CARDIAC REMODELLING IN HYPERTROPHIC CARDIOMYOPATHY AND DIABESITY

Wei Wen Lim

BSc. (Hons)

Centre for Heart Rhythm Disorders

The School of Medicine

The University of Adelaide

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To my parents, Yong Meng and Florence,

my sister, Shu Ping,

and my partner, Melissa

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice and contributes to significant morbidity and mortality risks in patients. Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiac disorder and whilst ventricular cardiomyopathy has been well characterised, the atrial substrate contributing to AF has not.

Chapter 2 assessed the underlying atrial electrophysiological, structural and biomarkers alterations in transgenic mice with a monogenic mutation in Troponin-I as a model of HCM. Also described are the changes in the atrial substrate with chronicity of HCM (30 vs. 50 weeks of age). Mice with established HCM (30 weeks) demonstrate increased bi-atrial mass associated with atrial myocyte hypertrophy, increased fibrosis and inflammatory cell infiltration. Electrophysiological parameters demonstrate decreased action potential durations, normal refractoriness, normal but heterogeneous conduction in the HCM atria. Conversely, biomarkers of extracellular matrix remodelling and inflammation were not altered in 30-week old HCM mice. With older age, HCM mice demonstrate progressively increased refractoriness and slowed conduction, as well as changes in biomarkers for extracellular matrix remodelling and inflammation.

Chapter 3 characterizes electrocardiography (ECG) changes that are indicative of conduction time within compartments of the heart and HRV as a measure of cardiac autonomic function in HCM mice. HCM mice demonstrated slowed atrial and atrioventricular conduction (as measured by P wave duration

and PR intervals respectively), as well as depressed HRV (as shown by decreased standard deviation of RR intervals (SDRR), coefficient of variation of RR intervals (CVRR), and standard deviation of heart rate (SDHR)). No significant age-related difference was observed in all ECG and HRV parameters.

Although diabetes and obesity (collectively termed as diabesity) are increasingly prevalent in humans and independently associated with AF development; the atrial substrate accounting for AF has not been fully understood. Animal models used in diabetes research are often of monogenic aetiology that demonstrates severe clinical phenotypes uncharacteristic of humans. Studies in polygenic models that better represent human diabesity are warranted.

Chapter 4 describes electrophysiological and structural changes in the atria of young (10-week old) and matured (30-week old) polygenic NONcNZO10/LtJ (RCS10) mice prone to diabesity development with high fat diet and/or increasing age. Young RCS10 mice with diet-induced progressive obesity and hyperglycaemia demonstrated increased refractoriness and action potential durations, slowed and heterogeneous conduction, increased myocyte hypertrophy, fibrosis and inflammatory cell infiltration in the atria. Matured RCS10 mice demonstrated similar electrophysiological and structural substrates with the exception of unchanged atrial refractoriness and action potential durations. Furthermore, biomarkers of extracellular matrix remodelling and inflammation in this model were altered.

Chapter 5 examines ECG and HRV modulations in the RCS10 mice with age and diet-induced diabesity. RCS10 mice demonstrated atrial and atrioventricular conduction delay (as evident by increased PR intervals and progressively prolonged P wave durations respectively). RCS10 mice also demonstrated reduced SDRR and RMSSD indicative of reduced HRV. Age was not a significant contributor of ECG and HRV changes. Increased severity of obesity and diabetes had a minor but significant correlation to worse P wave duration and depressed RMSSD.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Wei Wen Lim
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PUBLICATIONS AND COMMUNICATION TO LEARNED SOCIETIES

Chapter 2

1. **Manuscript:** Lim WW, Neo M, Thanigaimani S, Kuklik P, Ganesan AN, Baumert M, Lau DH, Tsoutsman T, Kalman JM, Semsarian C, Saint DA, Sanders P. Atrial Electrophysiological and Structural Remodelling in Hypertrophic Cardiomyopathy in a Murine Model of Troponin-I Mutations: Implications for Atrial Fibrillation (prepared in publication format)
2. **Presentation:** Presented at the Australian Physiological Society November 2014, Brisbane, Australia
3. **Presentation:** Presented at the Florey Postgraduate Research Conference September 2014, Adelaide, Australia

Chapter 3

1. **Manuscript:** Lim WW, Baumert M, Neo M, Kuklik P, Ganesan AN, Lau DH, Tsoutsman T, Semsarian C, Sanders P, Saint DA. Slowed Atrial and Atrioventricular Conduction and Depressed HRV in a Murine Model of Hypertrophic Cardiomyopathy. *Clinical and Experimental Pharmacology and Physiology* (accepted manuscript)
2. **Presentation:** Presented at the Australian Physiological Society November 2014, Brisbane, Australia
3. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand August 2015, Melbourne, Australia

Chapter 4

1. **Manuscript:** Lim WW, Neo M, Kuklik P, Ganesan AN, Baumert M, Lau DH, Kalman JM, Semsarian C, Saint DA, Sanders P. Atrial Electrophysiological and Structural Remodelling in Diabesity: Implications for Arrhythmogenesis in Diet-induced Obesity in a Murine Model of Type II Diabetes. (prepared in publication format)
2. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand August 2015, Melbourne, Australia and published in abstract form (*Heart, Lung and Circulation* 22 (2013): S94)
3. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand August 2015, Melbourne, Australia and published in abstract form (*Heart, Lung and Circulation* 22 (2013): S96)
4. **Presentation:** Presented at the Cardiac Society of Australia and New Zealand August 2015, Melbourne, Australia and published in abstract form (*Heart, Lung and Circulation* 21 (2012): S100)

Chapter 5

1. **Manuscript:** Lim WW, Neo M, Kuklik P, Ganesan AN, Baumert M, Lau DH, Kalman JM, Semsarian C, Saint DA, Sanders P. Depressed HRV and Slowed Atrial and Atrioventricular Conduction in Diabesity: A Polygenic Mouse Model of Diabetes and Obesity (prepared in publication format)

PRIZES AND AWARDS DURING CANDIDATURE

1. Adelaide Graduate Research Scholarship (2011-2014)
2. Australian Physiological Society Student Travel Claim for AUPS 2014
3. International Society for Heart Research Travel Bursary for CSANZ 2015