was determined after an 8-beat pacing train [using the formula $SACT = (\text{return} - \text{basic cycle length})/2$] (Narula et al. 1978) 3 times and averaged; and (iii) CSNRT was determined after a 30-second drive train at cycle lengths of 600 and 450ms, correcting for the baseline cycle length. At each cycle length, CSNRT was determined 3 times and averaged.

2.2.4 Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median and inter-quartile range as appropriate. Categorical variables are reported as number and percentage. Proportions were compared using Fisher’s Exact test. Comparisons between means were analysed using paired or unpaired t-tests as appropriate. Comparisons with adjustment for multiple sampling within patients were performed using a Mixed Linear Model for continuous data or a logistic Generalised Estimating Equation for categorical data. Statistical tests were performed using SPSS 15 (SPSS Inc) and statistical significance was set at $p<0.05$. 
2.3 Results

2.3.1 Baseline Details

Baseline patient characteristics are summarised in Table 2.1. Patients with atrial fibrillation had a median arrhythmia history of 72 months and a mean longest episode of 2.8±1.9 days. Groups were well matched for age, gender, left ventricular wall thickness and function. However, patients with atrial fibrillation had significantly larger left atria (p=0.004). None of the patients with atrial fibrillation had atrial arrhythmias (>30 seconds) by continuous monitoring in the 7 days prior to the procedure.

2.3.2 Atrial Refractoriness

For patients with atrial fibrillation, the mean ERP across all sites was greater than that of reference patients (at 600ms: 255±25 versus 222±16ms, p<0.001; at 450ms: 234±20 versus 212±14ms, p=0.004). Figure 2-2 demonstrates the ERP at the ten sites tested following 600 and 450ms drive trains in patients with atrial fibrillation versus reference patients, and indicates those areas where significant differences were seen. The differences in ERP between patients with atrial fibrillation and reference patients were not uniform across all sites (p=0.02). At each site, patients with atrial fibrillation demonstrated either an increase or no significant change in ERP when compared to the reference group. The ERP was higher following a 600ms drive train than after a 450ms drive train for both patients with atrial fibrillation (p<0.001) and reference patients (p=0.02); that is, there was preservation of physiological rate-adaptation of ERP in both groups (p=0.1).
2.3.3 Atrial Conduction Time

The conduction time along the catheters at the left atrial roof, inferior left atrium, coronary sinus and lateral right atrium was significantly longer in patients with atrial fibrillation compared to the reference group (57±18 versus 47±10ms, p=0.01). However, there was no significant interaction between patient group and site of conduction measurement (p=0.3), suggesting a homogenous slowing of conduction in patients with atrial fibrillation.

The P wave duration was significantly prolonged in patients with atrial fibrillation compared to reference patients (128±8 versus 95±10ms, p<0.001).

2.3.4 Site-Specific Conduction Abnormalities

Site-specific conduction abnormalities at the crista terminalis during sinus rhythm were more apparent in patients with atrial fibrillation than reference patients. During sinus rhythm, patients with atrial fibrillation had a greater number of bipoles demonstrating double potentials or fractionated signals on the crista terminalis catheter than reference patients (4.9±1.8 versus 0.7±0.8, p<0.001) of which the maximum electrogram duration was longer (84±15 versus 52±11ms, p<0.001). These differences were even more marked during pacing and increased further with extra-stimulus (Figures 2-3 and 2-4). These data highlight the functional nature of the conduction delay at the crista terminalis, as evidenced by variation in the extent of conduction abnormalities depending on the rate and site of stimulation.
2.3.5 Sinus Node Function

Patients with atrial fibrillation had a longer baseline sinus cycle length (975±131 versus 762±129ms, p<0.001), SACT (154±58 versus 83±31ms, p<0.001) and CSNRT at 600ms (265±57 versus 185±60ms, p=0.002) but not 450ms (261±96 versus 241±76ms, p=0.6) compared to reference patients.

2.4 Discussion

2.4.1 Major findings

This study utilised electrophysiological mapping to demonstrate new information on the nature of abnormalities within the atria of patients with paroxysmal “lone” atrial fibrillation, remote from an arrhythmic event.

The major findings are as follows:

(i) Conduction abnormalities characterised by prolongation of conduction times along linearly placed catheters, longer P wave duration and site-specific conduction delay.

(ii) Impaired sinus node function indicated by prolonged SACT and CSNRT.

(iii) An increase in ERP, which is consistent with prior studies evaluating clinical substrates for atrial fibrillation but is in contrast to the remodelling attributed to atrial fibrillation itself.

Thus, this suggests that patients with paroxysmal lone atrial fibrillation have an abnormal atrial electrophysiological substrate. We posit that these abnormalities
contribute to the “second factor” that promotes progression of atrial fibrillation and why sinus rhythm does not beget sinus rhythm.

2.4.2 Rate-Related Electrical Remodelling

The seminal observations by Wijffels et al. (1995) that “atrial fibrillation begets atrial fibrillation” has as its central tenet the observation of reduction in atrial ERP by repeated induction of atrial fibrillation thereby allowing atrial fibrillation to sustain itself. Many experimental studies have confirmed this finding (Morillo et al. 1995; Elvan et al. 1996; Goette et al. 1996; Fareh et al. 1998; Lee et al. 1999). While these initial studies fail to observe any conduction abnormalities, subsequent studies by Gaspo et al. (1997) demonstrated that progressively longer episodes of atrial fibrillation also resulted in conduction slowing. Thus, the electrical remodelling of the atria in response to atrial fibrillation lends toward the perpetuation of arrhythmia by a shortening of the reentrant “wavelength”. In addition, several investigators have also observed remodelling of the sinus node that develops soon after the initiation of arrhythmia and reverses after restoration of sinus rhythm (Kumagai et al. 1991; Elvan et al. 1996; Hocini et al. 2003).

Clinical studies have also observed similar effects of rate on the atria. Patients with recent atrial fibrillation have been shown to have shorter ERP than control groups, as well as sinus node dysfunction and conduction delay (Cosio et al. 1983; Kumagai et al. 1991). Yu et al. (1999) demonstrated shorter ERP with impaired rate adaptation and depressed conduction following cardioversion for longstanding atrial fibrillation, with the ERP gradually increasing after 4 days of sinus rhythm. Kojodjojo et al. (2007)
studied patients with paroxysmal and persistent atrial fibrillation at their ablation procedure and demonstrated a reduction in ERP at 3 sites compared to patients with no atrial fibrillation. In this study, patients with persistent atrial fibrillation had just 10 minutes of sinus rhythm prior to study and those with paroxysmal atrial fibrillation had a mean atrial fibrillation burden of 3.2±3.7 hours in the preceding 72 hours. However, with the known experimental evidence of rate-related remodelling, it is unclear if the abnormalities observed in such patients with atrial fibrillation form the underlying substrate for or are a consequence of atrial fibrillation.

2.4.3 Progression of Atrial Fibrillation

Garratt et al. (1999) evaluated the effect of repeated episodes of atrial fibrillation on atrial electrical remodelling. While marked remodelling was observed with five days of atrial fibrillation, two days of sinus rhythm was adequate to reverse all abnormalities. Despite repetitive episodes of atrial fibrillation, there were no additive changes observed in atrial electrical remodelling. Fynn et al. (2002) evaluated the strategy of repeated cardioversion of atrial fibrillation in the clinical setting. Early and repeated cardioversion was performed to maintain sinus rhythm but failed to prevent the progression to more atrial fibrillation. Indeed, their findings suggest that sinus rhythm does not beget sinus rhythm in patients with a history of atrial fibrillation.

These findings have led Allessie and co-workers to propose the existence of a “second factor” for the initial substrate and subsequent progression of atrial fibrillation (Garratt et al. 1999). To identify this factor we studied patients with paroxysmal lone atrial fibrillation who were remote from an episode of atrial fibrillation (thereby removing
the effects of acute rate-related remodelling). When studied distant from an arrhythmic event, patients with lone atrial fibrillation demonstrate an increase in atrial refractoriness, widespread and site-specific conduction abnormalities, and evidence of sinus node remodelling. We put forward that these changes in conduction seen in lone paroxysmal atrial fibrillation, when studied remote from arrhythmia, contribute to the “second factor” which plays an important role in the development and progression of atrial fibrillation.

2.4.4 Substrate Predisposing to the Development of Atrial Fibrillation

Although the abnormalities that have been observed to result from atrial fibrillation itself have been proposed as the mechanisms by which atrial fibrillation begets atrial fibrillation, it is not likely that rate-related remodelling forms the substrate predisposing to the development of atrial fibrillation in the first place. This has led several investigators to evaluate the atrial abnormalities in conditions predisposed to the development of atrial fibrillation.

Li et al. (1999) developed a canine model of congestive heart failure to evaluate effects on atrial remodelling and demonstrated "atrial remodelling of a different sort" to that seen due to atrial fibrillation alone. A significant increase in ERP at short cycle lengths associated with an increase in the heterogeneity of conduction and marked interstitial fibrosis was seen. Despite the increase in ERP, these abnormalities resulted in a significant increase in the duration of atrial fibrillation. Verheule et al. (2003) observed a propensity for atrial fibrillation despite an increase in ERP in a canine model of mitral
regurgitation, again due to abnormalities in conduction and profound structural remodelling.

Clinical studies of the atrial substrate in patients known to be predisposed to atrial fibrillation but without antecedent arrhythmia have demonstrated similar observations. Morton et al. (2003) studied the right atrial substrate in patients with atrial septal defects and observed prolonged ERP and delayed conduction across the crista terminalis compared to reference patients. Sanders et al. showed similar findings of prolonged ERP with widespread and site-specific conduction abnormalities in patients with congestive heart failure (2003) and sinus node disease (2004a). Kistler et al. (2004) demonstrated such changes in a progressive manner with increasing age. While these findings have been restricted to right atria, comparable results have recently been observed in the left atria of patients with mitral stenosis (John et al. online early).

In patients with atrial fibrillation there is a paucity of clinical electrophysiological studies performed outside the context of recent arrhythmia. In order to minimise the confounding effects of electrical remodelling, we have undertaken meticulous screening to identify patients who were in sinus rhythm for a minimum of 7 days prior to their ablation procedure. Using such stringent enrolment criteria, the observations of the current study are remarkably consistent with the findings observed in the above conditions on the substrate predisposing to atrial fibrillation. Taken together, these studies provide compelling evidence that the significant contributors giving rise to the substrate underlying atrial fibrillation are not the changes in refractoriness, but rather the conduction abnormalities discussed above.
2.4.5 Implications

The electrical remodelling seen in conjunction with ongoing arrhythmia and thought to perpetuate atrial fibrillation is known to normalise within days of sinus rhythm (Garratt et al. 1999). However, strategies of repeated cardioversion have not been successful in retarding progression of disease (Fynn et al. 2002). By studying patients remote in time from the arrhythmia itself, we have been able to show that a significant contributor to the underlying substrate in patients with atrial fibrillation is in fact that of conduction abnormalities, which may account for the progression of the atrial fibrillation disease. Future strategies to treat atrial fibrillation should therefore focus on modification of atrial conduction. Finally, while pulmonary vein isolation is currently considered to be highly successful for the majority of patients with paroxysmal atrial fibrillation, there is yet to be definitive long-term data on outcome. This study showing an abnormal substrate in lone atrial fibrillation raises the possibility of progressive disease continuing despite early procedural success.

2.4.6 Limitations

While the abnormalities observed in this study are proposed to constitute the substrate predisposing to atrial fibrillation, the development of clinical atrial fibrillation is complex and depends not only on substrate but also on other factors such as triggers and perpetuators that were not addressed by this study. Patients with persistent atrial fibrillation were not studied and may differ in substrate, however many patients with persistent atrial fibrillation start with paroxysms initially. Finally, while we monitored patients for a week prior to the procedure to ensure our evaluation was remote from
an episode of atrial fibrillation, we cannot exclude an effect of rate-related remodelling from previous episodes. However, prior studies have demonstrated no additive effects of episodic atrial fibrillation and resolution of remodelling within days (Garratt et al. 1999).

2.5 Conclusion

Patients with paroxysmal lone atrial fibrillation, remote from an arrhythmic episode, demonstrate electrophysiological abnormalities characterised by widespread and site-specific conduction abnormalities, altered sinus node function and prolonged atrial refractoriness. These abnormalities contribute to the “second factor” critical to the development and progression of atrial fibrillation.
Table 2.1

Patient characteristics

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<td>Interventricular septum (mm)</td>
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<td>Left Ventricular ejection fraction (%)</td>
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<td>58±8</td>
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Figure 2-1

Catheter positions on fluoroscopy

Left anterior oblique views of a decapolar catheter in the coronary sinus, a duodecapolar catheter along the crista terminalis with its stabilising sheath, a duodecapolar catheter along the lateral right atrium and a decapolar catheter with its stabilising sheath in the left atrium. The left atrial catheter was sequentially positioned by looping the catheter to record along the left atrial roof (left) and then withdrawn to record the inferior left atrium (right). Subsequently, the decapolar catheter was positioned at the left atrial appendage, posterior left atrial wall and the high-septal right atrium (not shown).
Figure 2-2

Regional effective refractoriness

Figure legend overleaf.
Mean (+ standard deviation) ERP at the ten sites tested following a 600ms drive train (top) and a 450ms drive train (bottom) in patients with atrial fibrillation and reference patients. All values for 600ms are higher than the same patient group and site value for 450ms. The difference in mean ERP between patients with atrial fibrillation and reference patients varied significantly according to the region of measurement (p=0.02).

*p<0.001, †p=0.01, ‡p<0.05 for post-hoc comparisons.

dCS – distal coronary sinus
pCS – proximal coronary sinus
LLRA – low lateral right atrium
HLRA – high lateral right atrium
HRAS – high right atrial septum
LSPV – junction of left superior pulmonary vein with left atrium
RSPV – junction of right superior pulmonary vein with left atrium
InfLA – inferior left atrium. LAA – left atrial appendage
PostLA – posterior left atrium.
**Figure 2-3**

Conduction characteristics at the crista terminalis

Number of abnormal electrograms

Mean (+ standard deviation) number of double potentials or fractionated signals along the crista terminalis during pacing at 600ms (S1, top) and with the earliest captured extra-stimulus (S2, bottom) from 4 sites in the atria in patients with atrial fibrillation and reference patients. *p<0.001, †p<0.01. pCS – proximal coronary sinus. LLRA – low lateral right atrium. InfLA – inferior left atrium. LAA – left atrial appendage.
Conduction characteristics at the crista terminalis

Maximum duration of abnormal electrograms

Mean (+ standard deviation) of the maximum duration of double potentials or fractionated signals along the crista terminalis during pacing at 600ms (S1) and with the earliest captured extra-stimulus (S2) from 4 sites in the atria in patients with atrial fibrillation and reference patients. *p<0.001, †p<0.01. pCS – proximal coronary sinus. LLRA – low lateral right atrium. InfLA – inferior left atrium. LAA – left atrial appendage.
Chapter 3.
Right and left atrial electroanatomical substrate of lone atrial fibrillation

3.1 Introduction

The initiation and maintenance of atrial fibrillation is brought about by intricate interactions between triggers and perpetuators within the atrial substrate (Allessie et al. 2001). The perpetuation of atrial fibrillation is aided by the electrical remodelling undergone by the atria and demonstrated repeatedly in the experimental setting (Morillo et al. 1995; Wijffels et al. 1995; Goette et al. 1996; Gaspo et al. 1997; Fareh et al. 1998). However, while this electrical remodelling is seen clinically, the effects are reversible once sinus rhythm is restored (Yu et al. 1999; Hobbs et al. 2000). Nevertheless, policies of early and repeated cardioversion to avoid self-sustaining arrhythmia have not halted the progression of disease (Fynn et al. 2002). This observation has prompted the hunt for a “second factor” promoting the evolution and advancement of atrial fibrillation.

The structural and electrical changes associated with atrial fibrillation are difficult to differentiate from that due to the affiliated conditions that may be giving rise to the arrhythmia; conditions such as heart failure and hypertension. Patients with “lone” atrial fibrillation however, are defined as a group without overt concomitant conditions (Kopecky et al. 1987; Kumagai et al. 1991; Jaïs et al. 2000) and study of these individuals may provide insight into the underlying substrate of the arrhythmia itself. Furthermore, the arrhythmia alone can lead to alterations in the atrial structure which may tend to perpetuate atrial fibrillation (Ausma et al. 2003). Studying patients with lone atrial fibrillation, after allowing sufficient time for electrical remodelling to
reverse, would allow conclusions to be drawn about the structural and electrical changes seen in the atrial substrate predisposing to atrial fibrillation, without the effects of associated heart disease and rate-related remodelling.

We hypothesised that the disease progression of patients with paroxysmal “lone” atrial fibrillation is determined by abnormal atrial substrate. In order to evaluate the substrate predisposing to atrial fibrillation, we evaluated the electroanatomical characteristics of atria in patients with paroxysmal “lone” atrial fibrillation, remote in time from the arrhythmia.

3.2 Methods

3.2.1 Study Population

This study comprised 12 patients undergoing first-time ablation for paroxysmal atrial fibrillation and a reference group of 12 patients with structurally normal hearts undergoing radiofrequency ablation for atrioventricular reentry tachycardia with left-sided accessory pathways and no history of atrial fibrillation. Patients in the study group were excluded if they had atrial fibrillation during the week prior to ablation (established by continuous monitoring) or any of the criteria that would prohibit the diagnosis of “lone” atrial fibrillation, previously defined as the absence of structural heart disease or stroke based on history, physical examination, chest X-ray, routine blood chemistry, and trans-thoracic as well as trans-oesophageal echocardiography (Kopecky et al. 1987; Kumagai et al. 1991; Jaïs et al. 2000). Coronary artery disease was excluded by clinical, ECG or stress test criteria. Pulmonary disease, hypertension,
hyperthyroidism and diabetes were eliminated by appropriate tests. Paroxysmal atrial fibrillation was defined according to the Expert Consensus Statement as recurrent atrial fibrillation that terminates spontaneously within 7 days (Calkins et al. 2007). Thus, of 106 patients with highly symptomatic atrial fibrillation presenting for ablation screened, 12 patients were suitable to be included in this study.

All anti-arrhythmic medication was ceased ≥ 5 half-lives prior to the study. No patient had received amiodarone. All patients provided written informed consent to the study protocol which was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

3.2.2 Electrophysiological Study and Ablation

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. In patients with atrial fibrillation the study protocol was performed before ablation, while in the reference group this was done after accessory pathway ablation. The left atrium was accessed using a single transeptal puncture following which repeated bolus unfractionated heparin was utilised to maintain the activated clotting time between 300-350 seconds.

Following the study protocol, patients with atrial fibrillation underwent circumferential pulmonary vein ablation with an end-point of isolation confirmed by circumferential mapping (Lasso, Biosense-Webster) with either elimination or dissociation of pulmonary venous potentials. Ablation of the pulmonary veins was performed using a delivered power of 30W with irrigation rates of 30mL/min (Thermocool, Biosense Webster). Additional substrate modification was performed in patients with an
episode of atrial fibrillation ≥48 hours or with a left atrial size ≥57mm (longest
diameter). This took the form of linear ablation along the left atrial roof with an end-
point of linear double potentials and conduction block demonstrated by an activation
detour during pacing of the left atrial appendage. Cavotricuspid isthmus ablation with
an endpoint of bi-directional isthmus block was performed only in patients with a
history of typical flutter or if mapping confirmed typical flutter during the procedure.
Linear ablation was performed with a delivered power of 30-35W with irrigation rates
of 30-60mL/min.

3.2.3 Electroanatomical Study Protocol

Electroanatomical maps were created of both atria during sinus rhythm using the
CARTO mapping system (Biosense-Webster). The electroanatomical mapping system
has been previously described in detail; the accuracy of the sensor position has been
previously validated and is 0.8mm and 5 degrees (Gepstein et al. 1997). In brief, the
system records the surface ECG and bipolar electrograms filtered at 30-400Hz from the
mapping and reference catheters. Endocardial contact during point acquisition was
facilitated by electrogram stability, fluoroscopy and the catheter icon on the CARTO
system. Points were acquired in the auto-freeze mode if the stability criteria in space
(≤6mm) and local activation time (≤5ms) were met. Mapping was performed with an
equal distribution of points using a fill-threshold of 15mm. Editing of points was
performed off-line. Local activation time was manually annotated to the peak of the
largest amplitude deflection on bipolar electrograms; in the presence of double
potentials this was annotated at the largest potential. If the bipolar electrogram
displayed equivalent maximum positive and negative deflections, the maximum negative deflection on the simultaneously acquired unipolar electrogram was used to annotate the local activation time. Points not conforming to the surface ECG P wave morphology or <75% of the maximum voltage of the preceding electrogram were excluded. Regional atrial bipolar voltage and conduction velocity were analysed as previously described and are detailed below (Sanders et al. 2003; Kistler et al. 2004; Sanders et al. 2004a; John et al. online early).

