

# **MECHANISMS OF THROMBOGENESIS IN ATRIAL FIBRILLATION**

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*To my wife Lufee  
and our daughter Gloria*

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## ABSTRACT

Atrial fibrillation (AF) is the commonest sustained heart rhythm disorder in clinical practice. Non-valvular AF confers a 5-fold increased risk of stroke. Stroke in AF is mainly due to thromboembolic phenomenon from the left atrium (LA). It is well known that atrial mechanical dysfunction contributes to thrombus formation. However, patients with AF are also known to exhibit a prothrombotic state and endothelial dysfunction, further contributing to this thromboembolic risk.

There is debate as to whether the prothrombotic state and endothelial dysfunction seen in patients with AF are due to AF per se or the patients' concurrent comorbidities. Chapter 2 examined the LA milieu in patients with lone non-valvular AF compared to patients with AF and comorbidities and controls. The study demonstrated increased platelet activation in the LA compared to the periphery in patients with lone AF. There was a step-wise increase in endothelial dysfunction in the lone AF cohort and AF with comorbidities compared to controls, indicating that both AF per se and its concurrent comorbidities contribute to endothelial dysfunction and thrombotic risk.

Chapter 3 investigated the effect of rapid atrial rates in patients with AF compared to patients with supraventricular tachycardia. The study demonstrated rapid atrial rates increased LA platelet activation and thrombin generation in patients with AF. Left atrial thrombogenesis was markedly accentuated with atrio-ventricular dyssynchrony.

In contrast, rapid atrial rates did not result in abnormal changes in patients with supraventricular tachycardia. These findings suggest rapid atrial rates, atrio-ventricular dyssynchrony and the abnormal substrate in patients with AF contribute to LA thrombogenesis in these patients.

The relative contribution of the atrial rate or rhythm to LA thrombogenesis is unknown. Chapter 4 examined the effects of atrial rate and abnormal rhythm on LA thrombogenesis and demonstrated both rapid atrial rates and AF result in increased platelet activation and thrombin generation in the LA. However, AF also induced endothelial dysfunction and inflammation, not seen with rapid atrial rates alone. These findings suggest that while rapid atrial rates increase the thrombogenic risk, abnormal rhythm may further potentiate this risk.

Catheter ablation therapy has emerged as an effective strategy for rhythm control in patients with AF. However, radiofrequency ablation is known to cause an increase in various markers of inflammation and patients are at risk of peri-procedural thromboembolic events. Chapter 5 examined inflammatory, myocardial injury and prothrombotic markers in AF patients undergoing catheter ablation during the peri-procedural period. The study demonstrated that patients exhibit an inflammatory response within the first few days post-ablation, and that this response predicted immediate AF recurrence. Prothrombotic markers were elevated one week post-ablation and may contribute to the increased peri-procedural thrombotic risk.

Whether catheter ablation for AF confers a benefit on prevention of future thromboembolic stroke is a vital question. Chapter 6 demonstrated that successful catheter ablation and maintenance of sinus rhythm leads to a decrease in platelet activation and improvement in endothelial function. These findings suggest that the prothrombotic state in patients with AF can be reduced with successful maintenance of sinus rhythm following catheter ablation.

## 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 Han Lim 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. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis (as listed below) resides with the copyright holder(s) of those works.

**Han Sung Lim**

**December 2011**

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## PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

### Chapter One

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## **Chapter Two**

1. Manuscript: Lim HS, Willoughby SR, Schultz C, Alasady M, Dang J, Gan C, Lau DH, Leong DP, Brooks AG, Roberts-Thomson KC, Young GD, Worthley MI, Sanders P. Platelet Activation and Endothelial Dysfunction in Patients with Atrial Fibrillation: Importance of Co-Morbid Conditions. Submitted for publication.
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## **Chapter Three**

1. Manuscript: Lim HS, Willoughby SR, Schultz C, Alasady M, Gan C, Lau DH, Leong DP, Roberts-Thomson KC, Young GD, Worthley MI, Sanders P. Thrombogenesis

in the Human Left Atrium in Patients with Atrial Fibrillation: Impact of Atrial Rates and Atrio-Ventricular Dyssynchrony. Submitted for publication.

2. Presentation: Presented at the European Society of Cardiology Congress, 2010, Stockholm, Sweden and published in abstract form (European Heart Journal 2010)
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#### **Chapter Four**

1. Manuscript: Lim HS, Willoughby SR, Schultz C, Gan C, Alasady M, Lau DH, Leong DP, Brooks AG, Young GD, Worthley MI, Sanders P. Effect of Atrial Fibrillation on Atrial Thrombogenesis in Humans: Impact of Rate and Rhythm. Submitted for publication.

2. Presentation: Presented at the American Heart Association Scientific Sessions 2010 in Chicago, United States of America and published in abstract form (Circulation 2010)
3. Presentation: Presented at the European Society of Cardiology Congress, 2011, Paris, France and published in abstract form (European Heart Journal 2011)
4. Presentation: Presented at the Heart Rhythm Society 32nd Annual Scientific Sessions, May 2010, San Francisco, United States of America and published in abstract form (Heart Rhythm 2011)
5. Presentation: Presented at the 4<sup>th</sup> Asia Pacific Heart Rhythm Society Scientific Sessions, Fukuoka, Japan, September 2011 and published in abstract form (Journal of Arrhythmia 2011)
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## Chapter Five

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5. Postgraduate Travel Fellowship Award, Faculty of Health Sciences, The University of Adelaide, 2010
6. National Heart Foundation of Australia (South Australia) EO Myers Trust Fund Travel Award, 2009
7. Faculty of Sciences Divisional Scholarship, Postgraduate Scholarship, The University of Adelaide, 2008
8. Biotronik Educational Grant for Asia Pacific Heart Rhythm Society Conference Registration, 2011
9. National Heart Foundation of Australia Travel Award, 2011