

Characterisation of the Substrate of Atrial Fibrillation and Flutter

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To my wife Christina and my children Isabelle and Liam

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Summary

Future Directions

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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

Stiles MK, John B, Wong CX, Kuklik P, Brooks AG, Lau DH, Dimitri H, Roberts-Thomson KC, Wilson L, De Sciscio P, Young GD, Sanders P. Paroxysmal lone atrial fibrillation is associated with abnormal atrial substrate: Characterising the “second factor”. J Am Coll Cardiol, in press

Stiles MK, Brooks AG, Kuklik P, John B, Dimitri H, Lau DH, Wilson L, Shashidhar, Roberts-Thomson RL, Mackenzie L, Young GD, Sanders P. High-density mapping of atrial fibrillation in humans: Relationship between high frequency activation and electrogram fractionation. J Cardiovasc Electrophysiol, 2008;19:1245-1253

Stiles MK, Brooks AG, Sanders P. Putting CFAE on the map. J Cardiovasc Electrophysiol 2008;19:904-906

Stiles MK, Brooks AG, John B, Shashidhar, Wilson L, Kuklik P, Dimitri H, Lau DH, Roberts-Thomson RL, Mackenzie L, Willoughby S, Young GD, Sanders P. Effect of electrogram duration on the quantification of complex fractionated atrial electrograms and dominant frequency. J Cardiovasc Electrophysiol 2008;19:252-258

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Publications and Communications to Learned Societies

Chapter 1

- i) Manuscript: Stiles MK, Brooks AG, Sanders P. Putting CFAE on the map. J Cardiovasc Electrophysiol 2008;19:904-906
- ii) Manuscript: Sanders P, Stiles MK, Young GD. Virtual Anatomy for Atrial Fibrillation Ablation. J Cardiovasc Electrophysiol 2006;17:349-351
- 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

- i) Manuscript: Stiles MK, John B, Wong CX, Kuklik P, Brooks AG, Lau DH, Dimitri H, Roberts-Thomson KC, Wilson L, De Sciscio P, Young GD, Sanders P. Paroxysmal lone atrial fibrillation is associated with abnormal atrial substrate: Characterising the “second factor”. J Am Coll Cardiol, in press
- 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

- i) Manuscript: Stiles MK, Brooks AG, John B, Shashidhar, Wilson L, Kuklik P, Dimitri H, Lau DH, Roberts-Thomson RL, Mackenzie L, Willoughby S, Young GD, Sanders P. Effect of electrogram duration on the quantification of complex fractionated atrial electrograms and dominant frequency. J Cardiovasc Electrophysiol 2008;19:252-258
- 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

- i) Manuscript: Stiles MK, Brooks AG, Kuklik P, John B, Dimitri H, Lau DH, Wilson L, Shashidhar, Roberts-Thomson RL, Mackenzie L, Young GD, Sanders P. High-density mapping of atrial fibrillation in humans: Relationship between high frequency activation and electrogram fractionation. J Cardiovasc Electrophysiol 2008;19:1245-1253
- 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

CFAE	Complex Fractionated Atrial Electrogram
CFE-mean	An automated measure of electrogram complexity
CI	Confidence Interval
CSNRT	Corrected Sinus Node Recovery Time
DF	Dominant Frequency
EA	Earliest Activation
ECG	Electrocardiogram
ERP	Effective Refractory Period
ICC	Intra-Class Correlation
IQR	Inter-Quartile Range
OR	Odds Ratio
SACT	Sino-Atrial Conduction Time
SBO	Sinus Break-Out

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.