3.2.3.1 Voltage Analysis

For the purposes of evaluating regional voltage differences, each atrium was segmented using previously validated offline software (Kuklik et al. 2004). The right atrium was segmented as the high- and low-lateral right atrium, high- and low-posterior right atrium, high- and low-septal right atrium, and anterior right atrium. The left atrium was segmented as posterior left atrium, anterior left atrium, septal left atrium, inferior left atrium, lateral left atrium and left atrial roof. The voltage of points identified by region was then exported for analysis. Low voltage points were defined as point with a bipolar voltage ≤0.5mV and electrically silent points as the absence of recordable activity or a bipolar voltage amplitude ≤0.05mV (the noise level of the system).

3.2.3.2 Conduction Velocity Analysis

Isochronal activation maps (5ms intervals) of the atria were created and regional conduction velocity determined in the direction of the wave-front propagation (least isochronal crowding). An approximation of conduction velocity was determined by expressing the distance between two points as a function of the difference in local
activation time. Mean conduction velocity for each region was determined by averaging the conduction velocity between 5 pairs of points, as previously described (Sanders et al. 2003; Kistler et al. 2004; Sanders et al. 2004a; John et al. online early). For the purposes of evaluating regional conduction differences, each atrium was segmented as above.

### 3.2.3.3 Complex Electrograms

The proportion of points demonstrating complex electrograms was determined using the following definitions: (i) Fractionated signals – complex activity of ≥50ms duration; and (ii) Double potentials – potentials separated by an isoelectric interval where total electrogram duration was ≥50ms.

### 3.2.4 Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median and inter-quartile range as appropriate. Categorical variables are reported as number and percentage. Proportions were compared using Fisher’s Exact test. Comparisons between means were analysed using paired or unpaired t tests as appropriate. Comparisons with adjustment for multiple sampling within patients were performed using a Mixed Linear Model for continuous data or a logistic Generalised Estimating Equation for categorical data. Statistical tests were performed using SPSS 15 (SPSS Inc) and statistical significance was set at p<0.05.
3.3 Results

3.3.1 Baseline Details

Baseline patient characteristics are summarised in Table 3.1. Patients with atrial fibrillation had a median arrhythmia history of 60 months and a mean longest episode of $3.2\pm2.6$ days. Groups were well matched for age, gender, left ventricular wall thickness and function. However, patients with atrial fibrillation had significantly larger left atria ($p=0.01$). None of the patients with atrial fibrillation had atrial arrhythmias (>30 seconds) by continuous monitoring in the 7 days prior to the procedure.

A total of $193\pm62$ points per patient were analysed in the left atrium and right atrium using electroanatomical mapping.

3.3.2 Structural and Voltage Abnormalities

Both right and left atrial volumes by electroanatomical mapping were significantly greater in patients with atrial fibrillation compared to reference patients; right atrium: $94\pm18$ versus $69\pm9mL$, $p=0.003$ and left atrium: $99\pm19$ versus $77\pm17mL$, $p=0.006$.

The mean bipolar voltage was reduced in patients with atrial fibrillation compared to reference patients (right atrium: $1.7\pm0.4$ versus $2.9\pm0.4mV$; left atrium: $1.7\pm0.7$ versus $3.3\pm0.7mV$, $p<0.001$). The difference in mean log bipolar voltage between patients with atrial fibrillation and reference patients varied significantly by Mixed Linear model according to the region of measurement (right atrium: $p=0.002$; left atrium: $p=0.03$). Regional differences in bipolar voltage with significant differences indicated are illustrated in Figure 3-1. Additionally, points in patients with atrial fibrillation at the
high-lateral right atrium, posterior left atrium and the left atrial roof were more likely to be low voltage (≤0.5mV) (OR 2.9, 95% CI 1.4-6.3; OR 1.7, 95% CI 1.1-2.6; OR 3.3, 95% CI 1.8-6.3, respectively). No significant areas of electrical silence (≤0.05mV) were observed in this cohort of patients. Representative examples of electroanatomical maps in representative patients are shown in Figure 3-2.

### 3.3.3 Abnormalities in Conduction Velocity

Patients with atrial fibrillation had a significantly slower mean conduction velocity during sinus rhythm compared to reference patients (right atrium: 1.3±0.3 versus 2.1±0.5mm/ms; left atrium: 1.2±0.2 versus 2.2±0.4mm/ms, p<0.001). Regional differences in conduction velocity with significant differences indicated are illustrated in Figure 3-3. The total atrial activation time was significantly prolonged in patients with atrial fibrillation compared to reference patients (128±17 versus 89±10ms, p<0.001).

### 3.3.4 Complex Electrograms

Patients with atrial fibrillation demonstrated a significantly greater number of points with double potentials or fractionated signals than reference patients (27±8 versus 8±5%, p<0.001). Patients with atrial fibrillation were more likely to have a point with a double potential or fractionated signal in any region than reference patients (p<0.02). These points were distributed throughout both atria with a clustering at the high-
posterior and high-septal regions of the right atrium, and the left atrial septum and roof (Figure 3-2).

3.4 Discussion

3.4.1 Major findings

This study utilised electroanatomical mapping to demonstrate new information on the nature of abnormalities within the atria of patients with paroxysmal “lone” atrial fibrillation, remote from an arrhythmic event.

The major findings are as follows:

(i) Structural abnormalities characterised by atrial dilatation and lower mean atrial voltage suggesting the loss of atrial myocardium.

(ii) Slower conduction velocities.

(iii) An increase in the proportion of electrograms characterised as double potentials or fractionated signals.

Thus, these findings suggest that patients with paroxysmal lone atrial fibrillation have an abnormal electroanatomical atrial substrate. We posit that these abnormalities, contribute to the “second factor” that promotes progression of atrial fibrillation and why sinus rhythm does not beget sinus rhythm.
3.4.2 Structural changes in Atrial Fibrillation

Despite the early occurrence and reversibility of electrical remodelling of the atria in response to rate, Ausma et al. (2003) have observed that ultrastructural changes evolve over a much longer time frame and are not completely resolved as late as four months after return to sinus rhythm from prolonged atrial fibrillation. These slowly resolving alterations have been characterised as an increase in myolysis and the fraction of extracellular matrix per myocyte, as well as changes in the expression of structural proteins. These observations were associated with longer episodes of induced atrial fibrillation when compared to baseline inductions.

Recent studies in patients with atrial fibrillation undergoing ablation have demonstrated the presence of areas of low voltage and electrical silence (Lo et al. 2007; Marcus et al. 2007), and have implicated this substrate as a marker of a worse outcome following an ablation procedure (Verma et al. 2005). However, these studies have included patients with structural heart disease and recent arrhythmia, and therefore may reflect the effects of the associated heart disease and/or remodelling due to atrial fibrillation itself.

3.4.3 Electroanatomical Studies in Atrial Fibrillation and Related Conditions

In patients with atrial fibrillation there has been little clinical mapping performed outside the context of recent arrhythmia. For example, Kojodjojo et al. (2007) studied the electroanatomical maps of patients with paroxysmal and persistent atrial fibrillation created at their ablation procedure and demonstrated slowing of wave-front propagation velocity compared to patients with no atrial fibrillation. In this study,
patients with persistent atrial fibrillation had just 10 minutes of sinus rhythm prior to study and those with paroxysmal atrial fibrillation had a mean arrhythmia burden of 3.2±3.7 hours in the preceding 72 hours. It is therefore uncertain how much of this observed change is due to electrical remodelling from recent arrhythmia and how much it is reflecting the actual underlying substrate.

One of the mechanisms by which atrial fibrillation begets atrial fibrillation has been suggested to be rate-related remodelling. However, it is unlikely that the abnormalities that have been observed to result from atrial fibrillation itself form the substrate predisposing to the development of atrial fibrillation in the first instance. Insights into the underlying substrate can be gained from looking at the atrial abnormalities reported in conditions known to be predisposed to atrial fibrillation. Many of these studies have used electroanatomical maps to illustrate such characteristics in patients with conditions associated with atrial fibrillation, but without atrial fibrillation themselves. Sanders et al. studied the right atrial substrate of patients with congestive heart failure (2003) and sinus node disease (2004a) and reported areas of low voltage and electrical silence in association with conduction abnormalities. Kistler et al. (2004) demonstrated progressive changes in older patients without significant heart disease, when compared to younger cohorts of patients. While these findings have been restricted to the right atrium, recently similar characteristics have been observed via electroanatomical mapping in the left atria of patients with mitral stenosis (John et al. online early).
3.4.4 Prior Studies Implicating Abnormalities in “Lone” Atrial Fibrillation

Although patients with “lone” atrial fibrillation are defined as a group with no structural heart disease, there is accumulating evidence of occult abnormalities. Frustaci et al. (1997) found abnormal atrial histology including patchy fibrosis and inflammatory infiltrates in all of 12 patients with paroxysmal lone atrial fibrillation, and in none of 11 control patients. The fibrosis has been characterised as an increased concentration of collagen type I in patients with lone atrial fibrillation compared to controls and this increase has been observed to be attenuated in those patients receiving angiotensin converting enzyme inhibitors (Boldt et al. 2006). There is further evidence that inflammation plays a role in atrial fibrillation, with the observation that C-reactive protein is elevated in patients with lone atrial fibrillation (Chung et al. 2001). Jais et al. (2000) have demonstrated by transeptal haemodynamic evaluation that diastolic dysfunction is present in patients with lone atrial fibrillation. Finally, there is some evidence to suggest that patients with lone atrial fibrillation have microvascular dysfunction in the coronary circulation (Skalidis et al. 2008). Thus, it is feasible that patients without overt structural heart disease may have fibrosis, inflammation, structural change and vascular dysfunction; all features that are consistent with and contribute to our observations of an abnormal substrate in “lone” atrial fibrillation.

3.4.5 Implications

Our understanding of the atrial substrate predisposing to atrial fibrillation is extended by this study. We have been able to show that the predominant underlying substrate in patients with atrial fibrillation is slowing in regional conduction, together with
structural change reflected by lower voltage and larger atria. Importantly, this data is from patients without overt structural heart disease and remote in time from the remodelling effect of recent arrhythmia in order to minimise the effects of associated heart conditions and the arrhythmia itself. Future strategies to treat atrial fibrillation should therefore focus on atrial myocardial structure and conduction. While there is yet to be definitive long-term data on the outcome of ablation treatments for patients with paroxysmal atrial fibrillation, this study raises the possibility of progressive disease continuing despite apparent procedural success due to the continuing evolution of abnormal substrate in lone atrial fibrillation.

3.4.6 Limitations

Patients with persistent atrial fibrillation were not studied and may differ in substrate, however many patients with persistent atrial fibrillation have progressed from paroxysms initially. While the abnormalities observed in this study are proposed to constitute the substrate predisposing to atrial fibrillation, the development of clinical atrial fibrillation is complex and depends not only on substrate but also on other factors such as triggers and perpetuators that were not addressed by this study.

3.5 Conclusion

Patients with paroxysmal lone atrial fibrillation demonstrate structural abnormalities characterised by loss of myocardial voltage, conduction slowing and an increase in the
proportion of complex electrograms. These abnormalities contribute to the “second factor” critical to the development and progression of atrial fibrillation.
Table 3.1

Patient characteristics

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<td>Left Ventricular ejection fraction (%)</td>
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Mean (+ standard deviation) bipolar voltage of the 7 right and 6 left atrial regions from the electroanatomical map.

*p<0.001, †p<0.01, ‡p<0.05. RA – right atrium. LA – left atrium. H – high. L – low.
Example electroanatomical bipolar voltage maps

Figure 3-2

Representative CARTO maps of a patient with atrial fibrillation (bottom) and a reference patient (top). Both atria are oriented in the posterior-anterior projection and are of the same scale. The colour scale is identical in both images with red representing voltage ≤0.5mV and purple being voltage ≥5mV. In addition to having greater regions of low voltage (red), the patient with atrial fibrillation has more evidence of conduction abnormalities in the form of fractionated signals (pink tags) and double potentials (blue tags).
Figure 3-3

Regional conduction velocity

Mean (+ standard deviation) conduction velocity in the 7 right and 6 left atrial regions from the electroanatomical map.

*p<0.001, †p=0.01, ‡p<0.05. RA – right atrium. LA – left atrium. H – high. L – low.
Chapter 4.
Right atrial electrical substrate of atrial flutter

4.1 Introduction

The circuit of typical atrial flutter has been well characterised with the crista terminalis and the tricuspid annulus defined as the posterior and anterior conduction barriers, respectively (Cosio et al. 1988; Olgin et al. 1995; Kalman et al. 1996; Nakagawa et al. 1996). Ablation of the cavotricuspid isthmus is a highly successful treatment for atrial flutter, however a significant proportion subsequently develop atrial fibrillation (Paydak et al. 1998; Chinitz et al. 2007; Ellis et al. 2007). Indeed, atrial flutter has a close inter-relationship with atrial fibrillation and the two rhythms frequently co-exist (Halligan et al. 2004). Key to the understanding of this relationship are the seminal observations by Waldo and colleagues that typical atrial flutter almost always develops from antecedent atrial fibrillation of variable duration (Shimizu et al. 1991; Waldo and Cooper 1996). One of the postulates for this observation has been that a period of atrial fibrillation facilitates the development of the functional conduction block along the crista terminalis required for atrial flutter to sustain.

It is well recognised that atrial fibrillation occurs in patients with structural heart disease and an abnormal atrial substrate (Kannel et al. 1982b). The atrial substrate has been extensively characterised in conditions predisposed to the development of atrial fibrillation such as heart failure, hypertension, valvular heart disease, congenital heart disease, sinus node disease and ageing (Li et al. 1999; Morton et al. 2003; Sanders et al. 2003; Verheule et al. 2003; Kistler et al. 2004; Sanders et al. 2004a; Kistler et al. 2006; John et al. online early). Whether similar such abnormal atrial substrate exists in
patients with atrial flutter to account for the frequent co-existence of both arrhythmias is not known.

We hypothesised that patients with atrial flutter would demonstrate an abnormal atrial substrate to account for the frequent development of atrial fibrillation. In order to evaluate the substrate without the electrical remodelling effects of the arrhythmia itself, we performed electrophysiological mapping of right atrium remote in time from the arrhythmia.

4.2 Methods

4.2.1 Study Population

This study comprised 8 patients without antecedent atrial fibrillation undergoing ablation for typical atrial flutter and a reference group of 12 patients undergoing radiofrequency ablation for atrioventricular reentry tachycardia or atrioventricular nodal reentry tachycardia. Patients with atrial flutter were selected on the basis of having ≥2 previous episodes of typical atrial flutter confirmed on a 12-lead electrocardiogram. These patients were documented to be in sinus rhythm and described no symptoms attributable to atrial flutter for at least 1 month prior to ablation. In addition, all patients underwent continuous monitoring for 7 days prior to the study and were excluded if they had evidence of any atrial arrhythmia >30 seconds.

All anti-arrhythmic medication was ceased ≥5 half-lives prior to the study. No patient had received amiodarone. All patients provided written informed consent to the study.
protocol which was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

4.2.2 Electrophysiological Study and Ablation

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. In patients with atrial flutter the study protocol was performed before ablation, while in the reference group this was done after ablation. Following the study protocol, patients with atrial flutter underwent cavotricuspid isthmus ablation with a delivered power of 35W with irrigation rates of 30-60mL/min and an endpoint of bi-directional isthmus block.

4.2.3 Electrophysiology Study Protocol

The following catheters were positioned for the study protocol: (i) a 10-pole catheter (2-5-2mm inter-electrode spacing, Daig Electrophysiology) within the coronary sinus with the proximal bipole at the coronary sinus ostium as determined in the best septal left anterior oblique position; (ii) a 20-pole “crista” catheter (1-3-1mm inter-electrode spacing, Biosense-Webster) placed along the crista terminalis with the distal tip superiorly such that the second bipole lay at the junction of the superior vena cava and right atrium, stabilised by a long sheath (CSTA, Daig Electrophysiology) to ensure close apposition to the postero-lateral right atrium; and (iii) a 20-pole catheter (2-5-2mm inter-electrode spacing, Daig Electrophysiology) placed initially along the lateral right
atrium and then moved to the high right atrial septum (Figure 4-1). The following parameters were determined:

4.2.3.1 Effective Refractoriness

Atrial ERP was evaluated at twice diastolic threshold at cycle lengths of 600 and 450ms using an 8-beat drive followed by an extra-stimulus, starting with a coupling interval of 150ms increasing in 10ms increments. ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site the ERP was measured 3 times at each cycle length and averaged. If ERP varied by >10ms an additional 2 measurements were made and the total number averaged. ERP was measured from the following sites: (i) distal coronary sinus; (ii) proximal coronary sinus; (iii) low-lateral right atrium; (iv) high-lateral right atrium; and (v) high-septal right atrium. Atrial fibrillation induced by ERP testing lasting >5 minutes was considered sustained; when this occurred, no further data was acquired.

4.2.3.2 Atrial Conduction

Atrial conduction time was assessed along linearly placed catheters by pacing the distal bipole (1,2) and determining the conduction time to a proximal bipole (9,10) at the coronary sinus and lateral right atrium. Conduction time at each site was averaged over 10 beats during stable capture at 600 and 450ms cycle lengths.

P wave duration was determined as a marker of global conduction by the average of 10 beats on ECG lead II.
4.2.3.3 Site-specific Conduction Abnormalities at the Crista Terminalis

The number of bipoles on the crista terminalis catheter with discrete double potentials separated by an isoelectric interval or complex fractionated activity of ≥50ms duration, and the maximum electrogram duration were determined during sinus rhythm, constant pacing and for the shortest-coupled captured extra-stimulus from the proximal coronary sinus and low-lateral right atrium.

4.2.3.4 Sinus Node Function

Sinus node function was evaluated as follows: (i) Baseline sinus cycle length was determined over 10 consecutive sinus cycles; (ii) SACT was determined after an 8-beat pacing train using the formula [SACT = (return - basic cycle length)/2] 3 times and averaged; and (iii) CSNRT was determined after a 30-second drive train at cycle lengths of 600 and 450ms, correcting for the baseline cycle length. At each cycle length, CSNRT was determined 3 times and averaged.

4.2.4 Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median and inter-quartile range as appropriate. Categorical variables are reported as number and percentage. Proportions were compared using Fisher’s Exact test. Comparisons between means were analysed using analysis of variance and paired or unpaired t tests as appropriate. Comparisons with adjustment for multiple sampling within patients were performed using a Mixed Linear Model for continuous data or a logistic
Generalised Estimating Equation for categorical data. Statistical tests were performed using SPSS 15 (SPSS Inc) and statistical significance was set at p<0.05.

4.3 Results

4.3.1 Baseline Details

Baseline patient characteristics are summarised in Table 4.1. Patients with atrial flutter had a median atrial flutter history of 6.5 months (IQR 3-13), however they had no history of any arrhythmia for at least 1 month (range 1-8 months) prior to the study. Groups were well matched for age, left ventricular dimensions and hypertrophy, while differences in atrial size did not reach significance on trans-thoracic echocardiogram.

4.3.2 Atrial Refractoriness

For patients with atrial flutter, the mean ERP across all sites trended to be greater than that of reference patients (at 600ms: 244±25 versus 227±15ms, p=0.07; at 450ms: 232±29 versus 213±12ms, p=0.06). At each site patients with atrial flutter demonstrated equal or higher ERP when compared to the reference group, however this difference was only statistically significant at one site, the high-lateral right atrium (Figure 4-2). The ERP was higher following 600ms drive trains than after 450ms drive trains for both patients with atrial flutter (244±25 versus 235±30, p=0.02) and reference patients (227±15 versus 213±12, p<0.001); no difference in physiological rate-adaptation of ERP was observed between groups (p=0.7).
4.3.3 Atrial Conduction Time

The conduction time along linear catheters at the lateral right atrium and the coronary sinus was significantly longer in patients with atrial flutter when compared with reference patients (p=0.04) and this difference depended on the site of measurement (p<0.001 for interaction). Post hoc tests performed within the statistical model revealed slower conduction observed along the lateral right atrium in patients with atrial flutter than the reference group (67±4 versus 47±3ms, p<0.001) and no difference in conduction time at the coronary sinus (45±4 versus 46±3ms, p=0.8).

The P wave duration was significantly prolonged in patients with atrial flutter compared to reference patients (122±18 versus 102±11ms, p=0.007).

4.3.4 Site-Specific Conduction Abnormalities

Site-specific conduction abnormalities at the crista terminalis during sinus rhythm were more apparent in patients with atrial flutter than in reference patients. During sinus rhythm, patients with atrial flutter had a greater number of bipoles demonstrating double potentials or fractionated signals on the crista terminalis catheter than reference patients (4.1±2.6 versus 1.0±1.1 respectively, p=0.001) of which the maximum electrogram duration was longer (80±26 versus 53±7ms respectively, p=0.004). These differences were even more marked during pacing and increased further with extra-stimulus (Figure 4-3). These data highlight the functional nature of the conduction delay at the crista terminalis, as evidenced by variation in the extent of conduction abnormalities depending on the rate and site of stimulation.
4.3.5 Sinus Node Function

Patients with atrial flutter had a longer baseline sinus cycle length than reference patients (1019±184 versus 777±137ms, p=0.003) and longer CSNRT at 450ms (318±71 versus 203±94ms, p=0.02). Differences in SACT (107±53 versus 82±35ms, p=0.2) and CSNRT at 600ms (266±113 versus 194±74ms, p=0.1) did not reach significance.

4.4 Discussion

4.4.1 Major Findings

This study utilised electrophysiological mapping to demonstrate new information on the nature of atrial abnormalities in patients with typical atrial flutter, remote from an arrhythmic event. The major findings are as follows:

(i) Conduction abnormalities characterised by prolongation of lateral right atrial conduction time, longer P wave duration and site-specific conduction delay.

(ii) Impairment of sinus node function.

(iii) An increase or no change in ERP, consistent with prior studies evaluating clinical substrates for atrial arrhythmia but in contrast to the remodelling attributed to atrial arrhythmia itself.

Thus, the present study suggests that patients with atrial flutter, studied remote from an arrhythmic event, have widespread and persistent abnormal atrial substrate. We
posit that these diffuse atrial abnormalities are partly responsible for the frequent development of atrial fibrillation in patients with atrial flutter.

4.4.2 The Inter-relationship between Atrial Flutter and Atrial Fibrillation

Ablation of atrial flutter has been observed to significantly reduce the occurrence of atrial fibrillation at 496±335 days post-ablation from 55% to 33% (Schmieder et al. 2003). Despite this reduction, reports from patient cohorts followed up after ablation for atrial flutter describe subsequent atrial fibrillation rates ranging from 25% after 20±9 months surveillance (Paydak et al. 1998) to 82% at 39±11 months follow up (Ellis et al. 2007). Thus, it is clear that although atrial flutter may be the only clinical arrhythmia initially apparent, progression to atrial fibrillation is not uncommon.

The atrial arrhythmias of atrial flutter and atrial fibrillation share many of the same aetiological factors and often co-exist in the same patient (Vidaillet et al. 2002). Liu et al. (2002) observed that ablation of conduction gaps in the crista terminalis can result in the organisation of atrial fibrillation to atrial flutter. Shimizu et al. (1991) demonstrated in dogs that the onset of atrial flutter in the sterile pericarditis model is preceded by atrial fibrillation. Ortiz et al. (1994) provided insights into the mechanism of atrial flutter by demonstrating that maintenance of stable atrial flutter was directly dependent on sufficient length of functional block being present in the right atrial free wall. The further observation that triggers in post-bypass patients led to transitional atrial fibrillation and then atrial flutter supported the notion that atrial fibrillation, however short-lived, was integral to the development of the necessary functional block (Waldo and Cooper 1996). Roithinger et al. (1997) subsequently observed regular
right atrial activation during atrial fibrillation which slowed and organised into atrial flutter, thereby implicating atrial fibrillation in the generation of atrial flutter.

Testing the hypothesis that atrial fibrillation was indeed necessary for subsequent atrial flutter, Wazni et al. (2003) studied the effect of trigger elimination by performing pulmonary vein isolation without cavotricuspid isthmus ablation in 59 patients with both atrial fibrillation and atrial flutter and found that although 32 of these patients developed episodes of atrial flutter acutely, only 3 had sustained atrial flutter after 8 weeks. Indeed, patients undergoing ablation for atrial fibrillation in whom atrial flutter has not been documented clinically or at electrophysiology study have no difference in outcome with or without cavotricuspid isthmus line (Shah et al. 2007). Patients with typical atrial flutter in addition to paroxysmal atrial fibrillation have been shown to have more frequent recurrence of arrhythmia following pulmonary vein cryoisolation with accompanying isthmus line than patients with atrial fibrillation alone, suggesting that the substrate of patients with atrial flutter harbours important non-pulmonary vein sites of arrhythmogenesis (Moreira et al. 2007).

4.4.3 Substrate Predisposing to the Development of Atrial Flutter

Experimental models have shown the development of an abnormal electrical substrate with atrial flutter. Morton et al. (2002) demonstrated that prolonged atrial flutter resulted in an abrupt reduction in refractoriness and a slower reduction in conduction velocity. Additionally, this study underlined the importance of critically-timed triggers in the conversion of atrial flutter to atrial fibrillation after the necessary substrate was allowed to develop after 4 weeks of atrial flutter.
Patients with chronic atrial flutter have been observed to have electrical remodelling by way of shortened monophasic action potential durations with impaired rate adaptation compared to control patients (Franz et al. 1997). Ramanna et al. (2005) have shown that an increase in the dispersion of refractoriness predicts the inducibility of atrial fibrillation in patients undergoing ablation for atrial flutter. Sparks et al. (2000) studied patients with paroxysmal atrial flutter and observed a reduction in ERP immediately following 5-10 minutes of induced atrial flutter with a return to baseline ERP over a period of minutes. In patients with chronic atrial flutter however, ERP remained low out to 30 minutes but was seen to recover (in addition to sinus node function) when retested at 3 weeks. Further evidence for remodelling of the sinus node with atrial flutter is reported by Daoud et al. (2002) who studied patients with chronic atrial flutter following ablation and observed impaired sinus node function which recovered over a 3 month period.

These reports of electrical remodelling as a result of atrial flutter characterised by ERP shortening and impairment of sinus node function have underlined the importance of recent arrhythmia in generating these features. Whether such features persist when tested remote from an episode of atrial flutter is critical when elucidating the features of the underlying atrial substrate (rather than the effects of rate related remodelling) that may aid the progression of arrhythmia to atrial fibrillation.

4.4.4 Substrate in Conditions Predisposed to Atrial Arrhythmia

While studies have implicated the role of shortened ERP resulting from arrhythmia itself in the development and maintenance of atrial arrhythmia (Morillo et al. 1995;
Wijffels et al. (1995), evaluation of conditions predisposed to atrial flutter and atrial fibrillation (but without arrhythmia) have provided evidence to the contrary. Li et al. (1999) developed a canine model of congestive heart failure and demonstrated "atrial remodelling of a different sort" to that seen due to atrial fibrillation alone. An increase in ERP at short cycle lengths associated with an increase in the heterogeneity of conduction resulted in longer durations of atrial fibrillation despite the increase in refractoriness. Verheule et al. (2003) observed an increase in ERP but a propensity for atrial fibrillation in a canine model of mitral regurgitation, presumed to be due to abnormalities in conduction and structural remodelling. In humans, patients with atrial septal defects have demonstrated prolonged ERP and delayed conduction across the crista terminalis compared to reference patients (Morton et al. 2003). Patients with congestive heart failure similarly have significant conduction abnormalities and sinus node dysfunction in association with prolonged ERP (Sanders et al. 2003). Kistler et al. (2004) have demonstrated widespread and site-specific conduction abnormalities in a progressive manner with increasing age. Similar changes have been documented by Sanders et al. (2004a) and John et al. (online early) in patients with sinus node disease and rheumatic mitral stenosis, respectively.

These experimental and clinical studies provide compelling evidence that the predominant electrophysiological features of the substrate for atrial arrhythmias, excluding the effect of arrhythmia itself, are related to conduction abnormalities rather than changes in refractoriness. In the current study we have shown that patients with atrial flutter, studied remote from arrhythmia, have right atrial conduction abnormalities and sinus node dysfunction, without obvious reduction in
refractoriness. These findings are consistent with the studies to have evaluated the substrate predisposing to atrial fibrillation.

4.4.5 Implications

This study has confirmed the existence of significant widespread remodelling of the atria in patients with atrial flutter remote from an arrhythmic event characterised by increased linear conduction times, sinus node dysfunction and site-specific conduction abnormalities. Patients were studied remote in time from the arrhythmia itself to evaluate the underlying substrate without the known confounding effects of arrhythmia itself, which may well further perpetuate atrial arrhythmia. These findings strongly argue that patients with atrial flutter have a pre-existing diffuse substrate which may contribute to both the frequent co-existence of atrial fibrillation and the development of atrial fibrillation after ablation for atrial flutter.

4.4.6 Limitations

While the abnormalities observed in this study may constitute the substrate predisposing to atrial fibrillation, the development of clinical atrial fibrillation is complex and depends not only on substrate but also on other factors such as triggers and perpetuators that were not addressed by this study (Allessie et al. 2001). Access to the left atrium was not mandated by the clinical procedure therefore no left atrial data could be collected. Finally, although no patient had symptoms for a month and patients were monitored for a week prior to the procedure to ensure our evaluation
was remote from an episode of atrial flutter, we cannot exclude an additive effect of rate-related remodelling, although there is a substantial amount of evidence that electrical remodelling reverses within a short time after restoration of atrial flutter to sinus rhythm (Sparks et al. 2000).

4.5 Conclusion

Patients with atrial flutter, remote from an arrhythmic episode, demonstrate conduction abnormalities and altered sinus node function, without reduction in atrial refractoriness. These findings suggest that the cause of the observed close inter-relationship of atrial flutter and atrial fibrillation may be reflected in this atrial substrate.
Table 4.1

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Atrial Flutter (n=8)</th>
<th>Reference (n=12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±8</td>
<td>59±12</td>
<td>0.2</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>2 (25)</td>
<td>1 (8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Left atrial parasternal size (mm)</td>
<td>41±8</td>
<td>38±7</td>
<td>0.5</td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td>22±5</td>
<td>19±4</td>
<td>0.3</td>
</tr>
<tr>
<td>Right atrial area (cm²)</td>
<td>19±3</td>
<td>13±6</td>
<td>0.1</td>
</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>49±4</td>
<td>46±6</td>
<td>0.3</td>
</tr>
<tr>
<td>LV end-systolic dimension (mm)</td>
<td>30±7</td>
<td>30±5</td>
<td>0.9</td>
</tr>
<tr>
<td>Interventricular septum (mm)</td>
<td>10±2</td>
<td>11±1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

LV = left ventricular.
Left anterior oblique view of a decapolar catheter in the coronary sinus, a duodecapolar catheter along the crista terminalis with its stabilising sheath and a duodecapolar catheter along the lateral right atrium. Subsequently, the duodecapolar catheter was positioned at the high-septal right atrium for ERP testing (not shown).
Mean (+ standard deviation) effective refractory period at the five sites tested following a 600ms drive train (top) and a 450ms drive train (bottom) in patients with atrial flutter and reference patients. All values for 600ms are higher than the same patient group and site value for 450ms.

*p<0.05. dCS – distal coronary sinus. pCS – proximal coronary sinus. LLRA – low lateral right atrium. HLRA – high lateral right atrium. HRAS – high right atrial septum.
Conduction characteristics at the crista terminalis

Mean (+ standard deviation) number (left) and maximum duration (right) of double potentials or fractionated signals along the crista terminalis during pacing (S1) at 600ms (top) and 450ms (bottom) and with the earliest captured extra-stimulus (S2) at the proximal coronary sinus (pCS) and low-lateral right atrium (LLRA) in patients with atrial flutter and reference patients. p<0.03 for all comparisons between atrial flutter and reference patients.
Chapter 5.
Right atrial electroanatomical substrate of atrial flutter

5.1 Introduction

The underlying substrate of typical atrial flutter is not fully understood. Atrial flutter has a close inter-relationship with atrial fibrillation and the two rhythms frequently co-exist (Halligan et al. 2004). Ablation of atrial flutter has been observed to significantly reduce the occurrence of atrial fibrillation in the short term (Schmieder et al. 2003). Despite this reduction a significant proportion, perhaps even the majority with long-term follow-up, eventually develop atrial fibrillation (Paydak et al. 1998; Chinitz et al. 2007; Ellis et al. 2007; Meissner et al. 2007; Moreira et al. 2008). Key to the understanding of the close inter-relationship for atrial flutter and atrial fibrillation is the recognition that typical flutter almost always develops from antecedent atrial fibrillation of variable duration (Shimizu et al. 1991; Waldo and Cooper 1996; Roithinger et al. 1997). Emerging evidence implicates abnormal atrial structural remodelling and its resultant electrophysiological milieu in clinical conditions known to be predisposed to atrial fibrillation (Li et al. 1999; Morton et al. 2003; Sanders et al. 2003; Verheule et al. 2003; Kistler et al. 2004; Sanders et al. 2004a; Kistler et al. 2006; John et al. online early). Whether patients with atrial flutter also demonstrate abnormal substrate outside of the well characterised circuit of typical flutter is not known.

Critical to our management of patients with both atrial flutter and atrial fibrillation is an understanding of the interactions and shared characteristics of these rhythms. Importantly, electrical characteristics of patients with atrial arrhythmia are known to
be affected by recent arrhythmia (Wijffels et al. 1995). We hypothesised that patients with atrial flutter would demonstrate an abnormal atrial substrate to account for the frequent development of atrial fibrillation. In order to evaluate this we performed high-density electroanatomical mapping of the right atrium to assess voltage and conduction characteristics of the atrial flutter substrate, remote from recent arrhythmia.

5.2 Methods

5.2.1 Study Population

This study comprised 12 patients without antecedent atrial fibrillation undergoing ablation for typical atrial flutter and a reference group of 9 patients undergoing radiofrequency ablation for atrioventricular reentry tachycardia or atrioventricular nodal reentry tachycardia. Patients with atrial flutter were selected on the basis of having ≥2 previous episodes of typical atrial flutter confirmed on a 12-lead electrocardiogram. These patients were documented to be in sinus rhythm and described no symptoms attributable to atrial flutter for at least 1 month prior to ablation. In addition, all patients underwent continuous monitoring for 7 days prior to the study and were excluded if they had evidence of any atrial arrhythmia >30 seconds.

All anti-arrhythmic medication was ceased ≥5 half-lives prior to the study. No patient had received amiodarone. All patients provided written informed consent to the study.
protocol which was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

5.2.2  Electrophysiological Study and Ablation

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. In patients with atrial flutter the study protocol was performed before ablation, while in the reference group this was done after ablation. Following the study protocol, patients with atrial flutter underwent cavitricuspid isthmus ablation with a delivered power of 35W with irrigation rates of 30-60mL/min and an endpoint of bi-directional isthmus block.

5.2.3  Electroanatomical Study Protocol

Electroanatomical maps were created of the right atrium during sinus rhythm using the CARTO mapping system (Biosense-Webster). The electroanatomical mapping system has been previously described in detail; the accuracy of the sensor position has been previously validated and is 0.8mm and 5 degrees (Gepstein et al. 1997). In brief, the system records the surface ECG and bipolar electrograms filtered at 30-400Hz from the mapping and reference catheters. Endocardial contact during point acquisition was facilitated by electrogram stability, fluoroscopy and the catheter icon on the CARTO system. Points were acquired in the auto-freeze mode if the stability criteria in space (≤6mm) and local activation time (≤5ms) were met. Mapping was performed with an equal distribution of points using a fill-threshold of 15mm. Editing of points was
performed off-line. Local activation time was manually annotated to the peak of the largest amplitude deflection on bipolar electrograms; in the presence of double potentials this was annotated at the largest potential. If the bipolar electrogram displayed equivalent maximum positive and negative deflections, the maximum negative deflection on the simultaneously acquired unipolar electrogram was used to annotate the local activation time. Points not conforming to the surface ECG P wave morphology or <75% of the maximum voltage of the preceding electrogram were excluded. Regional atrial bipolar voltage and conduction velocity were analysed as previously described and are detailed below (Sanders et al. 2003; Kistler et al. 2004; Sanders et al. 2004a; John et al. online early).

5.2.3.1 Voltage Analysis

For the purposes of evaluating regional voltage differences, each atrium was segmented using previously validated offline software (Kuklik et al. 2004). The right atrium was segmented as the high- and low-lateral right atrium, high- and low-posterior right atrium, high- and low-septal right atrium, and anterior right atrium. At each of these regions an average voltage of 10 points was determined. The voltage of points identified by region was exported for analysis. Low voltage points were defined as points with a bipolar voltage ≤0.5mV and electrically silent points as the absence of recordable activity or a bipolar voltage amplitude ≤0.05mV (the noise level of the system).

5.2.3.2 Conduction Velocity Analysis

Isochronal activation maps (5ms intervals) of the atria were created and regional conduction velocity determined in the direction of the wave-front propagation (least
isochronal crowding). An approximation of conduction velocity was determined by expressing the distance between two points as a function of the difference in local activation time. Mean conduction velocity for each region was determined by averaging the conduction velocity between 5 pairs of points, as previously described (Sanders et al. 2003; Kistler et al. 2004; Sanders et al. 2004a; John et al. online early). For the purposes of evaluating regional conduction differences, each atrium was segmented as above.

5.2.3.3 Complex Electrograms

The proportion of points demonstrating complex electrograms was determined using the following definitions: (i) Fractionated signals – complex activity of ≥50ms duration; and (ii) Double potentials – potentials separated by an isoelectric interval where total electrogram duration was ≥50ms.

5.2.4 Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median and interquartile range as appropriate. Categorical variables are reported as number and percentage. Proportions were compared using Fisher’s Exact test. Comparisons between means were analysed using analysis of variance and paired or unpaired t tests as appropriate. Comparisons with adjustment for multiple sampling within patients were performed using a Mixed Linear Model for continuous data or a logistic Generalised Estimating Equation for categorical data. Statistical tests were performed using SPSS 15 (SPSS Inc) and statistical significance was set at p<0.05.
5.3 Results

5.3.1 Baseline Details

Baseline patient characteristics are summarised in Table 5.1. Patients with atrial flutter had a median atrial flutter history of 16 months (IQR 8-22), however they had no history of any arrhythmia for at least 1 month (range 1-7 months) prior to the study. Groups were well matched for age, left ventricular dimensions and hypertrophy, however patients with atrial flutter had significantly larger left atria on trans-thoracic echocardiogram.

A total of 97±19 points per patient were analysed in the right atrium using electroanatomical mapping.

5.3.2 Structural and Voltage Abnormalities

Mean right atrial volume by electroanatomical map was significantly greater in patients with atrial flutter compared to reference patients (121±30 versus 83±24mL, p=0.005). The mean right atrial bipolar voltage was reduced in patients with atrial flutter compared to reference patients (2.1±0.5 versus 3.0±0.5mV, p<0.001). Regional differences in bipolar voltage are illustrated in Figure 5-1; significant differences between patients with atrial flutter and reference patients were seen in high-lateral, high-posterior and anterior regions. Additionally, points at the high-posterior region were more likely to be low voltage (≤0.5mV) in patients with atrial flutter (odds ratio 3.7, 95% CI 2.1-6.7). No significant areas of electrical silence (≤0.05mV) were observed.
Illustrative examples of electroanatomical maps in representative patients are shown in Figure 5-2.

5.3.3 Abnormalities in Conduction Velocity

Patients with atrial flutter had slower mean conduction velocity during sinus rhythm compared to reference patients (1.2±0.2 versus 2.1±0.6mm/ms, p<0.001). Figure 5-3 illustrates regional conduction velocities, which were significantly slower in patients with atrial flutter compared to reference patients at the high-lateral, low-posterior, low-septal and anterior right atrium.

The right atrial activation time was significantly prolonged in patients with atrial flutter compared to reference patients (107±23 versus 85±14ms, p=0.02).

5.3.4 Complex Electrograms

Patients with atrial flutter demonstrated a significantly greater number of points with double potentials or fractionated signals than reference patients (16±4 versus 10±6%, p=0.006). These points were distributed throughout both atria with a clustering at the high-posterior, high-lateral and high-septal regions of the right atrium (Figure 5-2).
5.4 Discussion

5.4.1 Major Findings

This study utilised electroanatomical mapping to demonstrate new information on the nature of atrial abnormalities in patients with typical atrial flutter, remote from an arrhythmic event. The major findings are as follows:

(i) Structural abnormalities characterised by atrial dilatation and lower mean right atrial voltage suggesting the loss of atrial myocardium.

(ii) Slower conduction velocities.

(iii) An increase in the proportion of electrograms characterised as double potentials or fractionated signals.

Thus, the present study suggests that patients with atrial flutter, studied remote from an arrhythmic event, have widespread and persistent abnormal atrial substrate. We posit that these diffuse atrial abnormalities are partly responsible for the frequent development of atrial fibrillation in patients with atrial flutter.

5.4.2 Substrate in Clinical Conditions Associated with Atrial Arrhythmia

Sanders et al. have demonstrated significant electroanatomical remodelling with areas of low voltage and electrical scar with associated widespread conduction abnormalities in patients with congestive heart failure (2003) and sinus node disease (2004a) compared to control groups. Kistler et al. (2004) have demonstrated by electroanatomical mapping studies that ageing is associated with progressive regional
conduction slowing and structural changes that include areas of low voltage. Perhaps the most marked changes have been shown in patients with rheumatic mitral stenosis in whom striking differences in voltage, conduction velocity and the proportion of complex electrograms are seen when compared to controls (John et al. online early). In addition to the clinical studies, animal models of such diseases have revealed similar features in the abnormal substrate contributing to the potential for arrhythmia (Li et al. 1999; Verheule et al. 2003; Kistler et al. 2006).

These studies provide compelling evidence that the predominant contributors to the substrate for atrial arrhythmias are diffuse structural and conduction abnormalities. In the current study we have shown that patients with atrial flutter, studied remote from arrhythmia, have right atrial structural remodelling with associated conduction abnormalities. These findings are thus consistent with the studies to have evaluated the clinical substrate predisposing to atrial fibrillation.

### 5.4.3 Substrate in Experimental Models of Atrial Flutter

Early work to create atrial flutter in animals included a crush injury model by creating a lesion between the venae cavae (Rosenbleuth and Garcia-Ramos 1947). Based on the epicardial maps, the authors deduced that the reentry loop circled around the atrial crush lesion. Much work on atrial flutter has been performed in the sterile pericarditis dog model which has been shown to dependably produce this arrhythmia to allow characterisation of the circuit (Page et al. 1986). One of the critical features demonstrated by this model is that a sufficient length of functional block is critical to the maintenance of atrial flutter (Ortiz et al. 1994). Interestingly, the time course of
atrial flutter developing is similar to that of the post-bypass arrhythmias seen clinically (Waldo and Cooper 1996); this underscores the role of pericardial inflammation in the genesis of arrhythmia in cardiac surgery patients. More recently, the role of inflammation in atrial flutter has been highlighted in a study in which the usually reliable induction of atrial flutter in the sterile pericarditis model was abolished by pre-treatment with prednisone (Goldstein et al. 2008). Histological and gross inspection of the atria revealed marked structural changes of inflammation only in the untreated group, all of whom (bar one with atrial fibrillation) developed atrial flutter as expected. A sheep model of atrial flutter demonstrated that sustained atrial flutter for 4 weeks allows the development of atrial substrate such that conversion to atrial fibrillation is achieved by extra-stimuli and that this new rhythm is able to be maintained (Morton et al. 2002).

5.4.4 Substrate in Clinical Atrial Flutter

Studies of human atrial flutter have been mainly concerned with elucidating the typical flutter circuit within the right atrium. This has now been well characterised with the posterior and anterior barriers to the circuit defined as the crista terminalis and the tricuspid valve, respectively (Olgin et al. 1995; Kalman et al. 1996). Differences in the atrial flutter circuit between young and old have been published, with younger patients tending toward slowest conduction in the lateral isthmus while older patients demonstrate a low voltage zone and slowest conduction in the medial isthmus (Huang et al. 2008). The substrate of patients with both atrial fibrillation and atrial flutter may differ from that seen in atrial fibrillation alone. Patients with typical atrial flutter in
addition to paroxysmal atrial fibrillation have been shown to have more frequent recurrence of arrhythmia following pulmonary vein isolation with accompanying isthmus line (Moreira et al. 2007). This suggests that non-pulmonary vein sites are more important to the maintenance of atrial fibrillation in patients with co-existent atrial flutter and supports the view that the atrial substrate in atrial flutter is indeed diffuse throughout the atria.

5.4.5 Implications

This study has confirmed the existence of significant diffuse remodelling of the atria in patients with atrial flutter remote from an arrhythmic event characterised by regional slowing in conduction and structural change reflected in lower voltage, larger atria and widespread conduction abnormalities. Patients were studied remote in time from the arrhythmia itself to evaluate the underlying substrate without the known confounding effects of arrhythmia itself, which may well further perpetuate atrial arrhythmia. These findings strongly argue that patients with atrial flutter have a pre-existing diffuse substrate which may contribute to both the frequent co-existence of atrial fibrillation and the development of atrial fibrillation after ablation for atrial flutter.

5.4.6 Limitations

Access to the left atrium was not mandated by the clinical procedure therefore no left atrial data could be collected. While the abnormalities observed in this study may constitute the substrate predisposing to atrial fibrillation, the development of clinical
atrial fibrillation is complex and depends not only on substrate but also on other factors such as triggers and perpetuators that were not addressed by this study (Allessie et al. 2001).

5.5 Conclusion

Patients with atrial flutter, remote from an arrhythmic episode, demonstrate structural abnormalities characterised by loss of myocardial voltage, conduction slowing and an increase in the proportion of abnormal electrograms. These findings suggest that the cause of the observed close inter-relationship of atrial flutter and atrial fibrillation may be reflected in this atrial substrate.
Table 5.1

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Atrial Flutter (n=12)</th>
<th>Reference (n=9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±10</td>
<td>59±15</td>
<td>0.5</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>2 (17)</td>
<td>1 (11)</td>
<td>1.0</td>
</tr>
<tr>
<td>Left atrial parasternal size (mm)</td>
<td>41±4</td>
<td>34±4</td>
<td>0.001</td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td>24±6</td>
<td>17±1</td>
<td>0.047</td>
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<tr>
<td>Right atrial area (cm²)</td>
<td>19±4</td>
<td>17±4</td>
<td>0.5</td>
</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>52±4</td>
<td>50±6</td>
<td>0.5</td>
</tr>
<tr>
<td>LV end-systolic dimension (mm)</td>
<td>30±6</td>
<td>34±5</td>
<td>0.2</td>
</tr>
<tr>
<td>Interventricular septum (mm)</td>
<td>12±5</td>
<td>10±2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

LV = left ventricular.
Figure 5-1

Regional bipolar voltage

Mean (+ standard deviation) bipolar voltage of the 7 right atrial regions from the electroanatomical map.

*p<0.05. H – high. L – low.
Representative CARTO maps of a patient with atrial flutter (right) and a reference patient (left). Both are oriented in the posterior-anterior projection and are of the same scale. The colour scale is identical in both images with red representing voltage ≤0.5mV and purple being voltage ≥5mV. In addition to having greater regions of low voltage (red), the patient with atrial flutter has evidence of conduction abnormalities in the form of fractionated signals (pink tags) and double potentials (blue tags).
Mean (+ standard deviation) conduction velocity in the 7 right atrial regions from the electroanatomical map.

*p<0.05. H – high. L – low.
Chapter 6.
High-density mapping of the sinus node to characterise the remodelling resulting from chronic atrial flutter

6.1 Introduction

The anatomical sinus node is a small localised structure that is located at the junction of the superior vena cava with the right atrium (James 1977; Anderson et al. 1979). In contrast, studies of the canine functional sinus node complex have identified that the area of initial cardiac depolarisation exceeds that of the anatomical sinus node by 3 to 4-fold (Boineau et al. 1980). Although this implicates the existence of widely distributed nodal cells capable of automaticity, histological sectioning of the region by a range of investigators has failed to identify islands of nodal cells separate from the sinus node itself (James 1977; Anderson et al. 1979; Boineau et al. 1980; Sanchez-Quintana et al. 2005). Boineau et al. (1988) undertook several of the early seminal evaluations of the sinus node and have proposed two alternative hypotheses for extranodal sinus complex origins; (i) the existence of specialised conduction tracts from the anatomically fixed nodal source to remote exit sites, and (ii) a coordinated exchange of dominance amongst competing pacemakers via autonomic modulation. For the former explanation, the presence of nodal radiations into adjacent atrial myocardium through electrically isolating connective tissue supports this theory, however no insulated rapidly-conducting tissue analogous to that found in the ventricles has been conclusively demonstrated (Anderson et al. 1981a). Supporting the latter hypothesis, autonomically-mediated shifts in activation sites appear linked to changes in heart rate (Littmann et al. 1990), however the mechanism by which a stable heart rate is maintained without faster pacemakers dominating is yet to be demonstrated.
The observations above were based on conventional mapping techniques. However, newer mapping technology has provided novel insights into arrhythmia mechanisms not previously afforded using conventional techniques. Higa et al. (2004) used non-contact mapping, and demonstrated “preferential pathways” from earliest activation to the site where break-out occurs to the remaining atria in ectopic atrial tachycardia. Whether similar pathways exist to account for the discrepancy between the anatomical and functional sinus node complex is not known.

This study aimed to characterise the electrical properties of the functional sinus node complex in the normal heart. To further explore the sinus node complex activity, the same characterisation was performed in a group known to have impaired sinus node function (Sparks et al. 2000; Daoud et al. 2002) to establish how sinus node activity is affected by atrial remodelling. The anatomical and electrical resolution provided by the three-dimensional, simultaneous, high-density EnSite Array mapping system (St Jude Medical) provides the ability to examine the extent and variability of endocardial sinus activation with detail not previously available.

### 6.2 Methods

#### 6.2.1 Study Population

Fifteen patients with structurally normal hearts undergoing radiofrequency ablation for atrioventricular nodal reentry tachycardia were studied as a reference group. To evaluate the effects of remodelling, a further 16 patients undergoing ablation for chronic typical atrial flutter (median 8 months, IQR 6-23) were studied. The latter
group was selected on the basis of the well documented occurrence of sinus node dysfunction with atrial flutter in previous studies (Sparks et al. 2000; Daoud et al. 2002).

All anti-arrhythmic medication including beta-blockers and calcium channel blockers, were ceased ≥5 half-lives prior to the study. No patient had received amiodarone in the preceding 6 months. All patients provided written informed consent to the study protocol that was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

6.2.2 Electrophysiological Study and Ablation

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. After confirming the arrhythmia mechanism, reference group patients underwent slow pathway ablation and patients with flutter underwent cavotricuspid isthmus ablation with an end-point of bi-directional block confirmed by activation mapping. The study protocol was conducted immediately following ablation for the clinical arrhythmia.

The following catheters were used for the study protocol: (i) a 10-pole catheter (2-5-2mm inter-electrode spacing, Daig Electrophysiology) positioned within the coronary sinus with the proximal bipole at the coronary sinus ostium as determined in the best septal left anterior oblique position; (ii) a 20-pole “crista” catheter (1-3-1mm inter-electrode spacing, Biosense-Webster) placed with the distal tip superiorly such that the second bipole lay at the superior vena cava-right atrial junction, stabilised by a long sheath (CSTA, Daig Electrophysiology) to ensure close apposition along the crista
terminalis; (iii) a roving 4mm ablation catheter (Celsius, Biosense-Webster); and (iv) a multi-electrode array (EnSite Array, St Jude Medical) mounted on a 7.5mL balloon positioned in the superior right atrium (Figure 6-1). Maps were created of the right atrial geometry using the roving catheter to trace the endocardial surface while the EnSite system recorded its three-dimensional position, as previously described (Schilling et al. 1998). Intra-cardiac echocardiography (Ultra ICE, Boston Scientific) was used to standardise catheter positioning and also to localise the crista terminalis and superior vena cava-right atrial junction (Figure 6-2).

6.2.3 Conventional Evaluation of Sinus Node Function

6.2.3.1 Baseline Sinus Cycle Length

The baseline sinus cycle length was determined over 10 consecutive sinus cycles after 10 minutes of rest.

6.2.3.2 Sino-atrial Conduction Time

The SACT was determined after an 8-beat pacing train according to the formula: $SACT = \frac{(\text{return} - \text{basic cycle length})}{2}$ (Narula et al. 1978). SACT was determined 3 times and averaged.

6.2.3.3 Corrected Sinus Node Recovery Time

The CSNRT was determined after a 30-second drive train at cycle lengths of 600 and 450ms, correcting for the baseline cycle length. At each cycle length, CSNRT was determined 3 times and averaged.
6.2.3.4 Conduction Properties at the Crista Terminalis

Site-specific conduction properties at the crista terminalis were quantified by recording the presence of electrograms with discrete double potentials separated by an isoelectric interval or complex fractionated activity of ≥50ms duration on each recording bipole of the crista terminalis catheter. Both the number of bipoles demonstrating these conduction characteristics and the maximum electrogram duration were determined over ten beats in sinus rhythm and one beat immediately after the cessation of each pacing train.

6.2.4 High-Density Simultaneous Unipolar Mapping of Sinus Node Function

Mapping of the sinus node complex was performed during baseline sinus rhythm and also after pace suppression of sinus pacemaker activity following 30-second drive trains at 600 and 450ms. Sinus node activation was characterised by determining the positions of earliest activation (EA) and sinus break-out (SBO). EA was defined as the earliest unipolar electrogram displaying a “QS” pattern and SBO as the earliest unipolar electrogram displaying an “RS” pattern and a sudden increase in \( \frac{dV}{dt} \) indicating rapid depolarisation of surrounding myocardium, as previously described (Higa et al. 2004). For review of the recorded data the high-pass filter was set to 1Hz to allow for slow conduction of the activation wave-front. The position of the virtual electrodes in the region of interest was repeatedly adjusted to find the points of interest. The following parameters were evaluated from simultaneous unipolar recordings of right atrial activation from the balloon array.
6.2.4.1 Location of Points of Earliest Activation and Sinus Break-out

The location of the EA and SBO were determined to define the position of sinus origin relative to the superior vena cava-right atrial junction and the crista terminalis during baseline sinus rhythm and following pace suppression of the sinus node at cycle lengths of 600 and 450ms on three occasions each. The superior vena cava-right atrial junction was defined as the lateral confluence of the superior vena cava, right atrium and right atrial appendage, as previously described (Callans et al. 1999). This was confirmed using intra-cardiac echocardiography demonstrating, at this level, the superior lateral crista terminalis in proximity with the orifice of the right atrial appendage (Figure 6-2). The crista terminalis was then marked along its length with a vertical reference line from the superior vena cava-right atrial junction to the inferior vena cava. The parallel distance from the origin of this line to the point of interest was recorded, as was the perpendicular distance (Figure 6-2). This gave a position in both the supero-inferior and antero-posterior dimensions. In the rare case of a multi-centric SBO point (Movie 6.1), the more cranial was measured.

6.2.4.2 Preferential Conduction Pathways

The path between the EA and SBO was defined as the route of preferential conduction (Figure 6-3), as previously described (Higa et al. 2004). We determined the time to conduct between EA and SBO, and the direction taken. The activation pattern from SBO to the right atrial in relation to the crista terminalis, including transverse conduction through the crista, was observed and atrial propagation qualitatively assessed. Additionally, right atrial activation time from EA to final discernable right atrial activation as recorded by the balloon array was determined.
6.2.4.3 **Voltage in the Right Atrium and Crista Terminalis**

Unipolar voltage at the points of EA and SBO was recorded. Electrograms for 100ms following EA were exported from the EnSite Array for further analysis. This included 256 evenly distributed electrograms throughout the right atrium and 10 evenly spaced electrograms along the length of the crista terminalis. From these exports, peak negative unipolar voltage of the entire right atrium and along the crista terminalis was determined. Additionally, right atrial surface area and distance to the array was able to be determined from the exported geometry.

6.2.5 **Statistical Analysis**

Continuous variables are reported as mean ± standard deviation or median and inter‐quartile range as appropriate to its distribution. Categorical variables are reported as number and percentage. Comparisons between groups were performed using unpaired t tests or Mann-Whitney U tests. Proportions were compared using Fisher’s Exact test. Comparisons with adjustment for multiple sampling within patients were performed using a Mixed Linear Model for continuous data or a logistic Generalised Estimating Equation for categorical data. Statistical tests were performed using SPSS 15 (SPSS Inc) and statistical significance was set at p<0.05.
6.3 Results

6.3.1 Baseline Details

Baseline patient characteristics are summarised in Table 6.1. Mean distance from the array to the right atrial geometry was 30±3mm and the crista terminalis was 23±3mm, well within the reported limits of accuracy (Thiagalingam et al. 2004b). Baseline sinus cycle length did not differ significantly between reference patients and those recently ceasing chronic flutter (775±104ms versus 784±193ms, p=0.9). Differences were seen between the reference group and patients with flutter in right atrial surface area (132±12 versus 163±34cm², p=0.003), P wave duration (109±13 versus 147±13ms, p<0.001), inter-caval distance (70±7 versus 87±8mm, p<0.001), and right atrial activation time (92±12 versus 120±15ms, p<0.001).

6.3.2 Sinus Node Dysfunction and Atrial Remodelling

Reference patients had normal measures of sinus node function, including SACT (83±33ms) and CSNRT (at 600ms: 245±88ms; at 450ms: 253±96ms). Patients with flutter demonstrated longer SACT (150±100ms, p=0.03) and longer CSNRT (at 600ms: 339±151ms, p=0.04; at 450ms: 498±409ms, p=0.03). Site-specific conduction abnormalities at the crista terminalis during sinus rhythm were significantly less in the reference group than in patients with flutter (Figure 6-4): the number of double potentials or fractionated electrograms was 2.1±1.8 versus 5.4±2.9, p=0.002; the maximum duration of such signals was 60±15 versus 72±14ms, p=0.04. These
differences were even more marked during and immediately following 30-second pacing trains (Table 6.2).

### 6.3.3 Extent and Shift of the Atrial Pacemaker Complex

As determined by the multi-polar array, the mean distance from the superior vena cava-right atrial junction to the point of EA was 4±4mm and SBO 9±6mm in reference patients. The mean distance from the crista terminalis in an anterior direction was 8±11mm for EA and 14±8mm for SBO. For patients with flutter, the distance inferiorly from the superior vena cava-right atrial junction was greater (EA: 15±12mm, p=0.003; SBO: 23±11mm, p<0.001). The distance from the crista terminalis anteriorly to the EA (5±14mm, p=0.5) or SBO (16±7mm, p=0.5) did not differ for patients with flutter. Normalised to mean inter-caval distance for this group with larger right atria, the distance inferiorly to EA (p=0.007) and SBO (p=0.003) remained significantly different from the reference group.

Following 30-second pacing trains the mean distance from the superior vena cava-right atrial junction to EA and SBO points changed significantly for reference patients (EA 4±4 to 13±8mm, p=0.006; SBO 9±6 to 16±10mm, p=0.02); representing a mean caudal shift for EA of 10±9mm and for SBO of 7±8mm. For patients with flutter the mean distance from the superior vena cava-right atrial junction to EA and SBO points also changed significantly (EA 15±12 to 19±12mm, p=0.045; SBO 23±11 to 28±9mm, p=0.02). However, caudal shift was markedly diminished in patients with flutter compared to the reference group; EA was 4±7mm and SBO 4±6mm. The change in distance from the crista terminalis anteriorly to the EA or SBO following pacing did not
significantly differ for either patient group. Figure 6-5 demonstrates the mean location and caudal shift of the physiological pacemaker complex and a representative example is shown in Figure 6-6. The median number of beats for activation to resume baseline position was 2 (IQR 1 to 4, range 1 to 28 beats) and did not significantly differ between patient groups.

6.3.4 Preferential Pathway Conduction

The mean time to conduct along the preferential pathway from EA to SBO was 15±5ms for the reference group. Patients with flutter took significantly longer (23±8ms, p=0.005) to conduct between the two points. While the SBO was located at or anterior to the crista terminalis in all patients, the preferential pathway between the EA to the SBO was directed inferiorly in 63%, anteriorly in 22%, posteriorly in 10% and superiorly in 5% of beats analysed; no difference was seen between patient groups.

6.3.5 Beat-to-beat Variation in Sinus Node Function

The beat-to-beat site of EA ranged within an individual from 0 to 41mm (median 19, IQR 7-31) from the superior vena cava-right atrial junction suggesting the capacity for multi-centric activation. We did not observe simultaneously occurring multi-centric EA points. Beat-to-beat variation of SBO ranged within an individual from 0 to 33mm (median 12, IQR 8-23). In contrast to EA, there were 3 controls who demonstrated dual near-simultaneous SBO points during a single beat (Movie 6.1). In all 3 instances, one of the SBO points was on the crista terminalis.
6.3.6 Crista Terminalis Conduction

More frequent transverse conduction through the crista terminalis was seen during sinus rhythm beats in the reference group than in the patients with flutter (38% versus 4%, \( p=0.003 \)), almost invariably through the superior third of the crista near the level of the SBO point. For those beats analysed in which there was no conduction through the crista terminalis, the delay between anterior and posterior activation of the crista was 17±6ms for reference patients and 24±7ms for patients with flutter (\( p=0.02 \)). The circuitous activation pattern subsequent to SBO in such patients was in 2 directions: inferiorly down the anterior border of the crista terminalis to the anterior right atrium, and supero-posteriorly over the basal appendage and then inferiorly down the posterior right atrium (Figure 6-7).

6.3.7 Voltage Findings

For reference patients, mean unipolar voltage was 1.8±0.6mV for the right atrium, 1.9±0.6mV along the crista terminalis, 0.12±0.10mV at the point of EA and 3.2±1.5mV at the point of SBO. The average maximum unipolar voltage recorded was 5.0±1.8mV for the right atrium and 3.5±1.4mV along the crista terminalis. Patients with flutter trended to lower mean right atrial voltage (1.4±0.6mV, \( p=0.1 \)), while mean voltage at the crista (1.3±0.6mV, \( p=0.009 \)) and point of SBO (1.5±1.4mV, \( p=0.005 \)) was significantly lower compared to reference patients. Voltage at the point of EA did not differ (0.12±0.13mV, \( p=0.9 \)). As with mean voltage, maximum voltage for the right atrium trended to lower for patients with flutter (3.9±2.1mV, \( p=0.2 \)) and was
significantly less at the crista terminalis (2.2±1.2mV, p=0.01). Differences in voltage parameters are shown in Table 6.3.

6.4 Discussion

6.4.1 Major Findings

This study utilised high-density simultaneous endocardial unipolar mapping of sinus rhythm to describe the characteristics of the functional sinus node complex and the effects of remodelling due to chronic atrial flutter. The major findings are as follows:

(i) The sinus node complex in normal hearts displays a dynamic range of activation sites along the postero-lateral right atrium.

(ii) Preferential pathways of conduction exist between the sinus node and the exit of sinus activity to the atria.

(iii) There were multiple origins of sinus activation (EA) and exit sites to the atria (SBO), providing evidence of multi-centricity of the sinus node complex.

(iv) Remodelled atria demonstrate structural change reflected by loss of voltage that was associated with more caudal activation, slower conduction time along preferential pathways, only modest shifts of the functional pacemaker complex and more frequent conduction block across the crista terminalis with resultant circuitous conduction of the sinus impulse.
These findings extend our knowledge of the function of the highly complex human sinus node by demonstrating the presence of preferential pathways of conduction within the functional sinus node complex.

6.4.2 The Sinus Node: Anatomical and Functional Considerations

The sinus node consists of specialised nodal cells lying immediately sub-epicardially at the superior pole of the sulcus terminalis of the right atrium and has a mean length of 13.5mm (range 8-21.5mm) (Sanchez-Quintana et al. 2005). The variability of the functional sinus node position exceeds that of the histologically defined sinus node by a factor of three to four (Boineau et al. 1980). Shifts in the origin of the sinus node impulse along the sulcus terminalis under autonomic influences have been observed by several investigators since early last century (Lewis et al. 1910; Geesbreght and Randall 1971).

Further evidence of a widely distributed functional pacemaker complex comes from clinical studies that have aimed to modify sinus activity in patients with inappropriate sinus tachycardia. In contrast to the single lesions effective for ectopic atrial tachycardia treatment, these procedures require extensive ablation along the length of the crista terminalis to achieve functional inhibition of the sinus node (Lee et al. 1995). Boineau et al. (1978; 1980; 1984) performed detailed epicardial mapping of animal hearts and observed that the sinus P wave may arise from a “pacemaker complex”, distributed over an extensive extra-nodal area spanning the superior vena cava-right atrial junction to the inferior vena cava. A strong correlation between heart rate and functional sinus origin was observed with vagal stimulation and isoprenaline infusion.
resulting in inferior and supero-anterior shifts, respectively. The authors concluded that the multi-centric nature of functional sinus origin was mediated through a complex system of separate atrial pacemakers with differential sensitivities to autonomic control (Boineau et al. 1980). However, while dismissing the presence of specialised conduction tissue, they acknowledged the potential role of preferential pathways for the rapid dispersion of the sinus impulse. In humans, Boineau et al. (1988) reported uni-focal nodal and extra-nodal sinus origins in addition to multi-centric origins over two to four widely distributed pacemaker sites. The functional sinus pacemaker complex in humans was estimated to exist over a zone centred about the long axis of the sulcus terminalis encompassing a 75 by 15mm area, with a cranial and caudal border of the superior and inferior vena cava, respectively. They suggested a model where neural and hormonal factors influence both the site of pacemaker activation and the point of exit from the sinus node, a hypothesis further supported by studies suggesting relative electrical isolation of the sinus node from surrounding atrial myocardium with distinct exit points from the node (Bromberg et al. 1995). Consistent with these observations, in the current study we observed dynamic variation in the position of atrial activation in the reference group in response to pacing, with early activation and break-out points to surrounding myocardium noticeably more caudal following pacing.

### 6.4.3 Atrial Remodelling and Sinus Node Function

Sinus node disease is thought to result from disordered impulse generation within the sinus node or impaired conduction of the impulse to the surrounding atrial tissue
(Ferrer 1968). While differentiation between these two potential aetiologies has been difficult owing to the absence of an appropriate experimental model, Sanders et al. (2004a) have performed atrial mapping studies in patients with sinus node disease and found evidence of a diffuse atrial myopathy as evidenced by low atrial voltage, slowed atrial conduction and prolonged P wave duration. Interestingly, the sinus node complex was more often uni-centric and localised to the low crista terminalis with evidence of regional conduction slowing and scar. While this study showed that patients with advanced sinus node dysfunction have evidence of structural atrial remodelling, other studies have shown that sinus node remodelling may occur in response to short duration atrial pacing or atrial arrhythmias and under these circumstances may be reversible. Elvan et al. (1996) demonstrated significant prolongation of CSNRT and the sinus cycle length after two to six weeks of atrial fibrillation in dogs. In humans, short durations of rapid atrial pacing resulted in similar sinus node inhibition (Hadian et al. 2002) and CSNRT was significantly longer in patients cardioverted from chronic lone atrial fibrillation compared to controls (Kumagai et al. 1991). Manios et al. (2001) also reported that sinus node inhibition did not revert within 24 hours after cardioversion. However, Hocini et al. (2003) demonstrated reversibility of sinus impairment in patients in whom atrial fibrillation was cured by pulmonary vein isolation when follow-up was continued out to 6 months. Remodelling of the sinus node has also been reported in clinical conditions such as asynchronous ventricular pacing (Sparks et al. 1999), atrial septal defects (Morton et al. 2003) or congestive heart failure (Sanders et al. 2004b). For the latter, Sanders et al. reported a more caudal localisation of sinus node complex and greater structural remodelling at the crista terminalis in heart failure patients when compared to
controls, raising the possibility that the sinus node remodelling may be a consequence of these changes via disruption of preferential pathways or loss of tissue capable of automaticity.

In the current study we have observed significant impairment of sinus node function following a median 8 months of continuous atrial flutter, consistent with previous reports. The findings were of similar type, with impairment of sinus node function associated with structural change, slowed conduction and caudal displacement of the sinus node complex, albeit to a lesser extent than that described in sinus node disease (Sanders et al. 2004a). In addition, these findings extend previous observations by demonstrating caudal shift of both sites of EA and SBO with longer conduction time within regions of preferential conduction in patients with atrial remodelling due to persistent arrhythmia.

6.4.4 Preferential Pathways of Conduction

Preferential conduction exists in the atria due to rapid conduction parallel to the orientation of non-specialised myocardial cell fibre bundles (Anderson et al. 1981b; Spach and Dolber 1986; Saffitz et al. 1994). Higa et al. (2004) used the EnSite array to demonstrate that in some patients with atrial tachycardia the traditionally mapped origin – the site from which centrifugal activation occurs to the remaining atria – was indeed the break-out point. Detailed inspection of the unipolar electrograms demonstrated a site of earliest activation (“QS” morphology) with a preferential pathway of conduction to the break-out point. These investigators were able to confirm the existence of the origin with a preferential pathway by curative ablation of
the tachycardia at EA and/or along the proximal portion of the path to the break-out point. It is tempting to draw parallels between the preferential pathways found in atrial tachycardia, 57% of which were found at the crista terminalis, and those we have demonstrated in the sinus node complex. With no histological evidence of specialised atrial conduction tissue, the mechanisms of preferential pathways in atrial tachycardia and in the sinus node complex is therefore likely to be “functional” relying on weak cell-to-cell coupling to allow conduction of intrinsic activity in an environment electrically isolated from the surrounding myocardium. This would provide an essential degree of redundancy to the pacemaker complex, so that while spontaneous depolarisation at a physiologically appropriate rate continues, several potential exit sites exist to convey the wave-front to the myocardium, perhaps with varying conduction properties determined by the degree of cell-to-cell coupling. The mechanism by which more caudal activation is seen with atrial remodelling, as demonstrated in this study and others (Sanders et al. 2004b; Sanders et al. 2004a), is uncertain. We hypothesise that a global remodelling process may affect proportionately more of a shorter superior preferential pathway than a longer inferior pathway, leaving superior pathways more susceptible to early development of conduction abnormalities. This study has demonstrated marked atrial remodelling in chronic atrial flutter with site-specific conduction delay and significant voltage reduction uniformly along the crista terminalis. Although it is feasible that the more caudal activation is due to impaired automaticity at the superior crista terminalis, this would require selective remodelling in this region which was not seen in the current study.
6.4.5 Implications

This study demonstrates that the functional sinus node complex is a dynamic and intricate entity. This complexity is required to balance the need for relative electrical isolation in order to generate an intrinsic heart beat without the influence of surrounding myocardium, against the need to conduct such activity to the atrium in a reliable and consistent fashion. The hypothesis of Boineau et al. (1988) whereby neural and hormonal factors influence both the site of pacemaker activation and the point of exit from the sinus node is further supported by our observation of shifting points of initial activity and exit sites in response to pacing. This study extends the understanding of the sinus node complex by demonstrating the existence of preferential pathways of conduction contributing to the diffuse sinus node complex. In addition, it demonstrates that patients known to have impaired sinus node function (Sparks et al. 2000; Daoud et al. 2002) have structural remodelling which diminishes sinus node variability, slows conduction time along preferential pathways, inhibits conduction across the crista terminalis and results in circuitous conduction of the sinus impulse.

6.4.6 Limitations

Several studies have now validated the morphology characteristics of virtual electrograms determined from the EnSite mapping system demonstrating them to match with high reliability those of conventional contact unipolar electrograms (Schilling et al. 1998; Thiagalingam et al. 2004b). The technology employed has specific
limitations addressed by previous studies and this study has endeavoured to minimise any inaccuracy by staying within reported limits of accuracy.

6.5 Conclusion

The functional sinus node complex displays a dynamic range of activation along the postero-lateral right atrium. Preferential pathways between the site of earliest activation and conduction to atrial myocardium exist. Remodelled atria demonstrate more caudal activity, longer conduction time along preferential pathways, diminished shifts in activation along a constrained functional sinus node complex, lower voltage, transverse conduction block along the crista terminalis and resultant circuitous wave-front propagation. These findings provide additional insight into the function of the highly complex human sinus node in both health and disease.
Table 6.1

Patient characteristics

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<td>Structural heart disease, n (%)</td>
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<td>4 (25)</td>
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</tr>
<tr>
<td>Right atrial area (cm$^2$)</td>
<td>15.1±2.8</td>
<td>20.2±4.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Interventricular septum (mm)</td>
<td>11±2</td>
<td>11±2</td>
<td>0.3</td>
</tr>
<tr>
<td>LV end diastolic diameter (mm)</td>
<td>49±6</td>
<td>53±8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

LV = left ventricular
### Table 6.2

Electrogram characteristics at the crista terminalis catheter under various conditions

<table>
<thead>
<tr>
<th>Type of beat</th>
<th>Reference (n=15)</th>
<th>Flutter (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of bipoles demonstrating double potentials or fractionated electrograms on the crista terminalis catheter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>2.1±1.8</td>
<td>5.4±2.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Pacing at 600ms</td>
<td>1.8±1.5</td>
<td>6.4±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacing at 450ms</td>
<td>2.1±1.8</td>
<td>6.7±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immediately following 600ms drive train</td>
<td>1.9±1.5</td>
<td>6.1±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immediately following 450ms drive train</td>
<td>1.8±1.6</td>
<td>6.4±3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>With shortest captured extra-stimulus</td>
<td>4.0±2.6</td>
<td>6.7±3.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Maximum duration of the longest electrogram on the crista terminalis catheter (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>60.3±14.7</td>
<td>72.4±14.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Pacing at 600ms</td>
<td>55.5±10.2</td>
<td>97.2±31.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacing at 450ms</td>
<td>58.9±11.4</td>
<td>96.5±30.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Immediately following 600ms drive train</td>
<td>59.2±13.3</td>
<td>76.2±13.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Immediately following 450ms drive train</td>
<td>59.7±15.0</td>
<td>80.1±18.5</td>
<td>0.004</td>
</tr>
<tr>
<td>With shortest captured extra-stimulus</td>
<td>91.2±61.7</td>
<td>104±30.8</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Table 6.3

Unipolar voltage recorded by the multi-polar balloon array

<table>
<thead>
<tr>
<th></th>
<th>Reference (n=15)</th>
<th>Flutter (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean right atrial voltage (mV)</td>
<td>1.78±0.63</td>
<td>1.36±0.63</td>
<td>0.1</td>
</tr>
<tr>
<td>Maximum right atrial voltage (mV)</td>
<td>4.96±1.84</td>
<td>3.88±2.07</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean voltage at crista (mV)</td>
<td>1.94±0.62</td>
<td>1.28±0.61</td>
<td>0.009</td>
</tr>
<tr>
<td>Maximum voltage at crista (mV)</td>
<td>3.50±1.39</td>
<td>2.16±1.20</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean voltage at point of EA (mV)</td>
<td>0.12±0.10</td>
<td>0.12±0.13</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean voltage at point of SBO (mV)</td>
<td>3.20±1.52</td>
<td>1.54±1.37</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Figure 6-1

Catheter positions on fluoroscopy

Right anterior oblique view of the multi-polar balloon array in the superior right atrium, the decapolar catheter in the coronary sinus and the duodecapolar catheter along the crista terminalis with its stabilising sheath.
Figure 6-2

Method of measuring the position of Earliest Activation and Sinus Break-Out

Figure legend overleaf.
Figure 6-2 (previous page)

A right anterior oblique view showing 3 cross-sectional intra-cardiac ultrasound views at the indicated levels of the right atrium. The superior vena cava-right atrial junction was defined using ultrasound at the level where the superior lateral crista terminalis is in proximity to the orifice of the right atrial appendage (middle panel). The crista terminalis was then marked along its length with vertical line. Vertical measurement from the superior end of the crista terminalis parallel to this line gives the distance from the superior vena cava-right atrial junction. Horizontal measurement perpendicular to this line gives the anterior distance.

Composite map of wave-front activation from earliest activation (1) via a preferential pathway (2,3) to sinus break-out (4) then diverging to the remaining atrium in a patient with flutter. Electrograms demonstrate a QS pattern at (1) and an RS pattern at (4).
Figure 6-4

Electrograms from the crista terminalis

Example electrograms from a reference patient (left) and a patient with flutter (right) demonstrating the extent and duration of electrograms with fractionated signals or double potentials.

II – Surface ECG lead II. CT – crista terminalis. CS – coronary sinus.
Figure 6-5

Distance from superior vena cava - right atrial junction to Earliest Activation and Sinus Break-Out points at baseline and following pacing

For the reference group, both Earliest Activation and Sinus Break-Out points are relatively superior during sinus rhythm. Immediately following pace-suppression a caudal shift is noted in both parameters. For the remodelled group with atrial flutter, Earliest Activation and Sinus Break-Out points are located more caudally during sinus rhythm and the caudal shift is diminished. *p<0.05 for comparisons indicated.
Figure 6-6

Example right atrial maps of Earliest Activation and Sinus Break-Out

Left map shows earliest activation (1) and sinus break-out (4) during sinus rhythm with accompanying electrograms demonstrating a QS morphology at electrogram 1 and an RS morphology at 4. Right map shows the same for the beat immediately following a 30-second pacing train in the same patient. Note the caudal displacement of earliest activation and sinus break-out.
Figure 6-7

Right atrial circuitous depolarisation pattern

Figure legend overleaf.
Figure 6-7 (previous page)

Typical activation sequence of the circuitous depolarisation pattern seen in patients without transverse conduction through the crista terminalis. Following break-out from the sinus node complex, activation proceeds down the anterior border of the crista terminalis and then down the posterior border due to the conduction barrier.

1 (top left) Earliest activation (QS) at virtual electrode 1
2 (top right) Sinus break-out (RS) at virtual electrode 4
3 (bottom left) Bi-directional depolarisation both inferiorly and supero-posteriorly
4 (bottom right) Continuing inferior movement of depolarisation either side of crista terminalis (note linear double potentials at crista terminalis)
Movie 6.1

Example of near-simultaneous dual Sinus Break-Out points

Please see files on CD supplied entitled Movie 6.1. This movie has been provided in .mpg, .avi and .wmv formats. The latter is the original version and plays with highest quality.

The initiation of 3 consecutive beats is shown. Virtual electrograms 1 to 4 placed along the preferential pathway from EA are displayed below the geometry. The “tracking virtual” feature of the EnSite tracks the instantaneous peak negative potential along this path for illustrative purposes. Break-out to the atrial myocardium is seen at position 4 and, within 5ms, at position 1 on the crista terminalis near-simultaneously.
Chapter 7.
High-density mapping of atrial fibrillation to determine the optimal recording duration for dominant frequency and automated detection of complex fractionated electrograms

7.1 Introduction

The understanding of the pathophysiology of atrial fibrillation has evolved such that ablation targeting the pulmonary veins is highly effective in treating many patients with paroxysmal atrial fibrillation. However, some patients with paroxysmal and most patients with persistent atrial fibrillation still require considerable additional substrate modification to improve ablation outcomes. Areas of CFAE and high DF have been proposed as critical regions maintaining atrial fibrillation (Berenfeld et al. 2000; Nademanee et al. 2004; Sanders et al. 2005a; Lin et al. 2006). CFAE have been implicated as identifying areas acting as pivot points, slowed conduction or anisotropy all capable of sustaining reentry (Cosio et al. 1986; Spach and Dolber 1986; Konings et al. 1994). Similarly, localised regions of high frequency activity demonstrating spatio-temporal periodicity have been suggested to act as drivers of atrial fibrillation (Karagueuzian et al. 1998; Skanes et al. 1998; Jalife et al. 2002; Everett et al. 2006). Thus, identifying such electrograms may allow more targeted ablation to improve outcomes. To date the evaluation of CFAE has been subjective and development of automated analysis is paramount for reproducible and objective assessment. Algorithms for quantification of electrogram fractionation and real-time DF calculation have become available and it is desirable that these process a sufficient density of points without unduly delaying the ablation procedure. The ideal duration of electrograms required to reproducibly identify sites of CFAE or highest DF is not
known. Prior studies have used lengths of electrogram recordings between 2 and 10 seconds to determine these measures (Mansour et al. 2001; Wu et al. 2002; Lazar et al. 2004; Sahadevan et al. 2004; Ravelli et al. 2005; Sanders et al. 2005a; Lin et al. 2006; Narayan et al. 2006; Ng et al. 2006; Rostock et al. 2006; Ryu et al. 2006; Sanders et al. 2006; Schuessler et al. 2006; Scherr et al. 2007). While longer electrogram recordings extend the data collection process unnecessarily, shorter durations may provide an inaccurate representation of the true degree of fractionation or frequency. This study aimed to determine the minimum duration of electrogram recording that provides accurate data without unduly lengthening the data collection process, by exploring the degree of correlation between progressively shorter electrogram recordings with the longest exportable data sample length.

7.2 Methods

7.2.1 Study Population

The study comprised 14 patients with symptomatic drug-refractory atrial fibrillation undergoing catheter ablation. All anti-arrhythmic drugs, with the exception of amiodarone, were ceased ≥5 half-lives before the study. Prior to the procedure all patients received anticoagulation with warfarin (International Normalised Ratio 2-4) for ≥6 weeks and underwent trans-oesophageal echocardiography to exclude left atrial thrombus. The study protocol was approved by the institutional Clinical Research and Ethics Committee and all patients provided written informed consent for the procedure.
7.2.2 Electrophysiological Study

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. The following catheters were utilised for mapping: (i) 10 pole catheter (2-5-2mm inter-electrode spacing, Daig Electrophysiology) positioned within the coronary sinus with the proximal bipole at the coronary sinus ostium as determined in the best septal left anterior oblique position; (ii) 5-spline, 20 pole catheter (1mm electrodes separated by 4-4-4 inter-electrode spacing; PentaRay; Biosense-Webster). The PentaRay catheter was stabilised using a long vascular sheath (Preface, Biosense-Webster or SL0 Braided, St Jude Medical); and (iii) 3.5mm tip externally irrigated ablation catheter (Celsius Thermocool; Biosense-Webster). The left atrium was accessed using a single transeptal puncture. Following transeptal access bolus unfractionated heparin was utilised to maintain the activated clotting time between 250-350 seconds. Following the mapping, patients underwent tailored, step-wise ablation comprising pulmonary vein isolation ± linear ablation lines ± CFAE site ablation.

7.2.3 High-Density Bi-atrial Mapping

Mapping was performed during spontaneous (n=8) or induced (n=6) atrial fibrillation of ≥10 minutes duration. Three-dimensional reconstructions of the right and left atria were made using the NavX (Version 6.0R, St Jude Medical) navigation system. High density mapping of both atria was performed using the PentaRay catheter by sequentially acquiring 15 simultaneous bipolar electrograms. After ensuring adequate endocardial contact by fluoroscopy the catheter was held stationary for 8 seconds; this
duration for comparator electrogram was chosen as this is the maximum duration electrogram exportable from the system used and is towards the high end of the range used in previous studies. These 8 second electrograms were sampled at 1200Hz, band pass filtered between 30-500Hz and their location on the 3-dimensional map annotated using the Diagnostic Landmark Mapping feature of the system. This ensured all areas of the atria, venae cavae and pulmonary veins were visited at least once and the spread of points was equal throughout both chambers. All electrograms were manually reviewed offline with those demonstrating an unacceptable signal to noise ratio excluded.

7.2.4 Complex Fractionated Atrial Electrograms

CFAE were defined as fractionated potentials exhibiting multiple deflections from the isoelectric line and were characterised using the NavX "CFE-mean" contact mapping tool. CFE-mean is defined as the average time duration between consecutive deflections during a specific time period set by the user and recorded at each site. Deflections are identified by a detection algorithm and annotated on the electrogram with yellow "tick-marks" (Figure 7-1). Detection is based on three criteria, set by the user, in which the deflection must: 1) exceed an adaptive "Peak-to-Peak Sensitivity" threshold that is set at a reference-amplitude slightly greater than the magnitude of baseline noise; 2) possess a "downstroke" morphology in which the leading local-maximum and the trailing local-minimum amplitude occurs within a time "Duration" that is set to avoid detection of broad, far-field events; and 3) exceed a "Refractory" period from the previous detection that is set to avoid multiple detections on a single
deflection. When all three of these criteria are met, a yellow tick-mark is placed on the electrogram at the instant of maximum-negative slope on the downstroke (Figure 7-1). In our study, CFE-mean values were calculated from the maximum possible recording duration of 8 seconds and exported for analysis by an external computer program. Also, 7, 6, 5, 4, 3, 2 and 1 second recordings were sub-sampled and exported for comparison with the original 8 second recordings. Our user settings included a Refractory Period of 30ms, a Peak-to-Peak Sensitivity typically between 0.05 and 0.1 mV and a Duration of 10ms. Sites with a CFE-mean value within the range of 40 and 250ms were included for analysis. This wide range was selected to determine comparative accuracy across the entire spectrum of potentially physiologically relevant values at differing electrogram durations.

7.2.5 Dominant Frequency

All electrograms were exported at 1200Hz to perform spectral analysis using offline custom designed software. The electrograms were initially rectified, filtered using Butterworth filters (Low pass 20Hz, High pass 1Hz) and edge-tapered with a Hanning window. Frequency spectra were calculated by Fast Fourier Transform and zero-padded for shorter electrogram durations, giving a consistent spectral resolution of 0.07Hz. DF was defined as the frequency containing maximum power within the frequency domain 3-15Hz (Figure 7-2). Points with a Regularity Index (defined as the ratio of the power within a 0.75Hz band at the DF to total power over 3-15Hz) of less than 0.2 calculated from 8 second electrograms were excluded from analysis (Sanders
et al. 2005a). DF values were calculated from the entire 8 second sample and from 7, 6, 5, 4, 3, 2 and 1 second sub-samples for comparison.

7.2.6 Statistical Analysis

Variables are reported as mean ± standard deviation. Left and right atrial CFE-mean data were compared using an independent samples t test. Comparison of CFE-mean data from 7, 6, 5, 4, 3, 2, and 1 second electrograms with CFE-mean data from the index 8 second electrograms from the same points were compared using analysis of variance with Scheffe’s post hoc comparison. Correlation of CFE-mean values from 7, 6, 5, 4, 3, 2 and 1 second electrograms with the CFE-mean values of the index 8 second electrograms from the same points were quantified using Intraclass Correlation Coefficients (ICC). Left and right atrial DF comparisons and correlation of sub-sampled values with index electrogram values were compared in the same fashion. Statistical tests were performed using SPSS 13.0 (SPSS Inc).

7.3 Results

7.3.1 Baseline details

Baseline patient characteristics, echocardiographic data and medications are summarised in Table 7.1. Electrograms from a total of 6967 points (498±174 points/patient) were analysed; 228±102 points/patient in the right and 270±86 points/patient in the left atria. Bi-atrial mapping took 37±13 minutes to complete.
For the index 8 second samples CFE-mean was 114±20ms for the right atria and 102±17ms for the left atria (p=0.01). Bi-atrial mean values for all electrogram durations are shown in Figure 7-3A. A trend to decrease with shorter electrograms is seen but these are not significantly different to the index mean for all points of 109ms (p=0.2). However, it is point-by-point accuracy that is more important for CFE-mean and under-estimations tend to cancel out over-estimations in mean values. The mean absolute differences between 8 second electrogram index CFE-mean and the 7, 6, 5, 4, 3, 2 and 1 second CFE-mean are therefore shown in Figure 7-3B. The increase in the magnitude of absolute difference as electrogram duration decreases reflects the poorer correlation of each shorter sub-sampled electrogram value with its index 8 second value. The percentage of sub-sampled electrograms where CFE-mean deviated from the 8 second index CFE-mean by more than 10% is shown in Figure 7-4. Progressively more points demonstrate >10% difference from the index value as electrogram duration shortens. Scatter plots of CFE-mean for the index 8 second value (y axis) versus the CFE-mean for the same point derived from the 7, 6, 5, 4, 3, 2 and 1 second sub-samples (x axes) are shown in Figure 7-5A. Intraclass Correlation Coefficients of sub-sampled electrogram CFE-mean as compared to the index 8 second electrogram CFE-mean quantify this weakening relationship as the electrogram duration becomes shorter.
7.3.3 Dominant Frequency

For the index 8 second samples DF was 5.7±0.8Hz for the right atria and 6.0±0.8Hz for the left atria (p=0.02). Bi-atrial mean values for all electrogram durations are shown in Figure 7-3A. Means for 4 second samples or shorter are significantly different to the 8 second index mean for all points of 5.9Hz (p<0.001). The mean absolute differences between 8 second electrogram index DF and the 7, 6, 5, 4, 3, 2 and 1 second DF are shown in Figure 7-3B. Similarly, the increase in mean absolute difference as electrogram duration decreases reflects the poorer correlation of each shorter sub-sampled electrogram value with its index 8 second value. The percentage of sub-sampled electrograms where DF deviated from the 8 second index DF by more than 10% is shown in Figure 7-4. Progressively more points demonstrate >10% difference from the index value as electrogram duration shortens. Scatter plots of DF for the index 8 second value (y axis) versus the DF for the same point derived from the 7, 6, 5, 4, 3, 2 and 1 second sub-samples (x axes) are shown in Figure 7-5B. Intraclass Correlation Coefficients of sub-sampled electrogram DF as compared to the index 8 second electrogram DF quantify this weakening relationship as the electrogram duration becomes shorter.

7.4 Discussion

7.4.1 Major Findings

This study presents new information about the duration of electrogram required to efficiently and accurately determine the degree of fractionation and DF. Recordings of
shorter durations were compared to the maximum duration recordable by the system using the following criteria: i) mean values, ii) mean absolute differences of >10ms or 0.5Hz, iii) proportion of points deviating >10% from the index value, and iv) ICC. CFE-mean values derived from electrogram durations of 3 seconds or less have a mean absolute error of more than 10ms (Fig 3B) and for electrogram durations of 4 seconds or less, at least 1 in 5 points deviate more than 10% from the index value (Fig 4). Intraclass Correlation Coefficients for CFE-mean demonstrate “substantial agreement” (ICC>0.8) for all sub-samples except 1 second electrograms. Visual inspection of CFE-mean scatter plots suggests electrograms of more than 4 seconds approximate the index 8 second electrogram value (Fig 5A). Mean DF derived from electrograms of 4 seconds or less differ significantly from the index 8 second mean (Fig 3A) and DF values from electrogram durations of 4 seconds or less have a mean absolute error of more than 0.5Hz (Fig 3B). With electrogram durations of 3 seconds or less, for at least 1 in 5 points DF deviates more than 10% from the index value (Fig 4). Intraclass Correlation Coefficients for DF demonstrate “substantial agreement” for 7 second sub-samples, “moderate agreement” (ICC 0.6-0.8) for 6 and 5 second sub-samples, and only fair or poor agreement for shorter electrograms. Visual inspection of DF scatter plots suggests electrograms of more than 4 seconds approximate the index 8 second electrogram value (Fig 5B).

These observations, based on the above criteria, suggest a minimum of 5 seconds is required to achieve accuracy comparable to the maximum recordable sample of 8 seconds.
7.4.2 Time Domain Analysis

The postulated mechanisms that bring about CFAE include anisotropic propagation (Spach and Dolber 1986), areas of slowed conduction (Cosio et al. 1983) and multiple wavelets leading to random or leading circle reentry. CFAE are observed at pivot points where wavelets rotate at zones of functional block (Konings et al. 1994). Selective elimination of CFAE by catheter ablation has been proposed to halt wavelet reentry, thereby preventing perpetuation of atrial fibrillation (Nademanee et al. 2004; Oral et al. 2007). Previous reports of CFAE mapping have used descriptive terms to subjectively determine which electrograms fit these criteria. Nademanee et al. (2004) defined CFAE as fractionated electrograms composed of ≥ 2 deflections, perturbation of the baseline with continuous deflection of a prolonged activation complex, or atrial electrograms with a cycle length ≤ 120ms. Rostock et al. (2006) used fractionated potentials with ≥ 3 deflections from the isoelectric line or continuous activity as their criteria for CFAE. Oral et al. (2007) targeted electrograms with a cycle length ≤ 120ms or shorter than the coronary sinus; or those that were fractionated or displayed continuous electrical activity. Few studies have tried to automate this procedure and the minimum electrogram duration required to accurately determine electrogram complexity is unknown. Ravelli et al. (2005) studied fibrillatory wave complexity using an automated wave similarity algorithm calculated over 5 second windows. Narayan et al. (2006) used a “gold-standard” of manually measured atrial fibrillation cycle length to validate an autocorrelation method of determining local cycle length. Atrial fibrillation cycle length estimates were more stable performed over 10 seconds rather than 2 seconds due to short term cycle length fluctuations. Scherr et al. (2007) have recently used another automated algorithm of 2.5 second recordings to classify 86% of
1904 left atrial sites from 19 patients as exhibiting CFAE, one third of which were deemed “highly repetitive”. No comparison between different electrogram durations was made.

7.4.3 Frequency Domain Analysis

Regions of high frequency activations demonstrating spatio-temporal periodicity have been suggested as local drivers of atrial fibrillation. Such “rotors” or “focal sources” would be identifiable by fast activity and may be constantly present. These drivers have been suggested to be present where structural remodelling of the atria has occurred, and absent where atrial fibrillation is due to electrical remodelling alone where multiple wavelets predominate (Everett et al. 2006). Further evidence for atrial fibrillation spatial organisation comes from optical mapping in animals using DF to demonstrate areas of periodic high frequency (Skanes et al. 1998; Kalifa et al. 2006). Retrospective analysis of ablation of paroxysmal atrial fibrillation shows that cycle length prolongation and eventual termination occurs at sites of high DF (Sanders et al. 2005a). Prior studies to localise DF sites have used electrogram sample lengths of between 2 to 10 seconds (Mansour et al. 2001; Wu et al. 2002; Lazar et al. 2004; Sanders et al. 2005a; Lin et al. 2006; Narayan et al. 2006; Ng et al. 2006; Ryu et al. 2006; Sanders et al. 2006; Schuessler et al. 2006). Ng et al. (2007) reported good correlation for DF calculated from 2 second sub-samples with atrial activation rates calculated in the time domain from 4 second recordings. Correlation between 1 and 4 second samples was less satisfactory, therefore a 2 second minimum electrogram was recommended. Additionally, the mean DF of 4 sequential 4 second electrograms
showed improved correlation with activation rates compared to the DF of a single 4 second electrogram, both for simulated and clinical electrograms (Ng et al. 2006).

Harmonics in the frequency spectrum are a source of error in the estimation of true atrial activation rate in the highly fractionated signal (Ng et al. 2006; Ryu et al. 2006). The use of indices such as the Regularity Index used here has sought to eliminate such conflicting information from analysis (Sanders et al. 2005a).

### 7.4.4 Differences in Effect of Electrogram Duration between CFE-mean and DF

For DF, shorter electrogram durations tend to over-estimate the value, predominantly due to more prominent harmonics in the frequency spectra. This can be seen in Figure 7-5B where an additional “line” at half the slope to the right of the regression line becomes more prominent as electrograms shorten. This explains the poorer ICC values for DF than CFE-mean; a significant number of points have twice the index value, whereas CFE-mean errors are more homogenously distributed around the regression line (Figure 7-5A). The harmonics also explain why shorter electrograms provide a significantly higher mean DF, whereas the average CFE-mean does not significantly change with shorter electrogram durations. Despite better ICC, CFE-mean has more points deviating >10% from the index value for electrograms of 5 seconds or less, compared with DF (Figure 7-4). This suggests that although errors in DF are less common from shorter electrograms, they are likely to be greater in magnitude.
7.4.5 Limitations

The results of this study pertain to the specific algorithms and pre-processing methods employed. CFAE-guided ablation has been established as an effective treatment for atrial fibrillation, but the definitions of targets differ. The CARTO system (Biosense-Webster) has recently added an automated fractionation detection algorithm to allow real-time annotation of fractionated sites (CFAE Software Module) using a fixed 2.5 second interval (Scherr et al. 2007). This algorithm differs to that employed in this study, in that it includes both low and high voltage thresholds (default 0.05 and 0.15mV), alternative interval thresholds (default 70 to 120ms), and indicates the degree of fractionation by Interval Confidence Level (intervals detected per 2.5 seconds). Given the differences between this algorithm and the one employed in this study, extrapolation of this study’s results regarding minimum electrogram duration to other CFAE detection algorithms may not be accurate. Finally, while this study aimed to determine the ideal recording duration for CFAE and DF analysis, it was not designed to evaluate the clinical efficacy of these parameters (or software) to guide ablation.

7.5 Conclusion

The minimum electrogram duration for accurate analysis of CFAE and DF by the methods described is 5 seconds. This is based on the comparison of values derived from electrograms of 1 to 7 seconds and their comparison with 8 second electrogram values. Electrograms of 4 seconds or less have unacceptable rates of error by the
methods used and may be misleading in the ablation of atrial fibrillation guided by these parameters.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>14</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>57±11</td>
</tr>
<tr>
<td><strong>History of atrial fibrillation (months)</strong></td>
<td>68±50</td>
</tr>
<tr>
<td><strong>Type of atrial fibrillation: Paroxysmal/Persistent</strong></td>
<td>5/9</td>
</tr>
<tr>
<td><strong>Structural heart disease</strong></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Left atrial dimension (mm)</strong></td>
<td>48±6</td>
</tr>
<tr>
<td><strong>Left atrial area (cm²)</strong></td>
<td>29±6</td>
</tr>
<tr>
<td><strong>Right atrial area (cm²)</strong></td>
<td>24±7</td>
</tr>
<tr>
<td><strong>Inter-ventricular septal thickness (mm)</strong></td>
<td>11±2</td>
</tr>
<tr>
<td><strong>Left ventricular end diastolic dimension (mm)</strong></td>
<td>52±5</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction (%)</strong></td>
<td>57±9</td>
</tr>
<tr>
<td><strong>Anti-arrhythmic preceding electrophysiology study</strong></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>4</td>
</tr>
<tr>
<td>Sotalol</td>
<td>5</td>
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<tr>
<td>Flecaainde</td>
<td>2</td>
</tr>
</tbody>
</table>
Figure 7-1

Composite image of bi-atrial high-density CFE-mean colour map, surface ECG and bipolar atrial electrograms

Figure legend overleaf.
Figure 7-1 (previous page)

A short example electrogram (centre) is given demonstrating 2 yellow tick-marks on
downstrokes between leading local-maximum and trailing local-minimum points. Tick-
marks along a full 8 second electrogram (bottom) indicate annotations of deflection
events in the electrogram according to the Refractory, P-P sensitivity and Duration
criteria defined in the text. CFE-mean is the average time duration between
annotations and the value for each point is displayed along a colour spectrum on the 3-
dimensional geometry (top).

AP – antero-posterior, PA – postero-anterior, SVC – superior vena cava, LSPV – left
superior pulmonary vain, RSPV – right superior pulmonary vein, LAA – left atrial
appendage, LIPV – left inferior pulmonary vein, RIPV – right inferior pulmonary vein,
Figure 7-2

Example electrogram with accompanying frequency spectra

Frequency spectra from 3 to 15Hz derived by Fast Fourier Transform analysis from 8, 7, 6, 5, 4, 3, 2 and 1 second samples of the 8 second bipolar electrogram shown at top.

Dominant frequency is the frequency with the highest power (y axis).

DF – dominant frequency, RI – regularity index.
Effect of electrogram duration for CFE-mean and DF (mean ± standard error of the mean) for (A) mean values and (B) mean absolute differences between sub-sampled electrogram values and index 8 second values.

*p<0.001 for comparison with index 8 second mean.
Figure 7-4

Effect of electrogram duration on accuracy

Percentage of electrograms deviating by more than 10% from the index 8 second value for CFE-mean and DF. Both parameters show a greater proportion of inaccurate values as electrogram duration shortens.
Figure 7-5

Scatter plots of CFE-mean and DF

Scatter plots of index 8 second values (y axis) versus the values for the same point derived from the 7, 6, 5, 4, 3, 2 and 1 second sub-samples (x axes) for (A) CFE-mean and (B) DF. Note the decreasing Intraclass Correlation Coefficients (ICC) with shorter electrogram durations. A value of 1 indicates perfect agreement and 0 indicates no agreement.
Chapter 8.
High-density mapping of atrial fibrillation to determine the relationship between activation frequency, complex fractionated electrograms and the anatomical substrate

8.1 Introduction

There have been significant advances in our understanding of the pathophysiology of atrial fibrillation over the last decade. These have led to ablation targeting the pulmonary veins being able to abolish atrial fibrillation in a significant proportion of patients with paroxysmal atrial fibrillation. However, some patients with paroxysmal and most patients with persistent atrial fibrillation still require considerable additional substrate modification to improve outcomes. Areas of CFAE and high DF have been proposed as critical regions maintaining atrial fibrillation (Berenfeld et al. 2000; Nademanee et al. 2004; Sanders et al. 2005a). The postulated mechanisms that bring about CFAE include anisotropic propagation, areas of slowed conduction, multiple wavelets leading to random or leading circle reentry, pivot points where wavelets rotate about sites of functional block and out of phase activation (Cosio et al. 1983; Spach and Dolber 1986; Konings et al. 1994). Selective elimination of CFAE by catheter ablation has been proposed to halt wavelet reentry, thereby preventing the perpetuation of atrial fibrillation (Nademahne et al. 2004; Oral et al. 2007; Schmitt et al. 2007; Nademanee et al. 2008). Similarly, localised regions of high frequency activity demonstrating spatio-temporal periodicity have been suggested to act as drivers of atrial fibrillation (Skanes et al. 1998; Jalife et al. 2002; Everett et al. 2006; Lin et al. 2006). Thus, identifying electrograms with these features may allow targeted ablation to improve success rates. However, there is a paucity of data on the relationship
between CFAE and DF. In particular it is not known whether they are markers of the same or provide complementary information on the pathogenesis of atrial fibrillation. Understanding the relationship between these targets may be useful in guiding radiofrequency ablation. In this clinical study we aimed to examine the relationship between sites of high frequency activation and fractionation during atrial fibrillation.

8.2 Methods

8.2.1 Study Population

The study comprised 20 patients with symptomatic drug-refractory atrial fibrillation undergoing catheter ablation. All anti-arrhythmic drugs, with the exception of amiodarone, were ceased ≥5 half-lives before the study. Prior to the procedure, all patients received anticoagulation with warfarin (International Normalised Ratio 2-4) for ≥6 weeks and underwent trans-oesophageal echocardiography to exclude left atrial thrombus. The study protocol was approved by the institutional Clinical Research and Ethics Committee and all patients provided written informed consent for the procedure.

For the purposes of the study atrial fibrillation was defined in accordance with the HRS Expert Consensus Statement (Calkins et al. 2007); paroxysmal atrial fibrillation was defined as atrial fibrillation episodes that terminate spontaneously within 7 days and persistent as having greater than 7 days of atrial fibrillation. Indeed, all patients with persistent atrial fibrillation in this study had a minimum of 6 months continuous atrial fibrillation at some point prior to their study.
Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. The following catheters were utilised for mapping: (i) 10 pole catheter (2-5-2mm inter-electrode spacing, Daig Electrophysiology) positioned within the coronary sinus with the proximal bipole at the coronary sinus ostium as determined in the best septal left anterior oblique position; (ii) 5-spline, 20 pole catheter (1mm electrodes separated by 4-4-4mm inter-electrode spacing; PentaRay; Biosense-Webster). The PentaRay catheter was stabilised using a long vascular sheath (Preface, Biosense-Webster or SL0 Braided, St Jude Medical); and (iii) 3.5mm tip externally irrigated ablation catheter (Celsius Thermocool, Biosense Webster). The left atrium was accessed using a single transeptal puncture. Following transeptal access, bolus unfractionated heparin was utilised to maintain the activated clotting time between 250-350 seconds.

After mapping, patients underwent circumferential pulmonary vein ablation with an end-point of isolation confirmed by circumferential mapping (Lasso, Biosense-Webster) with either elimination or dissociation of pulmonary venous potentials. Ablation of the pulmonary veins was performed using a delivered power of 30 W with irrigation rates of 30mL/min. Additional substrate modification by linear ablation (roofline or mitral isthmus ablation) or targeting regions of CFAE was performed in patients with atrial fibrillation episodes persisting for > 48 hours, structural heart disease or with marked left atrial dilatation (longest diameter >57mm). Cavotricuspid isthmus ablation with an endpoint of bi-directional isthmus block was performed only in patients with a history of typical atrial flutter or if mapping confirmed typical atrial
flutter during the procedure. The endpoint of substrate modification was either electrophysiologically confirmed linear conduction block established via pacing manoeuvres or the elimination of local fractionation. Substrate modification was performed using a delivered power of 30-35 W with irrigation rates of 30-60mL/min. Detailed DF or CFE-mean analyses were not available to guide the procedure.

8.2.3 Study Protocol

Mapping was performed during spontaneous or induced (n=9) sustained atrial fibrillation of >10 minutes duration. Three-dimensional reconstructions of the right and left atria were made using the NavX navigation system (Version 6.0R or 7.0, St Jude Medical). High-density mapping of both atria was performed using the PentaRay catheter by sequentially acquiring 15 simultaneous bipolar electrograms. After ensuring adequate endocardial contact by fluoroscopy the catheter was held stationary for 8 seconds. These 8 second electrograms were sampled at 1200Hz, band pass filtered between 30-500Hz and their location on the 3-dimensional map annotated using the Diagnostic Landmark Mapping feature of the system. This ensured all areas of the atria, venae cavae and pulmonary veins were visited at least once and aimed to have the spread of points equal throughout both chambers. All electrograms were manually reviewed offline with those demonstrating an unacceptable signal to noise ratio excluded from analysis. For the purpose of regional evaluation, points were designated as belonging to one of 4 right atrial areas (anterior, septal, posterior or lateral) or 8 left atrial areas (roof, anterior, septum, lateral, posterior, inferior, pulmonary veins or appendage) using previously validated software (Coperniqs,
Medicalgorithmics) (Kuklik et al. 2004). Points designated at pulmonary veins were well within the veins, not at the ostia or antra which were considered part of a left atrial area.

The baseline atrial fibrillation cycle length within the coronary sinus was determined as previously described by averaging intervals over 1 minute using automated cycle length monitoring software (Bard Electrophysiology). Inter-electrogram intervals of <100ms and continuous electrical activity were counted as a single interval. At each time point, the automated annotation was manually verified and corrected with online calipers at a paper speed of 100mm/s (Sanders et al. 2005a).

8.2.4 Complex Fractionated Atrial Electrograms

CFAE were defined as fractionated potentials exhibiting multiple deflections from the isoelectric line. For the purposes of the study, CFAE were quantified using the automated NavX "CFE-mean" contact mapping tool, recently shown to effectively guide CFAE-targeted ablation (Verma et al. 2008), which provided a measure of electrogram fractionation as the average time duration between consecutive deflections during the 8 second electrogram. Deflections were identified by a detection algorithm and annotated on the electrogram with yellow "tick-marks". Detection is based on three user-defined criteria in which the deflection must: 1) exceed an adaptive "Peak-to-Peak Sensitivity" threshold set at a reference-amplitude slightly greater than baseline noise; 2) possess a "downstroke" morphology in which the leading local-maximum and the trailing local-minimum amplitude occurs within a time "Duration" that is set to avoid detection of broad, far-field events; and 3) exceed
a "Refractory" period from the previous detection that is set to avoid multiple
detections on a single deflection. When all three of these criteria are met, a yellow
tick-mark is placed on the electrogram at the instant of maximum-negative slope on
the downstroke (Figure 8-1). Our user settings were a Refractory Period of 30ms, a
Peak-to-Peak Sensitivity of 0.1mV and a Duration of 10ms. Points with a CFE-mean
value from the minimum of 40ms (Refractory + Duration) up to 250ms were included
for analysis to ensure inclusion of all potentially relevant data.

8.2.5 Activation Frequency

All electrograms were exported at 1200Hz to perform spectral analysis using offline
software (Coperniqs). The electrograms were initially rectified, filtered using
Butterworth filters (Low pass 20Hz, High pass 1Hz) and edge-tapered with a Hanning
window. Frequency spectra were calculated by Fast Fourier Transform with a spectral
resolution of 0.07Hz. DF was defined as the frequency containing maximum power
within the frequency domain 3-15Hz. Points with a Regularity Index (defined as the
ratio of the power within a 0.75Hz band at the DF to total power over 3-15Hz) of less
than 0.2 were excluded from analysis (Sanders et al. 2005a).

8.2.6 Relationship between Activation Frequency and Fractionation

The relationship between CFAE and DF were evaluated as follows: (i) Point-by-point, to
explore correlation at each sample location in every patient; (ii) Patient-by-patient, to
explore correlation between medians of CFE-mean and DF for a bi-atrial map; and (iii)
Spatial distribution, to examine the relative positions of fractionation to high DF points. The latter was determined by displaying the 20 highest DF points for each patient and grouping them in clusters (for points <5mm apart) showing a frequency gradient to the surrounding atria as previously described (Sanders et al. 2005a). The distance from these clusters to areas of low CFE-mean (multiple contiguous points within 5mm demonstrating CFE-mean<80ms) was measured on the 3-dimensional maps. In addition, activation mapping was performed on the 15 simultaneously acquired PentaRay bipolar electrograms at sites of high DF. Activation mapping was only performed during periods of organised atrial fibrillation as previously described (Haïssaguerre et al. 2006b). Local activation was manually annotated to the peak or trough of the largest amplitude deflection on the bipolar contact electrogram.

8.2.7 Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median and inter-quartile range as appropriate. Categorical variables are reported as number and percentage. Proportions were compared using Fisher’s Exact test. Comparisons were analysed using paired or unpaired t tests, or the Mann-Whitney U test as appropriate. To analyse differences in CFE-mean or DF according to atrial fibrillation type and region, a linear mixed effects model was fitted to the data. In the model, atrial fibrillation type, region, and the interaction between atrial fibrillation type and region were fitted as fixed effects. Random effects were included in the model to account for the dependence in observations both within a patient and within a given region of a patient, following which post-hoc pair-wise comparisons were performed within the
model. Correlation between variables was measured by Pearson’s r statistic. Statistical significance was set at p<0.05.

8.3 Results

8.3.1 Baseline Details

There were 10 patients with paroxysmal and 10 with persistent atrial fibrillation. Baseline patient characteristics are summarised in Table 8.1. Structural heart disease was present in 2 patients, 1 with ischaemic and the other with hypertrophic cardiomyopathy. In addition, 5 patients had hypertension, 2 had prior transient cerebrovascular events and 1 had obstructive sleep apnoea. Left atrial size and left ventricular hypertrophy were greater in the persistent compared to paroxysmal atrial fibrillation group.

Electrograms from a total of 10,133 points were analysed (507±150 points/patient); 238±79 points/patient in the right and 268±102 points/patient in the left atria. Atrial fibrillation cycle length as measured in the coronary sinus at the commencement of the study was 174±20ms (184±20ms for paroxysmal atrial fibrillation, 163±14ms for persistent atrial fibrillation, p=0.02).

8.3.2 Complex Fractionated Atrial Electrograms

Median CFE-mean was 103ms (IQR 76-143ms) for right atrial points and 98ms (IQR 72-139ms) for left atrial points (p<0.001). Median CFE-mean was 117ms (IQR 85-161ms) in
paroxysmal atrial fibrillation and 92ms (IQR 70-127ms) in persistent atrial fibrillation (p<0.001). Figure 8-2A demonstrates the regional variation in CFE-mean, with high CFE-mean values indicating less fractionation. CFE-mean was significantly lower in persistent atrial fibrillation compared to those with paroxysmal atrial fibrillation for all 12 regions (p=0.009). The difference between regions was not dependent on type of atrial fibrillation by the statistical model employed (p=0.7), hence the comparisons presented between areas for CFE-mean are across all patients, regardless of atrial fibrillation type. The areas of greatest fractionation within the left atrium were the roof, septum, posterior, anterior and inferior walls. All right atrial regions demonstrated a higher CFE-mean than these areas (p<0.05, Figure 8-2A).

Areas containing multiple points with low (<80ms; lowest quartile) CFE-mean were located on the 3-dimensional maps (Off et al. 2008). The mean number of such areas per patient was 10.3±4.2 and these areas were compared in location to clusters of high DF points (see below). More areas of low CFE-mean per patient were seen in persistent compared to paroxysmal atrial fibrillation (13±3.5 versus 7.5±3.5; p=0.002).

Median CFE-mean correlated moderately with atrial fibrillation cycle length (r=0.47, p=0.04) and there was an inverse correlation (r=-0.45, p<0.05) between mean atrial fibrillation cycle length and the number of areas of low CFE-mean.

### 8.3.3 Dominant Frequency

Median DF was 5.49Hz (IQR 4.91-6.15) for right atrial points and 5.57Hz (IQR 4.91-6.23) for left atrial points (p=0.02). Median DF was 5.27Hz (IQR 4.69-5.71) in paroxysmal atrial fibrillation patients and 5.93Hz (IQR 5.35-6.67) in persistent atrial fibrillation
patients (p<0.001). Regional differences in DF are illustrated in Figure 8-2B. DF was higher in persistent atrial fibrillation for all regions compared to paroxysmal atrial fibrillation (Figure 8-2B). The differences between regions across type of atrial fibrillation were not uniform (p=0.01), hence the comparisons presented between regions are made only within paroxysmal or within persistent atrial fibrillation groups. For paroxysmal atrial fibrillation the DF of pulmonary veins, left atrial appendage and roof was significantly higher than in the inferior and lateral left atrial regions (p<0.05, Figure 8-2B). For persistent atrial fibrillation no significant differences were seen between left atrial areas, except that the inferior left atrium had lower DF than the 3 highest areas; lateral and posterior left atrium, and left atrial appendage (p<0.05, Figure 8-2B).

The 20 highest DF points for each patient were located on the 3-dimensional maps. These 20 highest DF points were clustered such that the mean number of high DF clusters was 5.2±1.7 per patient. These clusters were compared in location to areas of low CFE-mean. Of 104 clusters, 68 (65%) were within the left atria, of which 24 were located in the pulmonary veins.

Median DF correlated well with atrial fibrillation cycle length (r=0.67, p=0.001); however, there was no significant correlation between atrial fibrillation cycle length and the number of high DF clusters (p=0.3).

8.3.4 Relationship between CFE-mean and Dominant Frequency

Correlation of CFE-mean and DF on a patient-by-patient basis shows a moderate inverse correlation (r=0.50, p=0.03; Figure 8-3), suggesting that for a given patient the
degree of fractionation (as indicated by low CFE-mean) increases with the DF. However, point-by-point correlation between CFE-mean and DF reveals a poorer correlation ($r=-0.17$, $p<0.001$; Figure 8-3), suggesting that these two parameters, while not the same, may co-exist within a common area. To further explore the relationship between these measures, the spatial relationship of the 104 clusters of high DF to CFAE areas were evaluated. The median distance between DF clusters and CFAE areas was 5mm (IQR 2-10). Eighty percent of DF clusters were at or less than 10mm from fractionation and in a further 10% they were found between 10-20mm. Figure 8-4 shows a representative example of the spatial relationship of fractionation to a high DF site. It shows the electrograms and their frequency spectra from high DF points, together with the electrograms from nearby low CFE-mean areas. The high DF site demonstrates a frequency gradient to the surrounding tissue with adjacent electrograms demonstrating more fractionation. In this example, the distance from the high DF site to the most fractionated electrogram shown was 7mm.

To further determine the relationship between sites of high DF and CFAE we performed activation mapping where possible using simultaneous electrograms from the PentaRay catheter at sites of high DF. Figure 8-5 demonstrates activation mapping at high DF cluster sites and reveals that during organised activity, varying patterns of wave-front activation and isochronal crowding are seen adjacent to the high DF site. Electrogram fractionation is observed to occur in close proximity to high DF sites in these examples.
8.4 Discussion

8.4.1 Major findings

This study utilised high-density endocardial mapping of atrial fibrillation to describe the relationship of activation frequency and electrogram fractionation within the atria.

The major findings are as follows:

(i) The left atrium is more highly fractionated than the right atrium and patients with persistent atrial fibrillation demonstrate a higher degree of fractionation than those with paroxysmal atrial fibrillation.

(ii) Activation frequency is higher in the left atrium than the right atrium and higher in persistent atrial fibrillation than paroxysmal atrial fibrillation. In paroxysmal atrial fibrillation regional analysis demonstrated significant variation in frequency, but these regional differences were less apparent in persistent atrial fibrillation.

(iii) Fractionation and activation frequency correlate with atrial fibrillation cycle length. While these variables do not demonstrate a relationship on a point-by-point basis, within an individual a moderate relationship is observed between them.

(iv) Exploration of their spatial relationship suggests that electrogram fractionation is observed in close proximity to sites of high frequency activation and is further supported by high-density simultaneous activation mapping at these sites.
8.4.2 Spatial Distribution of Complex Fractionated Atrial Electrograms

The finding of a higher degree of fractionation in the left atrium than the right is consistent with previous reports. Jaïs et al. (1996) initially described regional bi-atrial disparities in endocardial fractionation in paroxysmal atrial fibrillation, at a time when much of the data were from epicardial studies. They found that complex electrical activity was more frequently found in the septal and posterior regions of both atria, with more regular activity seen in the trabeculated atria. This group has further gone on to describe the characteristics of CFAE predictive of favourable ablation targets (Takahashi et al. 2008). Proponents of CFAE-targeted ablation have found fractionation predominantly in left atrial sites: the pulmonary vein ostia; inter-atrial septum; mitral annulus; basal left atrial appendage; left atrial roof; and the posterior left atrium (Nademanee et al. 2004; Oral et al. 2007; Schmitt et al. 2007; Porter et al. 2008). They reported that such sites were found more widely spread amongst those with longer duration atrial fibrillation, consistent with the greater number of electrogram fractionation areas found in the patients with persistent atrial fibrillation in the current study.

8.4.3 Spatial Distribution of Dominant Frequency

The initial evidence for organisation of atrial fibrillation came from optical mapping in animal studies which used spectral analysis to demonstrate repetitive high frequency activity with temporal and spatial periodicity during atrial fibrillation, consistent with the hypothesis of “driving” rotors (Skanes et al. 1998; Kalifa et al. 2006). More recently, similar findings have been reported in humans (Wu et al. 2002; Lazar et al.
Our finding of higher DF in the left atrium in humans is consistent with previous published reports on paroxysmal atrial fibrillation (Lazar et al. 2004; Lin et al. 2006). Furthermore, the maximal DF has been reported in the pulmonary veins in patients with paroxysmal atrial fibrillation (Sanders et al. 2006). However, persistent atrial fibrillation had a less conclusive regional pattern of DF distribution. Although previous publications have shown a higher mean DF in the left atria, particularly around the pulmonary veins (Wu et al. 2002), others have shown that this distinction disappears for longstanding atrial fibrillation where other sites are observed to predominate (Lazar et al. 2004; Atienza et al. 2006). Isolation of the pulmonary veins abolishes this left-to-right gradient in paroxysmal atrial fibrillation and for the subset of patients with persistent atrial fibrillation in whom a left-to-right gradient exists, success of pulmonary vein isolation alone exceeds that of persistent atrial fibrillation without such gradient (Lazar et al. 2006). Retrospective analysis of ablation of paroxysmal atrial fibrillation shows that atrial fibrillation cycle length prolongation and eventual termination occurs at sites of high DF (Sanders et al. 2005a). This has not been shown for persistent atrial fibrillation and may be in part due to our study’s finding that DF is distributed more evenly throughout atrial regions, making targeting any one region a less effective strategy for ablation in this sub-group. Indeed, a more aggressive, multi-region approach for ablating longstanding persistent atrial fibrillation has been advocated (Haïssaguerre et al. 2005c).
8.4.4  Relationship between Activation Frequency and Fractionation

Few studies have examined the relationship between CFAE and DF. Lemola et al. (2006) examined the DF before and after atrial fibrillation ablation by 2 techniques; circumferential-pulmonary-vein and electrogram-guided ablation. Using CFAE to guide ablation, the mean left atrial DF was seen to reduce by 17% and this decrease was associated with less recurrent atrial fibrillation for patients with persistent atrial fibrillation. No such prognostic advantage of DF reduction was seen for the pulmonary vein encircled group, suggesting that differing mechanisms are eliminated by the 2 ablation strategies. Rostock et al. (2006) have shown that dynamic changes in CFAE are dependent on regional atrial fibrillation cycle length, in that shortening of local cycle length preceded development of CFAE. Our finding of significant correlation between atrial fibrillation cycle length and number of areas of low CFE-mean, and the proximity of DF clusters to CFAE areas, is consistent with this observation. A recent study evaluating the potential role of ganglionated plexi in atrial fibrillation has demonstrated that following local administration of acetyl choline there was a significant gradient of decreasing DF and incidence of CFAE from ganglionated plexi toward distant sites (Lu et al. 2008). While we did not evaluate the role of ganglionated plexi, this inter-relationship of CFAE and DF is supported by our study.

Kalifa et al. (2006) have investigated the relationship between focal drivers and sites of fractionation using optical mapping in the experimental setting. In 8 isolated sheep hearts they were able to show maximal DF regions in which fractionation was lowest and an increased band of fractionation observed at border-zones with areas of lower DF in the posterior left atria. They therefore conclude that alongside areas of fast,
regular atrial activation, there are zones where propagation pattern variability and fractionated activity occur most frequently. In the current study, high-density mapping in human atrial fibrillation identified clusters of high DF points, predominantly within the left atrium, with fractionation observed at or adjacent to these sites. These findings are consistent with data from the findings of Kalifa et al. (2006). These investigators suggested that the success of the CFAE-targeted ablation is due to anatomical barriers being created to isolate the influence of high frequency “driver” sites on the rest of the atria. The current clinical study suggests that such ablation in the beating heart could additionally involve the closely positioned sites of high activation frequency.

8.4.5 Clinical Implications

Activation mapping during atrial fibrillation has been notoriously difficult to perform in the clinical setting. In addition, for longer duration atrial fibrillation, CFAE are observed in many regions of the atria making identification of critical CFAE sites difficult. In this setting, mapping activation frequency with DF may be of particular value in guiding ablation in patients with more complex substrate such as in longstanding persistent atrial fibrillation. A combined approach using both CFAE and DF mapping may allow a more expeditious and targeted approach to ablation of the critical atrial substrate, which further studies should address.
8.4.6 Limitations

Although this clinical study has provided high-density contact mapping to evaluate the relationship of CFAE and DF, its relative density does not approach that achieved by optical mapping in the experimental setting. Higher density mapping may have allowed identification of mechanisms leading to these phenomena. Nevertheless, our findings on the relationship between CFAE and DF are similar to that achieved in such studies. This study was unable to determine the effects of ablation on these sites due to the off-line nature of the analysis. In addition, the coronary sinus was not studied. Finally, the questions of optimal sample length and the temporal stability of DF and CFE-mean over periods of minutes or more was not addressed by this study, but have been studied elsewhere (Lazar et al. 2004; Sanders et al. 2005a; Lin et al. 2008; Stiles et al. 2008).

8.5 Conclusion

Greater fractionation and higher activation frequency are seen in persistent atrial fibrillation and in the left atria. Significant regional variation in activation frequency is observed in paroxysmal atrial fibrillation and this distinction diminishes in persistent atrial fibrillation. CFAE and DF demonstrate no relationship on a point-by-point basis. However, there is a relationship between CFAE and DF at an individual level. High-density exploration of their spatial relationship confirms the occurrence of CFAE adjacent to areas of high frequency activation.
<table>
<thead>
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<th>Paroxysmal (n=10)</th>
<th>Persistent (n=10)</th>
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</tr>
</tbody>
</table>

AF = atrial fibrillation, LV = left ventricular
Figure 8-1

Integrated bi-atrial high-density CFE-mean colour maps with example bipolar atrial electrogram

Figure legend overleaf.
Figure 8-1 (previous page)

The electrogram demonstrates yellow tick-marks at the instant of maximum-negative slope on downstrokes between leading local-maximum and trailing local-minimum points. Tick-marks indicate annotations of deflection events in the electrogram according to the Refractory, Peak-to-Peak Sensitivity and Duration criteria defined in the text. CFE-mean is the average time duration between annotations and the value for each point is displayed along a colour spectrum on the 3-dimensional geometry.

Figure 8-2

(a) Median CFE-mean by atrial region

(b) Median DF by atrial region

Figure legend overleaf.
(a) CFE-mean was significantly lower in persistent compared to paroxysmal atrial fibrillation for all regions (p<0.01). For post-hoc pair-wise comparisons regardless of type of atrial fibrillation; *p<0.04 compared to all other regions, †p<0.05 compared to LAA, ‡p<0.05 compared to any right atrial region, and §p<0.05 compared to LA Lat.

(b) All regions were significantly higher in persistent compared to paroxysmal atrial fibrillation (p<0.01), except for RA Lat and RA Ant. Post-hoc pair-wise comparisons for Paroxysmal atrial fibrillation; PVs, LAA and LA Roof were significantly higher than LA Lat and LA Inf (p<0.05), and RA Ant was significantly higher than the 6 lowest areas. Post-hoc pair-wise comparisons for Persistent atrial fibrillation; no significant differences were seen between LA areas except LA Inf and the 3 highest areas (p<0.05), and RA Lat, RA Post and RA Sept were significantly lower than many of the LA areas and RA Ant (p<0.05).

Figure 8-3

Scatter plots of DF and CFE-mean with “line of best fit”

Left panel: Point-by-point correlation for every sample location in every patient.

Right panel: Patient-by-patient correlation between medians of CFE-mean and DF.
High DF areas (blue-purple) are seen in the pulmonary veins, basal left atrial appendage and the left atrial roof. A zoomed view of the area of high DF at the roof is shown with the corresponding points (inset). One second electrograms, frequency spectra (3-15Hz), and corresponding DF and CFE-mean values for each of the local 7 points contributing to the colour map are shown in linked boxes. The central point of highest DF is fast and regular, with surrounding points showing either increased fractionation, lower DF or both.
Figure 8-5

Integrated CT images with activation maps from the 5-spline catheter at high DF cluster sites and accompanying bipolar electrograms.

Figure legend overleaf.
(a) Activation map at the left inferior pulmonary vein of a patient with paroxysmal atrial fibrillation. Dominant frequency at this site was 7.5Hz (median DF 5.4Hz for this left atrium). In this example, activation seems to radiate out from a distinctly early site (A2). Note the increase in fractionation in Spline E with delayed conduction.

(b) Activation map at the left atrial roof of a patient with persistent atrial fibrillation. Dominant frequency at this site was 8.4Hz (median DF 7.2Hz for this left atrium). Earliest activation is seen in distal Spline B with Splines C and D activated soon after. Delayed conduction is seen in the direction of Splines A and E with isochronal crowding and fractionation.

(c) Activation map at the posterior left atrial wall of a patient with paroxysmal atrial fibrillation. Dominant frequency at this site was 6.4Hz (median DF 5.8Hz for this left atrium). Activation can be seen to move in an anti-clockwise direction around the splines with block between Splines A and E, evidenced by double potentials in Spline E.
Chapter 9.
Summary

This thesis has examined aspects of the underlying substrate present in atrial fibrillation and atrial flutter. The insights gained into the characteristics of the atrial myocardium that initiate and sustain atrial arrhythmia have advanced our understanding of the mechanisms responsible for this disease. This knowledge may contribute to strategies aimed at prevention and treatment of atrial arrhythmia.

Studies of patients with recent atrial arrhythmia have demonstrated electrical and structural remodelling within the atria. However, it is not known if this remodelling precedes, occurs in association with, or results from the atrial arrhythmia. These studies have suggested an important role for a decrease in atrial refractoriness and are central to the observation that "atrial fibrillation begets atrial fibrillation". Clinical studies have shown reversal of electrical remodelling over time after termination of arrhythmia, however strategies of prompt termination of atrial fibrillation to avoid this cycle of adverse remodelling have failed to show benefit. These observations have led to the search for a “second factor” integral to the development and progression of atrial fibrillation. Characterisation of the atrial substrate distant in time from episodes of atrial fibrillation removes the effect that recent arrhythmia is known to have on atrial electrophysiology. Chapter 2 has characterised the electrical substrate of the right and left atria of patients with paroxysmal lone atrial fibrillation, remote from recent arrhythmia, and demonstrated conduction abnormalities characterised by prolongation of conduction times along linearly placed catheters, longer P wave duration and site-specific conduction delay; impaired sinus node function indicated by prolonged SACT and CSNRT; and an increase in ERP, which is consistent with prior
studies evaluating clinical substrates for atrial fibrillation but is in contrast to the remodelling attributed to atrial fibrillation itself. This suggests that patients with paroxysmal lone atrial fibrillation have an abnormal atrial electrophysiological substrate and that these abnormalities contribute to the “second factor” that promotes progression of atrial fibrillation. Chapter 3 has characterised the electroanatomical substrate present in lone atrial fibrillation. Several animal models and clinical conditions known to be associated with atrial fibrillation have demonstrated structural remodelling and conduction abnormalities without reduction in refactororiness, but the changes observed may be influenced by the underlying disease itself. Patients with “lone” atrial fibrillation do not have overt cardiovascular disease to influence the underlying substrate. Therefore, electroanatomical characterisation of the atria of patients with lone atrial fibrillation has aimed to minimise the effects of associated disease and look at the substrate related to the arrhythmia itself. In addition, this characterisation was performed remote from recent episodes of arrhythmia to diminish the transient effects of rate-related remodelling. This study demonstrated bi-atrial structural abnormalities characterised by atrial dilatation and lower mean atrial voltage suggesting the loss of atrial myocardium; slower conduction velocities; and an increase in the proportion of electrograms characterised as double potentials or fractionated signals. These findings suggest that patients with paroxysmal lone atrial fibrillation have an abnormal electroanatomical atrial substrate and that these abnormalities also contribute to the “second factor” that promotes atrial fibrillation.

The course of the typical atrial flutter circuit has been well characterised and ablation of the cavotricuspid isthmus is a highly successful treatment. However, despite this
therapy a significant proportion subsequently develop atrial fibrillation. Indeed, atrial flutter has a close inter-relationship with atrial fibrillation and the two rhythms frequently co-exist. Chapter 4 postulates that causes for the propensity for future atrial fibrillation in this population may be found by investigation of the underlying electrical substrate of the right atrium in atrial flutter. Major findings from this study include conduction abnormalities characterised by prolongation of lateral right atrial conduction time, longer P wave duration and site-specific conduction delay; impairment of sinus node function; and an increase or no change in ERP. Thus, the abnormal electrical substrate of atrial flutter is found to be present diffusely throughout the right atrium and not confined to the barriers of the known typical flutter circuit. Chapter 5 has characterised the electroanatomical substrate of atrial flutter to further define abnormalities throughout the right atrium. Findings include structural abnormalities reflected in atrial dilatation and lower mean right atrial voltage suggesting the loss of atrial myocardium; conduction abnormalities in the form of slower mean conduction velocity; and an increase in the proportion of complex electrograms. Together with the electrical substrate determined in the prior chapter, these changes reflect a diffusely abnormal right atrial substrate characteristic of the changes seen in atrial fibrillation with prior studies and indeed earlier in this thesis. Perhaps it is these abnormalities that predispose many patients with atrial flutter to progress to atrial fibrillation.

Several investigators have observed remodelling of the sinus node that develops soon after the initiation of arrhythmia and reverses after restoration of sinus rhythm. In addition, it is known that several conditions predisposed to the development of atrial arrhythmias demonstrate sinus node remodelling. Furthermore, atrial fibrillation not
uncommonly complicates sinus node disease. This frequent co-existence of atrial
arrhythmia and sinus node disease may be due to a slow sinus rate increasing
vulnerability to atrial fibrillation, a common disease substrate and/or arrhythmia
directly impairing sinus node function. The anatomical sinus node is a small localised
structure located at the junction of the superior vena cava with the right atrium. In
contrast, the functional sinus node complex has been demonstrated to extend the
length of the crista terminalis and indeed beyond. This discrepancy is difficult to
reconcile and various hypotheses have been proposed. Newer mapping technology has
provided novel insights into arrhythmia mechanisms not previously afforded using
conventional techniques, demonstrating “preferential pathways” from earliest
activation to the site where break-out occurs to the remaining atria in ectopic atrial
tachycardia. Whether similar pathways exist to account for the discrepancy between
the anatomical and functional sinus node complex is not known. Chapter 6 aimed to
characterise the electrical properties of the functional sinus node complex in the
normal heart with the anatomical and electrical resolution provided by a 3-
dimensional non-contact mapping system. To further explore the sinus node complex
activity, the same characterisation was performed in patients with chronic atrial flutter
(a group known to have impaired sinus node function) to establish how sinus node
activity is affected by atrial remodelling. This chapter found that the sinus node
complex in normal hearts displays a dynamic range of activation sites along the
postero-lateral right atrium and preferential pathways of conduction do indeed exist
between the sinus node and the exit of sinus activity to the atria. There were multiple
origins of sinus activation and exit sites to the atria, providing evidence of multi-
centricity of the sinus node complex. Lastly, remodelled atria demonstrate structural
change reflected by loss of voltage that was associated with more caudal activation, slower conduction time along preferential pathways, only modest shifts of the functional pacemaker complex and more frequent conduction block across the crista terminalis with resultant circuitous conduction of the sinus impulse. These findings extend our knowledge of the function of the highly complex human sinus node by demonstrating the presence of preferential pathways of conduction within the functional sinus node complex. The abnormalities in the sinus node complex shown for the patients with atrial flutter underscore the important association between impaired sinus node function and atrial arrhythmia.

As ablation techniques are used to treat patients with atrial fibrillation, it has become apparent that many patients require not just trigger elimination but also substrate modification. There is much work being done on identifying the appropriate atrial substrate to be modified. Areas of CFAE and DF have been suggested as critical regions maintaining atrial fibrillation. Techniques to modify the underlying atrial substrate by ablation of these targets in order to treat atrial fibrillation have been proposed. CFAE-targeted ablation is one such technique and has been reported as highly successful, although attempts to emulate the outcomes initially reported have shown more modest improvements. Perhaps one reason for this non-reproducibility is that the evaluation of CFAE has been based on the operator’s subjective analysis. Mapping to identify sites of high DF may identify the position of “drivers” of atrial fibrillation and targeting these electrograms is a promising area of research. The development of automated algorithms for both quantification of electrogram fractionation and real-time DF calculation aims to deliver a reproducible and objective assessment of electrogram characteristics and thereby standardise the approach to substrate
modification. The ideal duration of electrograms required to reproducibly identify sites of CFAE or highest DF is not known. While longer electrogram recordings extend the data collection process unnecessarily, shorter durations may provide an inaccurate representation of the true degree of fractionation or frequency. Chapter 7 aimed to determine the minimum duration of electrogram recording that provides accurate data without unduly lengthening the data collection process, by exploring the degree of correlation between progressively shorter electrogram recordings with the longest exportable data sample length. Recordings of shorter durations were compared to the maximum duration recordable by the system using several criteria including mean values, mean absolute differences, the proportion of points deviating >10% from the index value and intra-class correlation coefficients. Using these criteria, a recording duration of less then 5 seconds was shown to disclose inaccurate data about the fractionation and activation frequency of the electrograms reflecting underlying substrate of atrial fibrillation. An electrogram duration of 5 seconds is therefore recommended with these techniques of automated analysis.

The relationship between CFAE and sites of high DF has not been previously demonstrated in humans. In particular, it is not known whether they are markers of the same or provide complementary information on the pathogenesis of atrial fibrillation. Understanding the relationship between these targets may be useful in guiding radiofrequency ablation. In Chapter 8, the relationship between sites of high frequency activation and fractionation during atrial fibrillation was examined by the creation of high-density bi-atrial maps. This study found that the left atrium is more highly fractionated than the right atrium and that patients with persistent atrial fibrillation demonstrate a higher degree of fractionation than those with paroxysmal
atrial fibrillation. Similarly, activation frequency is higher in the left atrium than the right atrium and higher in persistent atrial fibrillation than paroxysmal atrial fibrillation. In paroxysmal atrial fibrillation regional analysis demonstrated significant variation in frequency, but these regional differences were less apparent in persistent atrial fibrillation. Correlation between fractionation and activation frequency exists but is much stronger on a patient-by-patient rather than a point-by-point basis, prompting the exploration of the spatial relationship between points of high DF and fractionation.

Detailed inspection of 3-dimensional high-density maps created during atrial fibrillation reveals that electrogram fractionation is observed in close proximity to sites of high frequency activation. This data is further supported by high-density simultaneous activation mapping at sites of high DF. The clinical implications of this relationship are that mapping activation frequency with DF may be of particular value in guiding ablation in patients with more complex substrate such as in longstanding persistent atrial fibrillation. A combined approach using both CFAE and DF mapping may allow a more expeditious and targeted approach to ablation of the critical atrial substrate, which further studies should address.
Chapter 10.
Future Directions

The characterisation of the underlying atrial substrate of atrial fibrillation and atrial flutter performed for the purpose of this thesis has provided important insights into the mechanism of the disease process associated with atrial arrhythmia. However, many questions remain unanswered, some of which are discussed below.

This thesis provides documentation of the substrate of atrial fibrillation and of atrial flutter under specific conditions. By design, the electrophysiological and electroanatomical studies were performed remote from recent arrhythmia to minimise the known transient effects of rate-related remodelling. As such, the conclusions drawn relate to the substrate present without the effects of recent arrhythmia which of course may not reflect the clinical situation of many patients with atrial arrhythmia. The complex interaction between the electrical and structural remodelling demonstrated here and the rate-related remodelling observed during and shortly after arrhythmia requires further study.

Additionally, the similarly complex interaction between substrate for atrial fibrillation and associated cardiovascular disease is an area for future investigation. The bi-atrial substrate identified for lone atrial fibrillation here necessarily excluded underlying heart disease and most patients with atrial fibrillation do indeed have related disorders which would variably impact on the atrial substrate.

The cause of atrial arrhythmia is widely recognised to be due to the presence of both triggers and substrate to initiate and maintain the abnormal rhythm. This thesis has concentrated on characterising the substrate underlying atrial arrhythmia. Although
extrapolation of data regarding sites of high DF as potential triggers sites could be made, this was not the primary aim of the study. Therefore, detailed examination of the electrophysiological characteristics of triggers of atrial arrhythmia is a potential area for future research that would complement the work on atrial substrate.

Clinical studies such as those performed in this thesis make some assumptions about disease process and observed findings – e.g. reduction in observed voltage is likely to reflect loss of atrial myocardium. Insights into the precise mechanisms contributing to the changes observed may come from animal studies where the methods by which abnormalities manifest are more readily established.

A substantial body of work exists on the effect of the autonomic nervous system on atrial fibrillation. This thesis did not set out to characterise the effect of the ganglionic plexi on the atrial substrate and future work on the contribution of vagal influence on the triggers and maintenance of atrial fibrillation is expected to increase our knowledge in this important area.

Sinus node disease is a significant cause of morbidity and a leading indication for permanent pacemaker implantation. The findings in this thesis of preferential pathways being integral to the function of the sinus node complex, and the observations of sinus node remodelling associated with atrial flutter being mediated via these pathways, has implications for the understanding and perhaps eventual management of this common condition.

Translating the findings regarding atrial substrate to a useful clinical intervention would be a worthy aim. The studies of CFAE and DF have a potential role in the effective guidance of ablation strategies aiming to modify the substrate of atrial
arrhythmia. Although the strategy of CFAE-targeted ablation is well accepted, that of targeting sites of high DF is not yet established. DF-guided ablation is a potential direct application of the data presented in Chapter 8 and future studies comparing standard ablation techniques with or without additional targeting of sites of high DF may show a difference in ablation efficacy. Furthermore, a combined approach (identifying both CFAE and sites of high DF) of electrogram-targeted ablation may utilise the complementary information obtained from each technique to increase effective ablation while decreasing unnecessary ablation of “bystander” myocardium not actively involved in the substrate maintaining atrial fibrillation. As the indications for atrial fibrillation ablation expand and the additional ablation required to maintain outcomes in the more complex patient increases, a method that could reduce ablation time and increase safety yet maintain efficacy would be welcome.
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DVD ‘Movie 6.1’ is available in the University of Adelaide Library.